Published in final edited form as:

Endocr Pract. 2015 March ; 21(3): 237–246. doi:10.4158/EP14118.OR.

EVALUATION, MEDICAL THERAPY, AND COURSE OF ADULT PERSISTENT HYPERINSULINEMIC HYPOGLYCEMIA AFTER ROUX-EN-Y GASTRIC BYPASS SURGERY: A CASE SERIES

John P. Mordes, MD¹ and Laura C. Alonso, MD²

¹Department of Medicine, Division of Endocrinology, University of Massachusetts Medical School, Worcester, Massachusetts

²Division of Diabetes, University of Massachusetts Medical School, Worcester, Massachusetts

Abstract

Objective—To describe the evaluation and treatment of hyperinsulinemic hypoglycemia in adults who had undergone gastric bypass surgery. A small number of patients who undergo Roux-en-Y bypass surgery develop postprandial hypoglycemia in the absence of dumping. In some cases, such patients have been treated with pancreatectomy.

Methods—We report the demographics, diagnostic results, response to medical therapy, and subsequent course of 6 referral patients with post-Roux-en-Y gastric bypass hypoglycemia.

Results—Characteristic clinical and metabolic parameters consistent with hyperinsulinemic hypoglycemia were identified. Parameters were similar for both spontaneous and glucose-challenge-induced hypoglycemia. In the context of exclusively postprandial symptoms, simultaneous glucose 55 mg/dL, insulin 17 μ U/mL, C peptide 3.0 ng/mL, and insulin to glucose ratio >0.3 were associated with Roux-en-Y gastric bypass hyperinsulinemic hypoglycemia. Five of six patients improved on therapy consisting of dietary modification plus either calcium channel blockade, acarbose, or both. Two patients have remained on therapy for 12 to 15 months. The nonresponder was atypical and had had hypoglycemic events for several decades. Three treated patients were subsequently observed to have undergone partial or complete remission from hypoglycemic episodes after 2 to 37 months of therapy. None of the six have undergone pancreatectomy, and none have evidence of insulinoma. Invasive diagnostic procedures were of limited utility.

Conclusion—In a subset of patients with post-Rouxen-Y gastric bypass hyperinsulinemic hypoglycemia, medical management can be efficacious and an alternative to partial pancreatectomy. In some cases, the disorder remits spontaneously.

Address correspondence to Dr. John P. Mordes, 364 Plantation Street, LRB 222, Worcester, MA 01605. john.mordes@umassmed.edu.

Author contributions: Dr. John P. Mordes and Dr. Laura C. Alonso researched the data and wrote the manuscript.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

INTRODUCTION

Beginning in 2005, a small number of cases of postprandial noninsulinoma hyperinsulinemic hypoglycemia were reported in adults who had previously undergone Roux-en-Y gastric bypass (RYGB) surgery for weight reduction (1–4). The cause of postprandial hypoglycemia in these patients is not clear (5), but the condition can be severe, recurrent, and intractable. In many cases, invasive assessment of pancreatic insulin secretion with a selective arterial calcium-stimulated insulin release study (SACS) (6) was performed. SACS in some (1,2), but not all (4), cases excluded insulinoma, documented diffuse release of excess insulin throughout the pancreas, and guided subsequent surgery. In one series, some patients were treated with reoperation to restore or increase gastric restriction (4). In other cases, because of the severity of symptoms, partial and sometimes total pancreatectomy was used to treat the hypoglycemia (1–4). Pancreatectomy in many cases led to the onset of diabetes. Effective medical therapy of hypoglycemia after RYGB has been reported in only 3 cases (7–9), although it appears to be an alternative to surgery for some cases of persistent neonatal hyperinsulinemic hypoglycemia (10–14). Medical therapy was not attempted in most series reporting reoperation or pancreatectomy (1–4). There is no consensus as to the optimal diagnostic and therapeutic strategies for patients who develop hypoglycemia after RYGB (15). To add additional information to the small existing dataset, we now report our experience with 6 patients referred for possible post-RYGB hypoglycemia. We suggest diagnostic criteria for its noninvasive evaluation and describe successful nonsurgical intervention. The series includes a 5-year follow-up of a previously reported case (9).

METHODS

Case Accrual

All cases were referrals to an endocrinology clinic at an academic medical center for evaluation of hypoglycemia. Cases 1 through 5 had undergone an RYGB procedure for obesity. Case 6 was atypical, having undergone RYGB surgery in childhood 35 years earlier as part of surgical correction of congenital pyloric stenosis.

Oral Glucose-Challenge Testing

Cases 3 through 6 underwent provocative glucose-challenge testing with 75 g of Trutol® to evoke postprandial hypoglycemia. Subjects were admitted to the outpatient diagnostic center after an overnight fast. All medications prescribed to prevent hypoglycemia, if any, were discontinued 12 hours before the study. Fingerstick glucose was measured every 20 minutes or whenever the patient reported symptoms. Blood for hospital laboratory determination of glucose, insulin, proinsulin, C peptide, and cortisol were obtained at baseline and again when symptoms occurred and a fingerstick glucose concentration <55 mg/dL was observed. Cases 1 and 2 were serendipitously observed to experience hypoglycemia in a setting in which simultaneous serum glucose, insulin, proinsulin, and C peptide were then measured, and were not challenged.

Selective Arterial Catheterization of the Pancreas

Cases 1 and 2 underwent SACS as described (1,6). With the patient under conscious sedation, each of the 3 arteries supplying the pancreas (splenic, superior mesenteric, and gastroduodenal) was cannulated and injected with 0.025 mEq of calcium per kilogram of body weight. Blood for determination of insulin concentration was obtained from a catheter in the right hepatic vein immediately before and then 30, 60, and 120 seconds after injection of the calcium solution. The ratio of stimulated to baseline insulin concentration for each arterial injection was determined at each time point. A ratio of 2 or greater was considered to be a positive response indicative of hypersecretion of insulin (6,16). Abnormal responses in multiple regions are interpreted as suggestive of diffuse hypersecretion and have been reported in cases of post-gastric bypass hyperinsulinemic hypoglycemia (1).

Diagnostic Criteria

The clinical diagnosis of hypoglycemia was based on satisfying Whipple's triad (17). SACS results (6) were interpreted according to published criteria (18). An algorithmic approach to the differential diagnosis of postsurgical hypoglycemia based on glucose, insulin, proinsulin, and C peptide has been proposed (19), but the evidence level supporting it remains low (15). To further evaluate this algorithm, we obtained these and additional measurements during hypoglycemia. The homeostasis model assessment-insulin resistance (HOMA-IR, <http://www.dtu.ox.ac.uk/homacalculator/>) was used to estimate steady-state beta-cell function (%B) and insulin sensitivity (%S) in fasting samples (20). As no patients came to surgery, no pathologic studies were performed.

Abdominal Imaging

Five of the 6 cases underwent abdominal imaging using computed tomography (CT) or magnetic resonance imaging (MRI) at some point prior to or during evaluation. Case 6 also underwent upper gastrointestinal endoscopy.

Treatment

All cases were treated with dietary modification plus either a calcium-channel blocker (nifedipine or verapamil), an alpha-glucosidase inhibitor (acarbose), or a combination of both. The dietary prescription is shown in Table 1 and consisted of 3 to 6 feedings with no concentrated carbohydrate; dietary adherence was by self-report. Nifedipine was used as the first-choice calcium-channel blocker. It was titrated to the maximum tolerated dose, starting at 10 mg daily. The minimum effective dose was 30 mg daily, which was effective as a single extended-release dose. If this dose of nifedipine was ineffective, acarbose was added, at an initial dose of 25 mg 3 times a day (t.i.d.) before meals. This was titrated upwards as tolerated to a maximum of 100 mg t.i.d. for patients eating 3 meals and 50 mg 6 times daily for patients on a frequent small-meal diet. For patients who preferred to try acarbose first, the process of adding a second drug was the inverse.

RESULTS

Clinical and Demographic Data

Demographic characteristics of the cases are given in Table 2. Additional data for case 1 have been reported previously (9). Five patients were female and class III obese before surgery (mean body mass index [BMI], 52.6 kg/m²; range 41 to 65 kg/m²) and when studied had lost substantial weight (mean BMI when evaluated, 29.4 kg/m²; range 24 to 37 kg/m²). One female patient (case 6) had undergone Billroth II followed by RYGB for pyloric stenosis in Mexico as a child; those medical records were not available. Endoscopic evaluation at our institution 1 year prior to endocrine evaluation confirmed the presence of anatomy consistent with RYGB. There were no unusual findings on physical examination in any case. At the time of surgery, 2 of the 6 patients were diabetic, but none were diabetic at the time of evaluation (average glycohemoglobin, 5.4%). None had gastrointestinal or vasomotor symptoms (diaphoresis, dizziness, or flushing) suggestive of dumping (21), but a formal dumping score (22) was not computed. All cases reported exclusively postprandial symptoms 30 minutes to 4 hours after eating. None reported symptoms that occurred before surgery, at night, before breakfast, or after missing a meal. Symptom frequency varied widely (Table 2).

In other respects, the sample was diverse. Median age at surgery was 37 years, with a range of 13 to 64 years. The interval between surgery and evaluation for hypoglycemia varied widely, from 1 to 35 years. The duration of symptoms between onset and evaluation varied between 1 and about 12 months. Two of 6 patients reported some postoperative dumping that resolved well before onset of symptoms; case 3 reported chronic constipation. Each case reported other intercurrent medical problems; these included chronic obstructive pulmonary disease, sarcoidosis, neurosarcoidosis, asthma, rheumatoid arthritis, hypertension, depression, and intrapancreatic mucinous tumor (IPMT; case 1). None of these intercurrent problems affected more than one of the cases. The IPMT was described previously (9) and has not changed during the 4 years since that report.

All patients had documented episodes of hypoglycemia witnessed by medical professionals. Both adrenergic and neuroglycopenic events were reported; there was one instance of loss of consciousness (case 1). Case 5 was evaluated extensively for vertigo and palpitations before hypoglycemia was suspected. No patients were taking medications for diabetes or medications reported to be associated with hypoglycemia (23). Before evaluation, all cases had been prescribed a low-carbohydrate diet consisting of 6 small feedings, which had failed to reduce symptom frequency substantially.

Metabolic Evaluation

The metabolic data are summarized in Table 3. In all cases, spontaneous postprandial hypoglycemia or induced hypoglycemia following oral glucose challenge provoked symptomatic hypoglycemia, with glucose <55 mg/dL, insulin >17 µU/mL, C peptide >3.0 ng/mL, and an insulin to glucose ratio >0.3. Screening for sulfonylureas was negative in all 6 cases. Assessments of fasting HOMA-IR in cases 3 through 6 documented normal to high

levels of insulin sensitivity (%S; mean 69 ± 22) and beta-cell function (%B; mean 184 ± 85) (Table 3).

Case 1 came to medical attention after losing consciousness, with a fingerstick glucose concentration of 25 mg/dL. Later, during a routine phlebotomy, she was observed to be hypoglycemic without symptoms (glucose, 39 mg/dL). Her proinsulin was elevated, C peptide was detectable, and the insulin to glucose ratio was 0.46 (Table 3). Asymptomatic hypoglycemia after RYGB has also been reported by Patti et al (5). SACS in this case revealed hypersecretion of insulin in all 3 arterial distributions (9).

Case 2 was serendipitously observed in clinic to be symptomatically hypoglycemic (glucose, 42 mg/dL). The patient's proinsulin and insulin were elevated, C peptide was detectable, and the insulin to glucose ratio was 0.67. Case 2 also underwent SACS, but hypersecretion of insulin was observed only in the distribution of the gastroduodenal artery and not the splenic or superior mesenteric arteries. It was also observed at only at one time point, and was, therefore, nondiagnostic of post-RYGB hypoglycemia according the criteria of Service et al (1), which require evidence of hypersecretion in all 3 arterial distributions to the pancreas.

Cases 3 through 6 underwent oral glucose challenge. As shown in Table 3, all had unremarkable baseline data. All experienced symptomatic hypoglycemia, with a mean glucose concentration of 46 mg/dL (range, 26 to 54 mg/dL). At glucose nadir, there were increases in insulin, C peptide, and proinsulin, and the insulin to glucose ratio was >0.30 . Serum cortisol concentration did not change appreciably in 3 of the 4 patients. Cases 3, 5, and 6 exhibited neuroglycopenic symptoms at glucose nadir; case 4 was minimally symptomatic. All cases also experienced nausea and, in one case, vomiting during the first hour.

CT and MRI Imaging

All cases had either an MRI or CT of the abdomen. Case 1 had a side-branch IPMT that has been described previously (9); it has not changed since that report. No other pancreatic abnormalities were detected.

Clinical Course

Management and clinical course of the 6 cases is summarized in Table 4. The period of observation ranged from 2 to 64 months. As summarized in Table 4, 5 of the 6 patients reported significant benefit from medical therapy. Clinical benefit occurred with continuation of prior dietary modification and the addition of a calcium-channel blocker (nifedipine or verapamil), acarbose, or a combination of both.

The successful treatment of case 1 with nifedipine, 30 mg daily, was reported through 22 months of therapy (9). She experienced complete remission of all symptoms through month 37, at which time she electively stopped the medication. During the subsequent 28 months, she has had 3 episodes of mild hypoglycemia. Her BMI increased from 32.7 kg/m^2 at initial evaluation to 40.2 kg/m^2 at her last visit (a gain in weight of 20.4 kg), but she has remained free of diabetes (glycohemoglobin, 5.6%).

Case 2 was treated with diet and nifedipine, which was titrated to the frequency of her symptoms. The maximum dose of 30 mg t.i.d. was reached at month 12. Before the highest dose was reached, acarbose was added (25 mg before each meal), but she found the gastrointestinal side effects intolerable. She remained on 90 mg of nifedipine through month 32, with complete resolution of symptoms. At month 32, the nifedipine was tapered and discontinued; during that time, her BMI had increased from 25.9 to 30.0 kg/m² (a gain in weight of 7.3 kg). She has remained free of symptoms off treatment for 11 months.

Case 3 was treated with diet and increasing doses of acarbose, ultimately 50 mg before each of her 6 feedings per day. On this program, she has achieved substantial resolution of her symptoms through month 17 of treatment. At her most recent visit at month 17, she recalled only 2 mild symptomatic events during the preceding 6 months. During the first year of treatment, an attempt was made to intensify therapy with the addition of nifedipine, 10 mg daily, but she discontinued the drug complaining of dizziness. During the period of drug therapy, her BMI rose from 32.9 to 33.5 kg/m² (a gain in weight of 2.3 kg).

Case 4 reported prompt and complete resolution of her hypoglycemic symptoms on acarbose; the dose was 25 mg before each of her 6 meals per day. After 2 months, she was hospitalized for severe diarrhea and dehydration, and acarbose was discontinued. She remained off the medication after discharge, and during the subsequent 9 months, she has experienced only 3 mild symptomatic events. During the period of observation, her BMI rose from 38.5 to 39.8 kg/m² (a gain in weight of 5.4 kg).

Case 5 was initially experiencing symptoms up to twice daily; resumption of a diet consisting of 6 small feedings reduced this to every other day, but her episodes were often severe. She was then treated with acarbose, 25 mg before each of her 6 meals per day, with partial, but significant reduction in the frequency and intensity of hypoglycemic symptoms. Nifedipine, initially 10 and then 20 mg 2 times a day was added to her program, which led to complete abolition of symptoms. After 5 months of nifedipine therapy, she developed pedal edema and weight gain. Nifedipine was discontinued, and verapamil 120 mg daily was started, but this also led to recurrent edema. After discontinuation of calcium-channel blockade, acarbose was increased to 50 to 75 mg before each feeding. During the most recent 6 months of acarbose monotherapy, she continues to have episodes 2 to 3 times weekly, but they are described as mild, slow, and easy to reverse with glucose. She has declined intensification of treatment with octreotide or diazoxide for now, stating that she feels she is 'in control' and wishes to avoid additional medication. While on medication, her BMI increased from 24.0 to 25.7 kg/m² (a gain in weight of 5.0 kg).

Case 6, the only patient whose RYGB was not performed for obesity, was intolerant of acarbose, nifedipine, and verapamil, none of which appeared to confer benefit while being taken. Alone among the patients in this study, she was given a trial of diazoxide (3 mg/kg daily), but she was also intolerant of this medication and appeared to receive no glycemic benefit. She characterized her medication intolerance as nausea and dizziness. She refuses to consider any form of surgical intervention. During the period of observation, her BMI increased by 1.5 kg/m² (a gain in weight of 1.3 kg).

DISCUSSION

Symptomatic hypoglycemia after RYGB is uncommon. Swedish registry data show that only 0.2% of more than 5,000 gastric bypass patients experience hypoglycemia (24). What fraction of these are due to hyperinsulinemia is not known. Many cases of post-RYGB hypoglycemia occur with dumping syndrome, and the majority of them can be managed with dietary modification (21).

Some cases, however, are severe, intractable, and refractory to dietary management (1–4). Some have been treated successfully with gastric banding, based on the hypothesis that some cases are due to “late severe dumping syndrome” (4). Others, including some that did not respond to banding (4), have been treated with partial or near-total pancreatectomy (1–4), and many have exchanged hypoglycemia for diabetes (1). Given that RYGB is being performed with increasing frequency as a consequence of the obesity epidemic, the number of individuals with this uncommon complication will increase.

Evaluation

The endocrine changes that occur after RYGB are becoming better characterized (3,25), but a definitive diagnostic approach to postbypass hypoglycemia has not been defined, and the evidence level for most algorithms is low (15).

Consistent with previous reports (1–4), the unifying characteristic of our 6 cases is postprandial adrenergic and neuroglycopenic symptomatology. Service et al (16) defined hyperinsulinemic hypoglycemia as a simultaneous serum glucose ≤ 55 mg/dL, insulin ≥ 3 μ IU/mL, C peptide ≥ 0.6 ng/mL, and negative sulfonylurea toxicology; they also used SACS to confirm the diagnosis. One algorithm (19) suggests screening on the basis of glucose <45 mg/dL and the measurement of proinsulin to discriminate between insulinoma (>5 pmol/L) and nesidioblastosis (<5 pmol/L). Patti et al (2) reported combinations of mixed-meal studies, random observations of hypoglycemic events, and SACS and published a detailed analysis of the metabolic responses seen in post-RYGB subjects with and without hypoglycemia following mixed-meal challenge (5).

The 6 cases reported here meet the criteria used by Service et al (16). This was true for both serendipitously observed hypoglycemia and after glucose challenge. Five of our cases had an insulin to glucose ratio of 0.3 or greater, but this did not hold true for half of the Service et al cases. Proinsulin responses were elevated in all cases and not consistent with some proposed guidelines (26). Goldfine et al (5) have also reported increases in insulin to glucose and C peptide to glucose concentration ratios in their evaluation of post-RYGB patients following a standardized mixed meal.

In the 4 cases for which we have data, HOMA-IR ranged from 0.4 to 1.1. Goldfine et al (5) also reported high insulin sensitivity in their post-RYGB patients. Further study of HOMA-IR in the evaluation (and perhaps biologic understanding) of these patients may be warranted.

To exclude insulinoma and confirm diffuse pancreatic hypersecretion of insulin, SACS is reportedly helpful in some (1), but not all, cases (4). In our hands, SACS proved informative only in case 1; results for case 2 were nondiagnostic. The single abnormal data point was suggestive of insulinoma, but the history and clinical course were not. This inconsistency in SACS outcome in patients with post-RYGB hypoglycemia is similar to that reported in another case series (4). Given its invasiveness and imperfect predictive power, we elected not to perform SACS in cases 3 through 6. Whether the variable results of SACS in these patients represents differences in technical proficiency or variation in underlying pathology is unclear. It may be of more utility when suspicion of insulinoma is higher. At least two instances of hypoglycemia due to insulinoma in bariatric surgery patients have been described (27,28), though in neither case was the procedure a Roux-en-Y.

Continuous glucose monitoring may also be helpful in the assessment of patients suspected of having post-RYGB hypoglycemia (26,29), but this was not used in our cases.

Treatment

The first 11 and several subsequent cases of refractory post-RYGB hypoglycemia were treated with pancreatectomy (1–4). Nonsurgical control of post-RYGB hypoglycemia has been reported in only a few cases (7–9). In 2007, Bantle et al (30) suggested that dietary intervention might be an alternative to surgery in 3 patients, but they did not report efficacy. In 2008, Moreira et al (7) reported a case of probable post-RYGB hypoglycemia who failed dietary therapy but did respond to verapamil plus acarbose. In 2009, Spanakis and Gragnoli (8) reported a case of well-documented post-RYGB hypoglycemia who responded to diazoxide for >16 months. A trial of glucagon therapy in a single patient produced unsatisfactory results (31). In 2010, we reported the response of case 1 to nifedipine monotherapy for 22 months (9). An atypical case of hypoglycemia occurring after fundoplication was reportedly responsive to octreotide (32).

Five of our 6 cases of post-RYGB hypoglycemia were managed medically with dietary modification plus a calcium-channel blocker, acarbose, or both, a regimen similar to that reported by Moreira et al (7). To what extent diazoxide (8) or octreotide (32) might also be effective, alone or in combination with other drugs, is unclear.

Patti et al (2) reported that a large number of drugs, including acarbose, nifedipine, diazoxide, octreotide, phenytoin, beta-blockers, and diltiazem, were ineffective in their 3 cases, but 2 of those cases were atypical. It is not clear what doses and combinations were used. Other series do not report medical interventions prior to surgery (1,3,4).

In our cases 1 and 2, nifedipine was effective for 32 and 37 months, respectively, but when discontinued, hypoglycemia did not recur. Case 4 reported a definite response to acarbose, with reduction of the frequency of hypoglycemic events from every other day to none. Since the medication was stopped, the patient has experienced only 3 mild episodes of symptoms during the subsequent 13 months. Among the 6 patients in this series, she had the mildest symptoms, the highest glucose level at nadir (56 mg/dL) when challenged, and the lowest insulin to glucose ratio (0.31). Remission in these cases may have been due to increased body weight, insulin resistance, age-related decline in beta-cell function, or a combination of

these factors. Identifying the mechanisms of both hypoglycemia and remission after RYGB will require the study of a larger series of patients.

Areas of Uncertainty

There is a lack of consensus concerning the underlying mechanism of the disease (5). It was initially attributed to the induction of nesidioblastosis (1,2,33), but this pathologic diagnosis has been called into question (34) and has not always been observed in pancreatectomy or pancreatic biopsy specimens (4). Hypoglycemia due to hypersecretion of insulin may be related to excess production of gut-derived incretin hormones (5). Post-RYGB hypoglycemia has also been ascribed to an ill-defined reactive process leading to, or unmasking, a defect in beta-cell function (35), perhaps in response to high-carbohydrate meals (30) or postsurgical dumping syndrome (21). Supporting the view that postbypass hyperinsulinemia and hypoglycemia may result from altered nutrient delivery rather than hyperfunction of beta-cells is a report of successful management of such cases with a gastrostomy tube (36) and the beneficial effects sometimes seen with gastric banding treatment (4). Given the observation that approximately 84% of diabetic patients experience complete remission of diabetes after undergoing RYGB (25), it has been argued that postsurgical hypoglycemia may represent “diabetes remission in the extreme” (37).

Hyperinsulinemic hypoglycemia can have a genetic basis. Familial hyperinsulinemic hypoglycemia of infancy has been associated with mutations in several genes, among them *Kir6.2*, which encodes a potassium channel, and *SUR1*, which encodes a sulfonylurea receptor (38). When looked for in cases of adult-onset noninsulinoma hyperinsulinemic hypoglycemia occurring spontaneously (16) or after gastric-bypass surgery (2), however, such mutations have not been found. The cases presented here were not studied for these mutations.

CONCLUSION

Based on our cases and others previously reported, we suggest that the initial evaluation of hypoglycemia following gastric-bypass surgery can be made without recourse to invasive testing. Clinically, these cases gave a history of exclusively postprandial symptoms consistent with hypoglycemia and had no vasomotor or bowel symptoms suggestive of dumping. For metabolic confirmation, our data are consistent with previous proposals (1,33) that the diagnosis of post-RYGB hypoglycemia can be established with simultaneous serum glucose 55 mg/dL, insulin 3 μ IU/mL, C peptide 0.6 ng/mL, and negative sulfonylurea testing. These values appear to be valid when obtained at random or using a 75-gram glucose challenge.

We also show that some cases can be controlled without recourse to pancreatectomy (1–4), secondary gastric restrictive surgery (4), or gastrostomy (36). Most medically treated cases required adherence to a low-carbohydrate, frequent-feeding diet supplemented by 1 or 2 medications independently targeted at insulin secretion or intestinal carbohydrate absorption. Perhaps the most compelling reason to attempt medical therapy documented in this series is its association with complete or partial remission of symptoms over time.

Although there is a common phenotype, there are likely to be multiple underlying pathogenic processes that contribute to post-RYGB hypoglycemia. No one diagnostic and therapeutic approach will fit all cases. In addition, there is clearly variation in the severity of post-RYGB hypoglycemia, and the fraction of cases that will respond to medical therapy is not known. In addition, the relative contribution of medical therapy and regained weight to eventual remission remains to be determined.

In summary, for post-RYGB hypoglycemia meeting our diagnostic criteria and unresponsive to dietary modification alone, a trial of combined dietary and pharmacologic therapy for symptom control and possible induction of remission is warranted before surgery is considered.

Acknowledgments

This study was supported in part by grants 7-11-BS-102 (J.P.M.) from the American Diabetes Association and R43DK085910 (J.P.M.) and R01DK095140 (L.C.A.) from the National Institutes of Health. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. We thank Dr. Samir Malkani, for a critical reading of the manuscript.

Abbreviations

BMI	body mass index
HOMA-IR	homeostasis model assessment–insulin resistance
IPMT	intrapancreatic mucinous tumor
%B	estimated steady-state beta-cell function
%S	estimated insulin sensitivity
RYGB	Roux-en-Y gastric bypass
SACS	selective arterial calcium-stimulated insulin release study

REFERENCES

- Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med*. 2005; 353:249–254. [PubMed: 16034010]
- 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; 48:2236–2240. [PubMed: 16195867]
- Clancy TE, Moore FD Jr, Zinner MJ. Post-gastric bypass hyperinsulinism with nesidioblastosis: subtotal or total pancreatectomy may be needed to prevent recurrent hypoglycemia. *J Gastrointest Surg*. 2006; 10:1116–1119. [PubMed: 16966030]
- Z'graggen K, Guweidhi A, Steffen R, et al. Severe recurrent hypoglycemia after gastric bypass surgery. *Obes Surg*. 2008; 18:981–988. [PubMed: 18438618]
- 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; 92:4678–4685. [PubMed: 17895322]
- Doppman JL, Chang R, Fraker DL, et al. Localization of insulinomas to regions of the pancreas by intra-arterial stimulation with calcium. *Ann Intern Med*. 1995; 123:269–273. [PubMed: 7611592]

7. Moreira RO, Moreira RB, Machado NA, Gonçalves TB, Coutinho WF. Post-prandial hypoglycemia after bariatric surgery: pharmacological treatment with verapamil and acarbose. *Obes Surg.* 2008; 18:1618–1621. [PubMed: 18566871]
8. Spanakis E, Gragnoli C. Successful medical management of status post-Roux-en-Y-gastric-bypass hyperinsulinemic hypoglycemia. *Obes Surg.* 2009; 19:1333–1334. [PubMed: 19551453]
9. Guseva N, Phillips D, Mordes JP. Successful treatment of persistent hyperinsulinemic hypoglycemia with nifedipine in an adult patient. *Endocr Pract.* 2010; 16:107–111. [PubMed: 19625246]
10. Shanbag P, Pathak A, Vaidya M, Shahid SK. Persistent hyperinsulinemic hypoglycemia of infancy--successful therapy with nifedipine. *Indian J Pediatr.* 2002; 69:271–272. [PubMed: 12003307]
11. Ba F, Darendeliler F, Demirkol D, Bundak R, Saka N, Günöz H. Successful therapy with calcium channel blocker (nifedipine) in persistent neonatal hyperinsulinemic hypoglycemia of infancy. *J Pediatr Endocrinol Metab.* 1999; 12:873–878. [PubMed: 10614546]
12. Glaser B, Hirsch HJ, Landau H. Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy. *J Pediatr.* 1993; 123:644–650. [PubMed: 8410523]
13. Thornton PS, Alter CA, Katz LE, Baker L, Stanley CA. Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism. *J Pediatr.* 1993; 123:637–643. [PubMed: 8410522]
14. Eichmann D, Hufnagel M, Quick P, Santer R. Treatment of hyperinsulinaemic hypoglycaemia with nifedipine. *Eur J Pediatr.* 1999; 158:204–206. [PubMed: 10094438]
15. Mechanick JI, Youdim A, Jones DB, et al. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient—2013 update: cosponsored by American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery. *Obesity (Silver Spring).* 2013; 21(suppl 1):S1–S27. [PubMed: 23529939]
16. Service FJ, Natt N, Thompson GB, et al. Noninsulinoma pancreatogenous hypoglycemia: a novel syndrome of hyperinsulinemic hypoglycemia in adults independent of mutations in Kir6.2 and SUR1 genes. *J Clin Endocrinol Metab.* 1999; 84:1582–1589. [PubMed: 10323384]
17. Whipple AO. The surgical therapy of hyperinsulinism. *J Int Chirurgie.* 1938; 3:237–276.
18. Doppman JL, Miller DL, Chang R, Shawker TH, Gorden P, Norton JA. Insulinomas: localization with selective intraarterial injection of calcium. *Radiology.* 1991; 178:237–241. [PubMed: 1984311]
19. Ceppa EP, Ceppa DP, Omotosho PA, Dickerson JA 2nd, Park CW, Portenier DD. Algorithm to diagnose etiology of hypoglycemia after Roux-en-Y gastric bypass for morbid obesity: case series and review of the literature. *Surg Obes Relat Dis.* 2012; 8:641–647. [PubMed: 21982939]
20. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care.* 2004; 27:1487–1495. [PubMed: 15161807]
21. Tack J, Arts J, Caenepeel P, De Wulf D, Bisschops R. Pathophysiology, diagnosis and management of postoperative dumping syndrome. *Nat Rev Gastroenterol Hepatol.* 2009; 6:583–590. [PubMed: 19724252]
22. Linehan IP, Weiman J, Hobsley M. The 15-minute dumping provocation test. *Br J Surg.* 1986; 73:810–812. [PubMed: 3768652]
23. Mordes JP, Thompson MJ, Harlan DH, Malkani S. Hypoglycemia. In: Irwin RS, Rippe JM, editors. *Intensive Care Medicine.* 7th. Philadelphia, PA: Lippincott, Williams & Wilkins; 2012. p. 1168–1182.
24. Marsk R, Jonas E, Rasmussen F, Näslund E. Nationwide cohort study of post-gastric bypass hypoglycaemia including 5,040 patients undergoing surgery for obesity in 1986–2006 in Sweden. *Diabetologia.* 2010; 53:2307–2311. [PubMed: 20495972]
25. Thaler JP, Cummings DE. Minireview: hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. *Endocrinology.* 2009; 150:2518–2525. [PubMed: 19372197]
26. Hanaire H, Dubet A, Chauveau ME, et al. Usefulness of continuous glucose monitoring for the diagnosis of hypoglycemia after a gastric bypass in a patient previously treated for type 2 diabetes. *Obes Surg.* 2010; 20:126–129. [PubMed: 19763705]
27. Abellán P, Cámara R, Merino-Torres JF, et al. Severe hypoglycemia after gastric bypass surgery for morbid obesity. *Diabetes Res Clin Pract.* 2008; 79:e7–e9. [PubMed: 17804109]

28. Zagury L, Moreira RO, Guedes EP, Coutinho WF, Appolinario JC. Insulinoma misdiagnosed as dumping syndrome after bariatric surgery. *Obes Surg*. 2004; 14:120–123. [PubMed: 14980046]
29. Halperin F, Patti ME, Skow M, Bajwa M, Goldfine AB. Continuous glucose monitoring for evaluation of glycemic excursions after gastric bypass. *J Obes*. 2011; 2011:869536. [PubMed: 21331295]
30. Bantle JP, Ikramuddin S, Kellogg TA, Buchwald H. Hyperinsulinemic hypoglycemia developing late after gastric bypass. *Obes Surg*. 2007; 17:592–594. [PubMed: 17658016]
31. Halperin F, Patti ME, Goldfine AB. Glucagon treatment for post-gastric bypass hypoglycemia. *Obesity (Silver Spring)*. 2010; 18:1858–1860. [PubMed: 20168313]
32. Bernard B, Kline GA, Service FJ. Hypoglycaemia following upper gastrointestinal surgery: case report and review of the literature. *BMC Gastroenterol*. 2010; 10:77. [PubMed: 20615254]
33. Cui Y, Elahi D, Andersen DK. Advances in the etiology and management of hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass. *J Gastrointest Surg*. 2011; 15:1879–1888. [PubMed: 21671112]
34. Klöppel G, Anlauf M, Raffel A, Perren A, Knoefel WT. Adult diffuse nesidioblastosis: genetically or environmentally induced? *Hum Pathol*. 2008; 39:3–8. [PubMed: 18070631]
35. 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; 29:1554–1559. [PubMed: 16801578]
36. McLaughlin T, Peck M, Holst J, Deacon C. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. *J Clin Endocrinol Metab*. 2010; 95:1851–1855. [PubMed: 20133462]
37. Patti ME, Goldfine AB. Hypoglycaemia following gastric bypass surgery—diabetes remission in the extreme? *Diabetologia*. 2010; 53:2276–2279. [PubMed: 20730413]
38. Fournet JC, Junien C. Genetics of congenital hyperinsulinism. *Endocr Pathol*. 2004; 15:233–240. [PubMed: 15640549]
39. Gayoso-Diz P, Otero-Gonzalez A, Rodriguez-Alvarez MX, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. *BMC Endocr Disord*. 2013; 13:47. [PubMed: 24131857]

Table 1**Dietary Prescription^a**

Three small meals plus 2–3 small snacks
60-g protein daily
No high-fat, high-carbohydrate foods and no sugar-containing fluids
64 ounces of calorie-free beverages daily, taken between, not with, meals
Vitamin supplements: multivitamins, B12, iron plus C, calcium, and vitamin D
Eat slowly over 30 minutes; eat protein first

^a Dietary prescription provided to all patients undergoing bariatric surgery or being evaluated for postprandial hypoglycemia at our institution.

Table 2

Demographic Characteristics of Cases^a

Case	Status at surgery			Status when evaluated							Fasting events?	A1c
	Age	BMI ^b	Diabetes	Age	BMI ^b	Years after surgery	Symptom duration at presentation for hypoglycemia	Symptom frequency	Symptom grade	Postprandial delay (hours)		
1	38	50.0	No	64	32.3	26.3	2 months	Weekly	1	1–2	No	5.4%
2	46	40.6	No	47	25.9	0.9	2 months	Monthly	1	1–2	No	4.8%
3	23	63.5	Yes	28	32.7	5.5	12 months	Monthly	1	1–1.5	No	5.7%
4	57	64.6	No	60	23.9	2.7	6–12 months	4–5 Times Weekly	1	3–4	No	5.9%
5	35	54.8	Yes	39	24.0	3.2	6 months	Up to twice daily	1	3–4	No	5.2%
6	13	Not known	No	49	25.6	36	35 years	Daily	1	1.5–2	No	5.0%
Mean	36	52.6		47.8	27.4							5.3%

Abbreviations: A1c = glycated hemoglobin; BMI = body mass index.

^a All cases were women, and surgery in all cases was Roux-en-Y gastric bypass. All reported persistence of intractable symptoms on a frequent small feeding low-carbohydrate diet. Symptom duration, frequency, and postprandial intervals are by self-report and approximate. Symptoms were graded from 1 (severe neuroglycopenia) to 3 (minimal) as described (4).^b Units: kg/m².

Metabolic Evaluation^a

Table 3

Fasting											
Case	Time	Glucose (70–99 mg/dL)	Insulin (<21 μU/mL)	Proinsulin (26.8 pmol/L)	C-peptide (0.9–7.1 μU/mL)	AM Cortisol (6.7–22.6 μg/dL)	Proinsulin/ Insulin ^b	Insulin/ Glucose ^c	%B	%S	IR ^d
3	Fasting	96	3	-	3.7	9.6	-	0.03	44.4	250.2	0.4
4	Fasting	108	8	8.4	2.8	14.2	1.1	0.07	68.1	92.1	1.1
5	Fasting	80	3	5.2	1.5	7.8	1.7	0.04	64.4	262.6	0.4
6	Fasting	82	6	<2.5	1.9	7.3	0.4	0.03	97.2	131.1	0.8
Mean ± SD		92 ± 13	5.0 ± 2.4	6.8	2.5 ± 1.0	9.7 ± 3.1	1.2 ± 0.8	0.05 ± 0.02	69 ± 22	184 ± 85	0.7 ± 0.3
When hypoglycemic	Time to hypoglycemia	Glucose	Insulin	Proinsulin	C-peptide	Cortisol	Proinsulin/ insulin	Insulin/ glucose			
1	Spontaneous	39	18	14.2	5.5	-	0.8	0.46	-	-	-
2	Spontaneous	42	28	37.3	3.2	-	1.3	0.67	-	-	-
3	3.2 h	37	37	19	7.7	9.6	0.5	1.00	-	-	-
4	4.8 h	54	17	32.7	6.0	9.7	1.9	0.31	-	-	-
5	2.3 h	26	22	14.1	4.7	9.9	0.6	0.85	-	-	-
6	2.8 h	24	51	4.5	8.6	19.4	0.1	2.13	-	-	-
Mean ± SD		39 ± 12	29 ± 13	22 ± 13	6.8 ± 1.8	11.9 ± 4.2	1.1 ± 0.8	0.9 ± 0.6	-	-	-

Abbreviations: IR = insulin resistance; %B = estimated steady-state beta-cell function; %S = estimated insulin sensitivity.

^a Shown are measurements obtained from normoglycemic fasting samples (upper 3 rows) and samples during spontaneous or postchallenge hypoglycemia, as described in the “Methods” section. Reference ranges and units are given in parentheses. Plasma glucose measurements were performed in the hospital laboratory. Homeostatic model assessment parameters were computed with the Oxford calculator (<http://www.dtu.ox.ac.uk/homacalculator/>).

^b (pmol/L)/(μU/mL).

^c (μU/mL)/(mg/dL).

^d The threshold for diagnosing insulin resistance varies with age, gender, and metabolic status, but in general is uniformly 1.6 (39).

Table 4Clinical Course^a

Case	Number of meals	Nifedipine	Acarbose	Diazoxide	Self-reported efficacy ^b	Duration of therapy (months)	Change in weight (kg)	Effect of medication withdrawal
1	3	30 mg ER	None	--	No further symptoms	40	20.4	No recurrence of symptoms
2	3	30 mg t.i.d.	None	--	Minimal residual symptoms	35	7.3	No recurrence of symptoms
3	3	None	50 mg t.i.d. before each meal	--	2 mild events to date	15	2.3	Not attempted
4	3	None	25 mg before each meal	--	No further symptoms	2	5.4	9 months without symptoms, then once monthly
5	6	20 mg t.i.d. ^c	50 mg t.i.d. before meals	--	Asymptomatic on both medications; mild symptoms on acarbose alone	5 on combined therapy; 6 on acarbose alone	5.0	Not attempted
6	6–8	10 mg daily ^d	25 mg. before meals ^d	3 mg/kg daily ^d	No effect on symptoms	<2	1.5	Daily hypoglycemia in the absence of frequent feeding

Abbreviations: ER = extended release; t.i.d. = three times a day.

^a Overview of responses to treatment. All patients were advised to adhere to a 6-meal low-carbohydrate diet as prescribed for them by their surgical providers.^b Details of clinical responses are given in results.^c Nifedipine discontinued in case 5 at 5 months due to pedal edema and weight gain.^d Medication discontinued by patient due to gastrointestinal side effects.