

Hypoglycemia After Gastric Bypass Surgery: Current Concepts and Controversies

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Context: Hypoglycemia, occurring after bariatric and other forms of upper gastrointestinal surgery, is increasingly encountered by clinical endocrinologists. The true frequency of this condition remains uncertain, due, in part, to differences in the diagnostic criteria and in the affected populations, as well as relative lack of patient and physician awareness and understanding of this condition. Postbariatric hypoglycemia can be severe and disabling for some patients, with neuroglycopenia (altered cognition, seizures, and loss of consciousness) leading to falls, motor vehicle accidents, and job and income loss. Moreover, repeated episodes of hypoglycemia can result in hypoglycemia unawareness, further impairing safety and requiring the assistance of others to treat hypoglycemia.

Objective: In this review, we summarize and integrate data from studies of patients affected by hypoglycemia after Roux-en-Y gastric bypass (RYGB) surgery, obtained from PubMed searches (1990 to 2017) and reference searches of relevant retrieved articles. Whereas hypoglycemia can also be observed after sleeve gastrectomy and fundoplication, this review is focused on post-RYGB, given the greater body of published clinical studies at present.

Outcome Measures: Data addressing specific aspects of diagnosis, pathophysiology, and treatment were reviewed by the authors; when not available, the authors have provided opinions based on clinical experience with this challenging condition.

Conclusions: Hypoglycemia, occurring after gastric bypass surgery, is challenging for patients and physicians alike. This review provides a systematic approach to diagnosis and treatment based on the underlying pathophysiology. (*J Clin Endocrinol Metab* 103: 2815–2826, 2018)

A 54-year-old nurse with a long-standing history of obesity, with a maximum weight of 237 pounds and body mass index (BMI) of 42 kg/m², had laparoscopic Roux-en-Y gastric bypass (RYGB) 9 years before presentation. She reported no previous history of diabetes or hypoglycemia. Surgery and the postoperative period were unremarkable; during the first year after surgery, she lost ~80 pounds. Approximately 5 years after surgery, she began to experience symptoms of palpitations, anxiety, and confusion, which increased gradually in frequency and severity, currently 5 times per week. Symptoms typically

occur within 1 to 2 hours after eating, are more likely to occur after eating simple carbohydrates, and are relieved by carbohydrate intake. The patient has not required assistance for her symptoms but has needed to switch her work role to allow a less-demanding schedule. She remains concerned that she will not be able to maintain her current position as a result of the erratic nature of her schedule, the need for accuracy and decisionmaking, and the requirement to drive to her job.

An initial evaluation included a meal test, during which she developed neuroglycopenia, characterized by

confusion and difficulty in responding to questions and instructions, associated with plasma glucose of 34 mg/dL at 105 minutes after eating; symptoms were relieved by drinking juice. These data fulfilled Whipple's criteria (1) (symptoms of hypoglycemia, concurrent low plasma glucose levels, and relief of symptoms by carbohydrate ingestion), thus documenting hypoglycemia (2). She was referred for evaluation and management. She reports that glucometer readings at the time of typical symptoms are usually in the 40 to 50 mg/dL range, but sometimes autonomic symptoms are also present when glucose is >200 mg/dL.

Diagnostic Evaluation

How can we establish whether hypoglycemia is the cause of her symptoms? If so, is it related to her RYGB or a result of another cause?

History remains a critical first step in the evaluation. Details about hypoglycemic episodes should include the severity (frequency, presence of neuroglycopenia, whether assistance is required) and timing (relationships to fasting, meals, specific provocative foods, activity, and presence of nocturnal symptoms). Detailed records of symptoms, food, and activity can be helpful in identification of patterns linked to symptoms. Although continuous glucose monitoring (CGM) is less accurate in the hypoglycemic range, blinded monitoring may be helpful to identify patterns of glycemic excursions but should not be used for diagnostic purposes. Typically, presentation with postbariatric hypoglycemia (PBH) first occurs >1 year after surgery. Symptoms usually occur 1 to 3 hours after eating. Symptomatic hypoglycemia, occurring very early in the postoperative period (<6 to 12 months), in the fasting state, or >4 hours after caloric intake, is not typical and should instead raise concern for other causes of hypoglycemia. Likewise, hypoglycemia with activity and during overnight hours (*e.g.*, 2 to 4 AM) is occasionally reported by patients, but these patterns should also prompt consideration of alternative diagnoses. A comprehensive history and physical exam also provide invaluable information to consider additional causes of hypoglycemia, such as malnutrition, side effects of medications or supplements, critical illness, hormone deficiencies, autoimmune hypoglycemia (3), or nonislet cell tumors (2). If hypoglycemia in well-appearing individuals occurs in the fasting state, then an additional workup should be performed to rule out insulinoma (4).

If the history is typical for PBH syndrome, then the next step is to determine whether symptoms are caused by hypoglycemia and relieved by carbohydrate ingestion (Whipple's triad). In an ideal world, an analysis of venous glucose at the time of a spontaneous episode of hypoglycemia would be optimal. However, this is often not

practical; patients may not be able to predict when they will develop symptoms as a result of day-to-day variability and may not be able to get to a laboratory safely to have blood sampling at the time they are experiencing symptoms.

Can provocative tests be used to induce hypoglycemia in patients with suspected PBH?

An oral glucose tolerance test (GTT) is not well tolerated in individuals with a history of upper-gastrointestinal surgery, as the hyperosmolar liquid load often provokes severe dumping syndrome. More importantly, 10% of healthy individuals without any previous history of gastrointestinal surgery have glucose levels <50 mg/dL within the first 180 minutes of the challenge, with no evidence of neuroglycopenia. Thus, an oral GTT should play no role in the evaluation of meal-induced hypoglycemia (2), particularly in the population of individuals after gastrointestinal surgery who may also experience symptoms consistent with dumping syndrome (5). Rather, provocative testing in this setting should ideally use a mixed meal containing protein, carbohydrates, and fat. Unfortunately, there is no currently accepted standard for meal testing; both solid and liquid mixed meals have been used in clinical practice and research studies, with carbohydrate content ranging from 40 to 75 g (6–8). Use of a liquid mixed meal in clinical diagnostic evaluation remains controversial; there is divergence of opinion among the authors, with some indicating that a liquid meal has no place in the evaluation of patients with accelerated and relatively unregulated transit of calories into the proximal small intestine, whereas others believe it provides a more reproducible stimulus. Regardless of the approach, the inducement of hypoglycemia with any provocative meal test poses the risk of severe hypoglycemia necessitating medical assistance and should be done in a safe environment with personnel trained to observe closely and respond appropriately in the event of severe hypoglycemia.

What glucose threshold should be used to define hypoglycemia and fulfill Whipple's triad during either spontaneous or provoked testing in such patients?

The answer is unclear for several reasons. Cryer *et al.* (9) defined hypoglycemia on the basis of the glucose threshold for insulin secretion in the fasting condition in healthy individuals; endogenous insulin secretion ceases when glucose falls below ~60 mg/dL. A similar definition for meal-induced hypoglycemia has not been established, especially for those with a history of upper-gastrointestinal surgery.

Typical patterns of glycemia in a post-bypass patient include normal fasting glucose but exaggerated

postprandial excursions compared with those without gastrointestinal surgery, with a rapid rise in glucose shortly after food intake and a fast decline thereafter (Fig. 1A). Glucose patterns alone cannot be used to define clinically meaningful hypoglycemia; integration with symptom profiles is essential. Moreover, many post-bariatric patients have postprandial autonomic symptoms, such as lightheadedness, palpitations, and fatigue, which may represent manifestations of the dumping syndrome (5) but also overlap significantly with autonomic symptoms of hypoglycemia. Given the complexity of distinguishing between symptoms of hypoglycemia and dumping syndrome, we propose that a strict definition of hypoglycemia be used in the postbariatric population—neuroglycopenic symptoms (such as behavioral changes, confusion or impaired cognitive function, seizure, loss of consciousness) with concomitant low plasma glucose (<50 mg/dL) (2, 11) with symptoms relieved by correction of the hypoglycemia, typically within a few minutes.

Once neuroglycopenic hypoglycemia has been documented in an individual patient, laboratory testing at the time of symptomatic hypoglycemia has been used by those with access to endocrine testing centers to assess β -cell peptide responses. Again, there are no normative data in this situation which can account for the patient's BMI or the meal size and composition, and it is important to remember that peripheral concentrations of a hormone or substrate represent the net sum of secretion and clearance at that given timepoint. Research studies have shown that insulin concentrations in individuals with post-RYGB hypoglycemia are not fully suppressed at the time of hypoglycemia occurring in the postprandial period (*e.g.*,

glucose <50 mg/dL, with insulin concentrations greater than the lower limit of the assay used) (12, 13). If a postbariatric patient has postprandial symptoms but no neuroglycopenia and/or normal mixed-meal testing, then further evaluation and treatment should be directed toward dumping syndrome or other nonhypoglycemic syndromes.

Which patients with hypoglycemia after bariatric surgery require a prolonged fasting test and imaging?

For postbariatric patients who have typical postprandial hypoglycemia and no fasting hypoglycemia, we do not routinely perform prolonged fasting tests. Rather, inpatient fasting is reserved for (and is essential for) patients with fasting hypoglycemia, hypoglycemia occurring early after bariatric surgery (*e.g.*, <6 months), or other atypical features, to exclude the rare insulinoma in postbariatric patients (4). In patients with fasting hypoglycemia who do not appear well, additional diagnostic testing should be considered to rule out other causes that may coexist in the postbariatric setting, *e.g.*, adrenal insufficiency, critical illness, or malnutrition associated with excessive weight loss or food aversion.

Imaging studies should not be performed unless the history and biochemical testing demonstrate that fasting hypoglycemia is present and is caused by excessive insulin secretion, or other atypical clinical features raise suspicion for other pathology. Even in this setting, noninvasive imaging studies fail to detect 20% to 25% of insulinomas so that a negative study does not exclude the diagnosis (14). Endoscopic ultrasound is sometimes challenging after RYGB but with experienced operators,

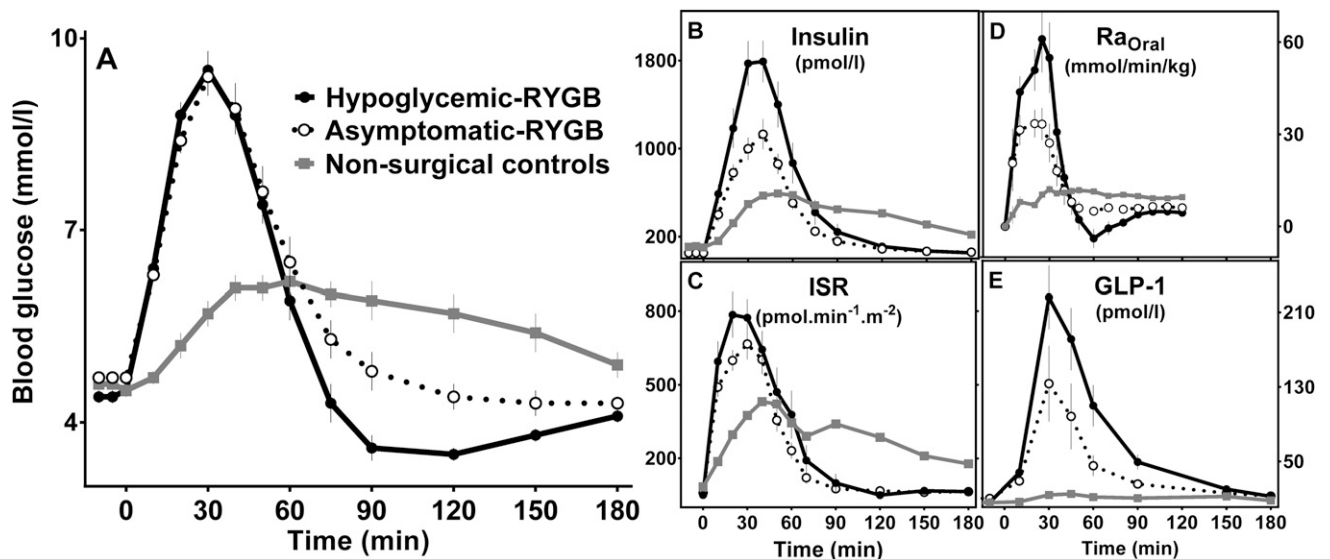


Figure 1. Typical glycemic and hormonal patterns in the fasting state and after mixed meal. (A) Blood glucose, (B) plasma insulin, and (C) insulin secretory response (ISR) to meal ingestion. (D) Systemic appearance of ingested glucose (R_{aOral}) and (E) circulating glucagon-like peptide 1 (GLP-1) levels during meal tolerance test in RYGB subjects with (black ● and solid line) and without (black ○ and dashed line) hypoglycemia and nonsurgical controls (gray ■ and solid line). Reproduced from Salehi *et al.* (6, 10).

can be successful in imaging the pancreas to identify suspected insulinoma. Insulin responses during selective arterial calcium-stimulation testing, often performed with arteriography, have been used in the past to exclude insulinoma (15) and to diagnose noninsulinoma pancreatogenous hypoglycemia syndrome in nonbariatric individuals (16, 17). Normative values for symptomatic or asymptomatic postbariatric patients are not available. Given the invasive nature of the test and its uncertain interpretation, selective arterial calcium-stimulation testing should not be used unless insulinoma is suspected, and other imaging has not been informative.

In summary, PBH can be diagnosed if the following criteria are met, and other causes of hypoglycemia have been ruled out: (1) history of postprandial neuroglycopenia occurring 1 to 3 hours after meals in a patient with history of bariatric surgery at least 6 to 12 months before symptom onset, (2) documented hypoglycemia (venous glucose <54 mg/dL) at time of neuroglycopenic symptoms, with resolution of symptoms with treatment to raise glucose, and (3) no hypoglycemia after a prolonged fast of at least 12 hours. If atypical symptoms are present, or response to therapy is incomplete, additional diagnostic evaluation may be required. See flowchart in Fig. 2 for schematic of suggested approach to evaluation.

Pathophysiology of PBH

The underlying mechanisms for glucose dysregulation among patients with post-RYGB hypoglycemia are

multifactorial and incompletely understood. However, the dominance of postprandial timing of hypoglycemia and disproportionate insulin response to food intake indicate that hypoglycemia is partly a result of an exaggerated systemic appearance of ingested glucose secondary to altered anatomy after upper-gastrointestinal procedures.

Glucose homeostasis after eating is tightly regulated by meal-induced gut factors promoting a greater β -cell secretory response to oral compared with intravenous glucose administration—the so-called incretin effect. Whereas hormonal factors of enteroinsular axis, glucose-dependent insulinotropic peptide, and glucagon-like peptide 1 (GLP-1) are better characterized, the incretin effect also includes direct nutrient and neural stimulation (18, 19).

RYGB-mediated bypass of the pylorus and proximal intestine results in a wider glycemic excursion after food intake, with an earlier and greater peak of glucose, as well as a lower glucose nadir (6, 8, 10, 20) (Fig. 1). In parallel with altered glucose pattern, as a result of the rapid delivery of nutrients to the proximal foregut, early postprandial secretion of insulin and GLP-1 is exaggerated after RYGB (10, 21, 22). Meal-induced GLP-1 response increases by 10-fold (6); thus, postprandial hyperinsulinemia after RYGB is typically attributed to the combined effects of more rapid nutrient transit from the gastric pouch to the gut, as well as an enhanced incretin effect (22–26). In fact, feeding through the remnant stomach, which results in slowing of food transit time, reduces postprandial glucose excursion and insulin

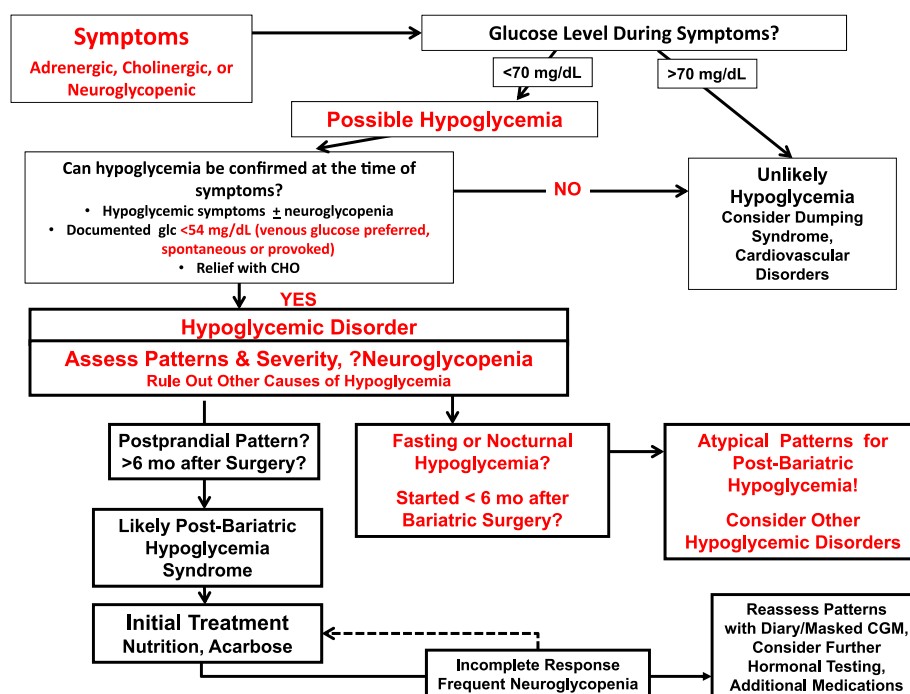


Figure 2. Suggested approach to possible hypoglycemia in a postbariatric patient. glc, glucose.

response (27, 28). Moreover, the blocking of the GLP-1 effect, using continuous infusion of exendin 9-39, a potent, specific GLP-1 receptor antagonist, has shown to have a larger effect to reduce meal-induced insulin response in nondiabetic subjects after RYGB compared with nonoperated individuals (7, 10, 23).

Given the continuum of variations in postprandial insulin secretion and nutrient transit time after RYGB, it is plausible that post-RYGB hypoglycemia simply reflects extreme glycemic effects of RYGB in a subgroup of susceptible individuals. This hypothesis has been supported by cross-sectional studies demonstrating that patients with RYGB-related hypoglycemia have greater systemic appearance of ingested glucose (10) and larger meal-induced insulin and GLP-1 secretion (6, 8, 10) compared with matched asymptomatic post-RYGB individuals (Fig. 1).

GLP-1 receptor blockade during oral nutrient ingestion has been shown to reverse hyperinsulinemia and prevent hypoglycemia in affected individuals (10, 29), indicating the pathogenic role of this peptide in hypoglycemia after RYGB. As the higher contribution of GLP-1 to postprandial insulin response is not a result of increased GLP-1 receptor expression in pancreatic sections (30) or β -cell sensitivity to GLP-1 (31), the enhanced GLP-1-induced hyperinsulinemia in affected subjects is likely a result of massive postprandial GLP-1 secretion after this procedure.

The role of additional components of the enteroinsular axis (direct nutrient or glucose-dependent insulinotropic peptide effects or neural factors) in mediating the glycemic effects of RYGB or in development of hypoglycemia remains largely unknown. As previously noted, meal-derived glucose appearance into the circulation is much larger in individuals with PBH compared with asymptomatic postbariatric individuals and is not affected by blocking GLP-1 receptors (10), indicating that factors beyond GLP-1 contribute to hypoglycemia. A recent report showed that meal ingestion stimulated insulin secretion in post-RYGB, even when plasma glucose was maintained at sub-basal levels (60 mg/dL) (13). It is also possible that the bypassing of the foregut effect on glucose metabolism is mediated by the increase of the portal-systemic gradient in glucose and gut factors, mainly GLP-1 (32–34).

Regardless of the cause of postmeal hyperinsulinemia after RYGB, several mechanisms may contribute to maintenance of inappropriately high levels of insulin, even when hypoglycemia has developed. Firstly, the ability to suppress insulin release in response to decreasing glucose levels is an important regulatory mechanism to prevent hypoglycemia. Post-RYGB patients have significantly lower β -cell suppression in response to glycemic reduction during hyperinsulinemic hypoglycemic clamp compared with the same individuals before surgery

or to matched nonsurgical individuals (13, 35). Delayed cessation of insulin secretion, in response to decreasing glucose, is also observed during meal studies, with higher β -cell output as glucose approaches basal levels in individuals with hypoglycemia compared with asymptomatic post-RYGB controls (6). Secondly, diminished insulin clearance may contribute to sustained elevations in plasma insulin levels. Insulin clearance is reduced by 30% in individuals with PBH compared with those without hypoglycemia (6) and could contribute to increased tissue glucose clearance in affected patients.

Initial reports indicated that increased β -cell mass might contribute to increased insulin secretion in post-RYGB hypoglycemia (16, 17) when compared with surgical controls. Subsequent analyses revealed no differences in overall β -cell mass when the same samples were compared with autopsy specimens (36). Other studies revealed substantial variability in both β -cell area and markers of proliferation (37). Whether these differences reflect heterogeneity in the population under study or are unrelated to functional differences in meal-stimulated insulin responses remains uncertain. Regardless, the finding that reduction in β -cell mass by partial pancreatectomy has not been effective in fully resolving hypoglycemia over time in post-RYGB patients (38) also suggests that increased β -cell mass is not the dominant contributor to PBH.

In addition to altered β -cell function after RYGB, α -cell responses are changed. Food intake enhances glucagon response after RYGB compared with nonsurgical controls via unknown mechanisms (20, 22, 23, 39). However, meal-induced glucagon secretion in post-RYGB patients, with and without hypoglycemia, is similar (8, 10). By contrast, hyperinsulinemic hypoglycemic clamp studies in nondiabetic patients, with and without RYGB (13), or in nondiabetic individuals before and 6 months after surgery (35) demonstrate a substantial reduction in glucagon response to hypoglycemia after RYGB. Diminished counter-regulatory responses after RYGB may perpetuate recurrent hypoglycemia and unawareness in affected individuals.

Insulin-independent modulation of glucose metabolism may also contribute to hypoglycemia. Noninsulin-dependent glucose disposal (glucose effectiveness), measured during intravenous GTT, is greater in patients with post-RYGB hypoglycemia compared with asymptomatic post-RYGB individuals (40), potentially contributing to enhancing tissue glucose uptake even at times when insulin levels and/or action are not increased.

Taken together, the bulk of evidence supports a multifactorial model of glucose abnormalities in PBH (Fig. 3), caused by enhanced β -cell secretion, in turn, secondary to a more rapid appearance of nutrients in the

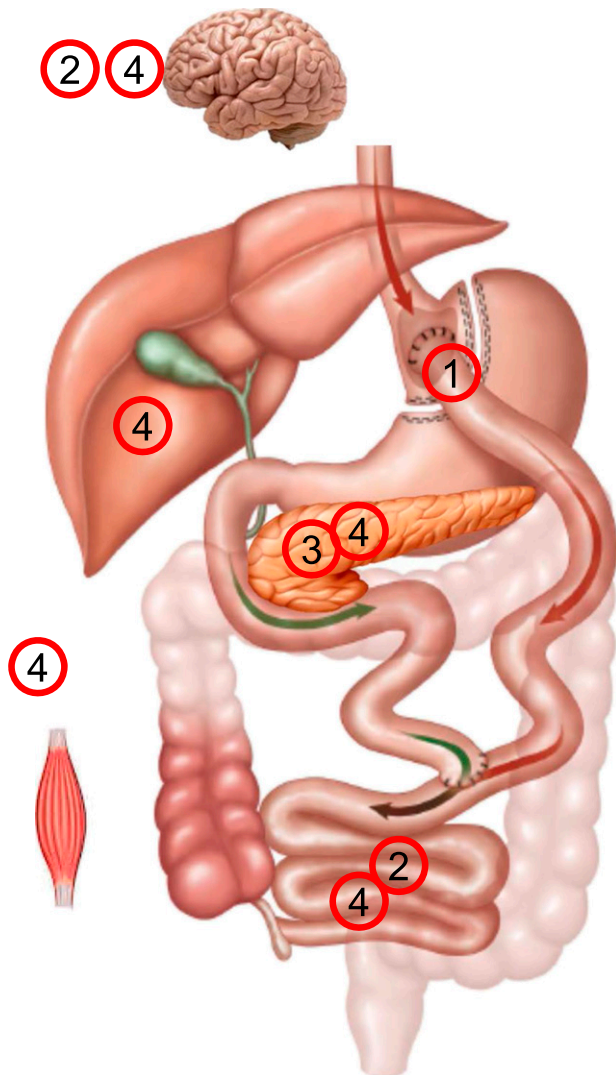


Figure 3. Potential contributors to the pathophysiology of PBH. Shown is anatomy following RYGB. Contributing factors include the following: (1) accelerated nutrient emptying from stomach pouch to intestine (roux limb), leading to increased rate of appearance of glucose into blood and increased peak postprandial glucose; (2) enhanced enteroinsulin axis activity, with increased secretion and action of GLP-1 and possible direct nutrient effects and neural factors; (3) postprandial hyperinsulinemia, resulting from increased β -cell glucose sensitivity with increased glucose, cessation of β -cell secretion during decreasing glycemia, decreased insulin clearance, increased portal-systemic gradient for postmeal glucose, and GLP-1, with potential heterogeneity of β -cell mass; and (4) noninsulin-dependent factors, with reduced counter-regulatory hormone response (e.g., glucagon), increased glucose effectiveness (noninsulin-dependent glucose uptake), and gut mucosal adaptations (altering nutrient absorption, bile acid uptake and metabolism, and microbiome).

circulation and enhanced secretion and action of GLP-1. Intrinsic alterations in α - and β -cell function and insulin-independent glucose disposal may further contribute to the risk of post-RYGB hypoglycemia. Whether this is an inherent metabolic phenotype, unmasked by the hormonal and metabolic changes occurring postoperatively or caused directly by RYGB, remains to be investigated.

Therapy

The goal of therapy in post-RYGB hypoglycemia is to reduce the frequency and severity of hypoglycemia, thus improving safety and allowing resumption of activities of daily living. With currently available therapies, the complete elimination of hypoglycemia in severely affected patients is unlikely, and ongoing vigilance to safety is essential.

Medical nutrition therapy

Diet is the cornerstone of therapy for post-RYGB hypoglycemia (Fig. 4) and is aimed at reducing the stimulus for glycemic spikes and insulin secretion [general clinical approach reviewed in Suhl *et al.* (41)]. Unfortunately, there are no well-designed studies comparing the long-term impact of meal plans with different nutrients and/or macronutrient composition. Later, we present our clinical experience with dietary management; rigorous studies comparing different dietary approaches would be helpful. In counseling patients, we emphasize that diet is not the cause of post-RYGB hypoglycemia but is an essential component of treatment.

Ingested carbohydrates, particularly rapidly digested/simple/high glycemic index carbohydrates, can rapidly increase plasma glucose, which stimulates insulin secretion and further increases the risk of subsequent hypoglycemia. In one study, a single meal severely depleted in carbohydrates (2 g) did not produce excursions in glucose and insulin, and hypoglycemia did not occur (42). Whereas some patients avoid all carbohydrates to reduce hypoglycemia, severe carbohydrate avoidance over time is not desirable, as it may contribute to malnutrition, risk of hypoglycemia during sleep or activity and reduced responsiveness to glucagon.

Dietary carbohydrate composition and food texture can also influence postprandial metabolism (43), but the optimal plan for long-term therapy has not been well defined. Our clinical experience indicates that a meal plan focused on elimination of simple sugars but including controlled portions of low glycemic index carbohydrates with multiple small meals and snacks containing up to 30 and 15 g, respectively (*i.e.*, 90 to 130 g/d), is usually well tolerated and often helpful in reducing hypoglycemia. Replacement of some glucose-based carbohydrates by fructose may also reduce glycemic excursions (44). We also recommend a “mixed meal” approach, in which complex carbohydrates are consumed together with protein and healthy fats; initial suggestions for preferred and nonpreferred food choices are provided in Supplemental Table 1 [expanded in Suhl *et al.* (41)]. These recommendations should be guided by the team dietitian and individualized based on review of

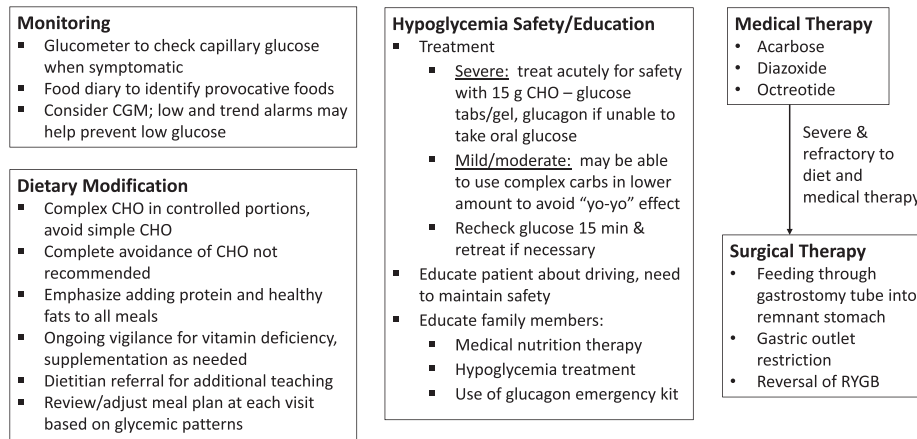


Figure 4. Suggested approach to the treatment of established post-RYGB hypoglycemia.

glucose at each visit, as glycemic responses to any given food vary substantially between patients.

Uncooked cornstarch is not readily absorbed by the small intestine but is slowly hydrolyzed by pancreatic amylase and intestinal glucoamylase to provide a steady supply of exogenous glucose. Cornstarch has been successfully used to treat hypoglycemia in glycogen storage disease (45), hyperinsulinemic hypoglycemia of infancy (46), and insulin–antibody-mediated hypoglycemia (47). It has not been studied in the PBH population but may be an option for preventing hypoglycemia. Commercial products containing cornstarch are reported by some to be helpful, especially for hypoglycemia occurring at night and during physical activity.

Proteins and fats are not only essential for a balanced meal plan but can also slow nutrient absorption, reducing glucose spikes and subsequent hypoglycemia. Adequate intake of protein and healthy fats should be guided by the team dietitian.

Additional recommendations include fully chewing food and eating slowly, avoiding liquids with meals to prevent dumping symptoms and instead drinking between meals, portion control to avoid weight regain, and avoidance of excessive caffeine and alcohol, which can cause hypoglycemia via inhibition of hepatic glucose release.

Treating acute hypoglycemia

When symptomatic hypoglycemia develops, we recommend use of oral carbohydrates (10 to 15 g) to relieve symptoms and reverse downward excursions in glucose. As oral carbohydrates can produce a glucose “yo-yo” effect in post-RYGB hypoglycemia patients, many patients find that complex carbohydrate or simple sugar mixed with fat/protein, such as two tablespoons of natural peanut butter, can be successful for episodes of mild hypoglycemia. However, if the patient is being treated with acarbose, we suggest initial treatment with

glucose exclusively. If severe neuroglycopenia has developed (defined as not being able to consume oral carbohydrates safely as a result of confusion or loss of consciousness), then glucagon can be administered by family members. Regardless of initial treatment, repeat testing of glucose is recommended to ensure resolution of hypoglycemia.

CGM

CGM has emerged as an effective adjunct for the management of diabetes. Although there are no data addressing the value of CGM in post-RYGB hypoglycemia at present, and accuracy of sensor glucose values is reduced in the hypoglycemic range, many patients find CGM to be a valuable tool in detecting patterns of dropping glucose, particularly in patients with hypoglycemia unawareness. Trend curves and alarms, available on some but not all CGM, can enable early treatment and prevention of severe hypoglycemia. The attainment of insurance coverage for patients with post-RYGB hypoglycemia can be very challenging; pre-authorization letters and appeals are typically required.

Additional ancillary components of management include education of patient and family members about hypoglycemia recognition and treatment, use of hypoglycemia medical alert identification, use of glucose and glucagon to treat established hypoglycemia, discussion about getting help at home for the patient and/or young children in the house, disability applications when patients cannot physically or safely work, and driving precautions—vs not driving at all if episodes of hypoglycemia are frequent, or hypoglycemia unawareness is present.

Pharmacotherapy

Medications are an important adjunct to medical nutrition therapy. Acarbose delays and reduces absorption of glucose by inhibition of intestinal α -glucosidase, which is

required to break down luminal carbohydrates into monosaccharides. This has the effect of reducing postprandial glycemic excursions (48–51). Although gastrointestinal side-effects of gas and abdominal cramping can limit tolerance, introduction of low doses (*e.g.*, 25 mg before each meal) and slow escalation to the maximal tolerated dose can be effective in limiting side-effects. Diazoxide, which reduces insulin secretion by inhibition of β -cell ATP-sensitive potassium channels, has been used in persistent hyperinsulinemic hypoglycemia of infancy, insulinoma, and noninsulinoma pancreatogenous hypoglycemia syndrome (52). Case reports in PBH show efficacy for doses of 50 mg twice daily (BID) (53) or 100 mg BID (54), but side-effects, including fluid retention, edema, nausea, hypotension, and headache, can limit patient adherence. Somatostatin analogs can also reduce insulin and GLP-1 secretion via binding to somatostatin receptor subtypes 2 and 5. We typically initiate octreotide at 25 to 50 μ g subcutaneously before meals and if effective and tolerated, consider monthly deep intramuscular injections (long-acting octreotide preparation). A few small studies have evaluated efficacy in PBH, with one showing successful prevention of hypoglycemia with octreotide 100 μ g BID for 6 months, followed by lanreotide for four years (55). Somatostatin analog therapy is limited by high cost, as well as side-effects, such as diarrhea, steatorrhea, and risks of cholelithiasis and QT prolongation. Screening abdominal ultrasound and ECG may be warranted before and/or during therapy if the latter conditions are concerning. Case reports or small series have suggested efficacy of calcium channel blockade (56) and GLP-1 agonists (57), but responses are not uniform in our clinical experience.

Surgical therapy

When diet, CGM, and pharmacotherapy fail, surgical treatments can be considered. The placement of the feeding gastrostomy tube (G-tube) into the remnant stomach (bypassed portion) allows liquid nutrients to traverse the foregut through the duodenum and proximal jejunum, approximating the route of transit in a normal, nonsurgical gastrointestinal tract and normalizing glucose, insulin, and incretin responses (27, 58). Feeds via this route can be bolus, overnight, or continuous, according to patient preference and comfort, and different formulas and rates may need to be trialed to minimize discomfort and bloating associated with increasing delivery rates. Oral intake of noncarbohydrate nutrients is permissible; patients should be advised that they will still develop hypoglycemia if they take carbohydrates by mouth, whereas carbohydrates given via G-tube are not likely to elicit hypoglycemia. Rare patients continue to have mild episodic hypoglycemia despite

continuous G-tube feeding, which may improve with the addition of carbohydrates to the tube-feeding formula. Whereas experience with this method varies among institutions, some individuals have been treated successfully for over 5 years (personal communication). This approach can be limited by reduced quality of life as a result of the presence of a feeding tube and discomfort during feeds, particularly upon initiation. It is important to work with the team dietitian before initiation of G-tube feeds to discuss expectations, compliance, insurance coverage for supplies and formulas, and the likely need for trials of different formulas and delivery rates.

Given that rapid emptying of food into the roux limb is a likely contributor to glycemic excursions after eating, gastric pouch outlet restriction, using a silastic ring or adjustable band, or endoscopic plication has been attempted for treatment of hypoglycemia. Whereas one report demonstrated improved symptoms (59), reflux and nausea may be aggravated by this procedure. Whereas experience is variable, these procedures may offer partial and/or temporary improvement of hypoglycemia.

More invasive options also exist. In the past, patients with PBH underwent partial pancreatectomy (16, 17); this procedure is no longer recommended, however, as a result of high morbidity and incomplete resolution and/or recurrence of hypoglycemia postoperatively (38). Surgical reversal of bariatric surgery has been considered for treatment of PBH unresponsive to other measures or for other complications of bariatric surgery, such as malnutrition or excessive weight loss (60). Improvement in frequency and severity of hypoglycemia have been observed in some, but not all, cohorts (61–64). Complications of reversal include persistent hypoglycemia, weight regain, and symptoms of delayed gastric emptying, such as persistent nausea and vomiting, potentially limiting tolerability of this approach. Variable responses to the previous treatments may be related to differences in underlying mechanisms causing this condition, as well as anatomical differences among the affected individuals.

Experimental approaches

Several pharmacologic treatments are presently being evaluated in phase 1 or 2 clinical trials. Exendin 9-39 competitively binds the GLP-1 receptor, thus reducing GLP-1 action (10). Two published human studies demonstrate efficacy of intravenous and subcutaneous exendin 9-39 in preventing hypoglycemia by reducing postload insulin secretion (29, 65). A second experimental approach under study is the use of glucagon, with delivery from a pump triggered by CGM sensor glucose data. Initial pilot studies have demonstrated the feasibility

of this approach (66, 67). Finally, antibody-mediated blockade of the insulin receptor, decreasing insulin signaling, can prevent hypoglycemia in mice (68) and may modify glucose patterns in pilot human studies (69). Until further clinical studies are performed, the role of these potential therapies remains uncertain.

Prevalence, Natural History, and Risk Factors

Estimates of the prevalence of post-RYGB hypoglycemia differ, likely as a result of differences in definitions of severe hypoglycemia, patient selection criteria, and duration of follow-up, but are likely <1% for hypoglycemia requiring hospitalization and <10% for clinically recognized hypoglycemia (70). Some studies have used patient self-reports to assess hypoglycemia prevalence; whereas these are subject to patient misinterpretation of nonspecific symptoms and reporting bias of the survey approach, it is interesting that symptoms potentially consistent with hypoglycemia are reported in as many as 38%, with severe symptoms requiring assistance reported in 12% of post-RYGB patients. Hypoglycemia has also been reported after sleeve gastrectomy (71) and fundoplication (72, 73) and rarely after adjustable gastric banding (74), but comprehensive prevalence data are not available at present.

With the use of various glycemic thresholds for the definition of hypoglycemia, studies using CGM demonstrated that low glucose values are observed, even in completely asymptomatic post-RYGB patients (75–78). In one study, 75% of 40 unselected RYGB patients had sensor glucose <55 mg/dL compared with none in nonsurgical controls (79). However, the physiologic relevance or health implications of asymptomatic low sensor glucose levels remain uncertain.

The natural history of post-RYGB remains uncertain. One series that identified hypoglycemia based on clinical and billing data (80) found that the median time from surgery to the hypoglycemic event was 41 months; 79% of cases identified eventually resolved. In our experience, dumping syndrome-related symptoms generally improve over time by avoiding triggers, whereas severe hypoglycemia does not. Given that recurrent hypoglycemia can also be associated with hypoglycemia unawareness, continued vigilance for asymptomatic hypoglycemia is suggested. Additional longitudinal studies will be required to address fully the natural history of both asymptomatic and symptomatic hypoglycemia.

Can risk factors for post-RYGB hypoglycemia be identified? If so, these could help to guide decisionmaking of patients and physicians alike during consideration of bariatric surgery. Lee and colleagues (81) reported that

modestly lower BMI and HbA_{1c} preoperatively, greater excess weight loss at 6 months, and longer duration of postoperative follow-up were associated with increased risk of incident hypoglycemia. Nannipieri and colleagues (82) reported that preoperative BMI, fasting glucose, and nadir glucose during an oral glucose were lower, and insulin sensitivity and β -cell glucose sensitivity were higher in those who self-reported hypoglycemia symptoms and had low glucose values during oral GTT postoperatively. In another cohort, higher preoperative β -cell function predicted postoperative hypoglycemia (83). In both of these studies, measures of plasma glucose and β -cell function were derived from oral GTT postoperatively—a nonphysiologic and nonspecific test in this population. Thus, it remains unclear whether baseline normoglycemia and insulin sensitivity, despite obesity in the preoperative state, are associated with increased risk; further studies will be required before clinical predictive tools can be developed.

Concluding Remarks

The clinical relevance of severe hypoglycemia with neuroglycopenia is undeniable, as patient safety, nutrition, cognition, and quality of life can be compromised. We do not yet know the long-term health outcomes of patients who experience severe post-RYGB hypoglycemia. Additional studies are required to determine the importance of glycemic variability or asymptomatic hypoglycemia in the postbariatric surgery setting and to identify and test novel approaches to prevent and treat severe hypoglycemia. Moreover, research aimed at understanding mechanisms of hypoglycemia after RYGB may yield important insights into intestinal regulation of glucose metabolism and diabetes risk and provide clues to resolution of type 2 diabetes after bariatric surgery.

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Disclosure Summary: M.S. has consulted for Eiger Pharmaceuticals. A.V. is an investigator in an investigator-initiated study, sponsored by Novo Nordisk, and has consulted for vTv Therapeutics, XOMA, Sanofi-Aventis, and Novartis in the past 5 years. T.M. has received research support from Novartis and Novo Nordisk and has consulted for Eiger Pharmaceuticals. M.-E.P. is a coinvestigator on a National Institutes of Health R44 grant together with Xeris Pharmaceuticals; has consulted for Eiger Pharmaceuticals; has received investigator-initiated grant support from Janssen Pharmaceuticals, Medimmune, Sanofi, Astra-Zeneca, Jenesis, and Nuclea; has been a site investigator for XOMA; acknowledges clinical trial research product support from Ethicon, Covidien, NovoNordisk, Nestle, and Dexcom within the past 5 years; and has submitted a patent application regarding plasma proteins contributing to hypoglycemia.

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