Hypoglycemia After Bariatric Surgery

M27
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SIGNIFICANCE OF THE PROBLEM
Hypoglycemia occurring after bariatric and other forms of upper gastrointestinal surgery is increasingly recognized as a condition commonly presenting to clinical endocrinologists (1). Although the true frequency of this condition remains uncertain, due to differences in diagnostic criteria and diverse populations under study (2), postbariatric hypoglycemia can be severe and disabling for some patients, with neuroglycopenia, seizures, falls, loss of consciousness, 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.

After bariatric and other upper gastrointestinal surgery (such as fundoplication), undigested food empties out of the stomach rapidly, contributing to postprandial “spikes” in glucose. Together with robust prandial incretin secretion (e.g., GLP1), high postprandial glucose levels trigger excessive insulin secretion, leading to extremely rapid drops in glucose. These rapid drops in glucose make it very difficult for patients to detect and successfully treat low blood glucose levels before neuroglycopenia develops. Additional defects contributing to hypoglycemia include reduced insulin clearance and insulin-independent glucose uptake (3). Thus, initial prevention strategies are focused on reducing postprandial glucose and insulin secretion by reducing intake of simple carbohydrates and slowing absorption with disaccharidase inhibitors.

BARRIERS TO OPTIMAL PRACTICE
• The need to differentiate whether symptoms are caused by hypoglycemia or other conditions commonly present in postbariatric patients
• The need to define the underlying cause of hypoglycemia
• Incomplete efficacy of current therapies

LEARNING OBJECTIVES
As a result of participating in this session, learners should be able to:
• Summarize the pathophysiology of postbariatric hypoglycemia
• Identify diagnostic strategies for evaluation of possible hypoglycemia in a postbariatric patient
• Identify staged management approaches for postbariatric hypoglycemia

STRATEGIES FOR DIAGNOSIS, THERAPY, AND MANAGEMENT

Diagnosis
The diagnosis of hypoglycemia is challenging in any patient, but even more so in a patient with a history of bariatric or other gastrointestinal surgery. The adrenergic and cholinergic symptoms of hypoglycemia are nonspecific and overlap considerably with those of the dumping syndrome. Thus, it is essential to first determine whether hypoglycemia is indeed present, whether it is associated with the symptoms, and whether symptoms respond to treatments that increase glucose (Whipple triad). Moreover, accurate determination of the glucose level in a venous sample at the time of symptoms is essential, as capillary glucose values determined by a glucometer can be misleading in the setting of poor blood flow (e.g., cold exposure or Raynaud disease). Simultaneous assessment of β-cell peptides would be ideal if hypoglycemia is confirmed. If glucose is not low at the time of symptoms, additional considerations would include dumping syndrome, anxiety, orthostatic hypotension, or cardiovascular disease.

Once hypoglycemia is diagnosed, the next step is to determine the cause of hypoglycemia. Detailed history, exam, and laboratory testing should be focused on the potential role of systemic and hormonal disease, such as adrenal insufficiency, nutritional adequacy, ethanol intake, and medications that may induce hypoglycemia.

Additional details more specific to the possibility of postbariatric hypoglycemia would include the following: (1) type and date of bariatric surgery, (2) weight trajectory postoperative, (3) nutritional adequacy, and (4) history of diabetes or gestational diabetes preoperatively. Specific details about hypoglycemia episodes should include the severity (frequency, neuroglycopenia, and requiring assistance of others) and timing (relationship to meals, provocative foods, activity, and fasting). Detailed records of symptoms, food, and activity can be helpful to identify patterns linked to hypoglycemia. Although continuous glucose monitoring (CGM) is less accurate in hypoglycemic levels, blinded monitoring can be useful to identify patterns of glycemic excursions related to specific foods and activity and to identify unawareness or nocturnal hypoglycemia (4).

Typically, postbariatric hypoglycemia is first noted 1 to 3 years after surgery and occurs 1 to 3 hours after eating, especially simple (high glycemic index) carbohydrates (example CGM results, Fig. 1). Hypoglycemia can also occur after activity/exercise and occasionally during overnight hours (e.g., 2:00 to 4:00 AM). Hypoglycemia occurring in the fasting state is not typical of postbariatric hypoglycemia; if fasting
If hypoglycemia is present, a detailed diagnostic evaluation for autonomous insulin secretion and insulinoma is needed (likely a 72-hour inpatient fast).

If the history is typical for postbariatric hypoglycemia, the next step is to determine whether insulin levels are increased at the time of hypoglycemia. In an ideal world, an analysis of venous glucose and β-cell peptides at the time of a spontaneous episode of hypoglycemia would be optimal. However, this is often not practical; patients may not be able to safely get to a laboratory setting to have blood sampling. Provocative testing, such as glucose or meal tolerance tests, is often considered as an alternative. However, glucose tolerance testing (GTT) is not well tolerated in individuals with a history of bariatric surgery, as the hyperosmolar glucose load often provokes severe dumping syndrome. Moreover, GTT is not advocated for the evaluation of reactive/postprandial hypoglycemia, as 10% of healthy individuals have glucose levels <50 mg/dL during a 4- to 6-hour GTT (5), and low glucose levels during oral GTT do not correlate well with symptoms or electroencephalogram changes (6). Mixed meal testing is preferable. Unfortunately, there is no current standard for meal testing; liquid versus solid and dietary composition vary across practices and clinical studies. Diagnostic criteria are also lacking, but typically postbariatric patients have elevated insulin and C-peptide levels early after the meal and nonsuppressed levels at the time of hypoglycemia (7,8). Such increases in meal-related insulin secretion are likely multifactorial, but a major contributor is very high postprandial levels of the incretin hormone GLP-1, as indicated by clinical studies demonstrating reduction in insulin secretion and partial normalization of glycemia with infusion of GLP1 receptor inhibitors (9,10).

Postbariatric hypoglycemia is characterized by normal suppression of insulin secretion in the fasting state. The question of when/how to rule out autonomous insulin secretion in this setting is often challenging. While postbariatric hypoglycemia is typically postprandial, 22% of insulinomas present with postprandial hypoglycemia only. In my opinion, not every patient needs a prolonged (72 hour) inpatient diagnostic fast. Rather, the approach needs to be individualized for each patient based on risk. If (1) postbariatric [Roux-en-Y gastric bypass (RYGB) or sleeve] patient reports no history of hypoglycemia with fasting, (2) suspicion is low for autonomous insulin secretion, and (3) patient can safely perform an overnight fast at home (does not live alone, can get ride in morning to laboratory, etc.), one could consider an overnight fast (after supper) with laboratory testing for glucose, insulin, and C-peptide the next morning. This should be repeated on several occasions and if hypoglycemia progresses or new patterns emerge despite therapy. Diagnostic CGM, although of lower accuracy in the hypoglycemic range, can be used to identify patterns of asymptomatic fasting or nocturnal hypoglycemia that require further testing (4). Prolonged inpatient fasting is essential for patients with documented fasting hypoglycemia or atypical features, or those for whom outpatient testing may not be achieved safely.

In summary, postbariatric hypoglycemia can be diagnosed if the following criteria are met: (1) history of postprandial hypoglycemia occurring >1 year after surgery, (2) documented hypoglycemia (venous glucose <70 mg/dL) at time of symptoms and resolution of symptoms with treatment to raise glucose, (3) elevated insulin and C-peptide at time of hypoglycemia, (4) normal fasting glucose, and (5) no evidence of autonomous insulin secretion, with workup as guided by clinical considerations (see flowchart, Fig. 2).

**Treatment**

The goal of therapy in postbariatric hypoglycemia is to reduce the frequency and severity of hypoglycemia, improving safety and allowing resumption of activities of daily living. With currently available therapies, the complete elimination of hypoglycemia is unlikely, and ongoing vigilance to diet and nutrition are essential.

The cornerstone of management of postbariatric hypoglycemia is medical nutrition therapy to reduce the stimulus for glycemic spikes and insulin secretion. Our team has recently published practical suggestions for medical nutrition therapy (11). In brief, because simple (high glycemic index) carbohydrates are rapidly digested and absorbed in a postbariatric patient, we advise complete avoidance of high-glycemic-index carbohydrates. Instead, we recommend selecting controlled portions of low-glycemic-index carbohydrates (<30 g per meal, 15 g per snack to begin). Adequate protein and heart-healthy fats provide required caloric needs.
Meal plan composition and carbohydrate content are subsequently adjusted as needed to minimize spikes in individual patients. Additionally, we recommend avoidance of liquids with meals (to minimize dumping-type physiology), avoidance of ethanol and excessive caffeine, and consistent vitamin and mineral intake, guided by laboratory testing.

If medical nutrition therapy is not sufficient to gain control of hypoglycemia, medications can be added. These include acarbose to slow absorption of glucose, reducing glycemic “spikes” and insulin secretion. Although gastrointestinal side effects of gas and abdominal cramping can limit tolerance of acarbose, slow introduction and escalation to a maximal dose of 300 mg/d are often effective. Somatostatin receptor analogues such as octreotide or pasireotide (12) can also reduce incretin and insulin secretion and can be administered at the time of meals (subcutaneous, before each meal, starting dose 25 to 50 μg) or in monthly deep intramuscular (IM) injections (LAR preparation). Octreotide therapy is limited by high cost, as well as side effects, including diarrhea, steatorrhea, and acute hypoglycemia (presumably linked to inhibition of glucagon secretion). Diazoxide, which reduces insulin secretion, can also be helpful in doses of 50 to 100 mg three times per day but can be limited by fluid retention, edema, and headache. Other reports have suggested efficacy of calcium channel blockade and GLP1R agonists, but we have not found these efficacious in our patient population.

Ancillary components of the management strategy include education of the patient and family members about hypoglycemia recognition and treatment, and use of glucose and glucagon to treat established hypoglycemia. CGM can be helpful to allow early detection and treatment of hypoglycemia (4). Sensor low-glucose alarms can allow patients to detect hypoglycemia even when they have unawareness. Moreover, the “rapid drop alarm” allows patients to initiate treatment even when glucose is within target range, before severe hypoglycemia and neuroglycopenia develop.

Additional therapeutic considerations can include the placement of a G-tube for feeding into the bypassed stomach (13). In some patients, continuous feeding into the remnant stomach (either 24 hours or overnight), and minimal oral intake, can reduce the frequency and severity of hypoglycemia, likely due to reduced glycemic excursions and near normalization of incretin and insulin secretion. Although initial reports described partial pancreatectomy for severe postbariatric hypoglycemia (14,15), pancreatic surgery is no longer recommended due to high morbidity and incomplete resolution and/or recurrence of hypoglycemia postoperatively (16). Some patients may benefit from surgical reversal of bariatric surgery, with reduced frequency and severity of symptoms, but results are variable, potentially related to interindividual differences in postsurgical anatomy and surgical team expertise (17–19).
CASES WITH QUESTIONS AND ANSWERS

Case 1
A 60-year-old female had a witnessed generalized seizure. The capillary glucose level obtained by ambulance personnel was 35 mg/dL. Glucose rose after IM glucagon and intravenous dextrose. Central nervous system imaging was negative. The patient has a history of uncomplicated RYGB 5 years previously. Over the last 6 months, she experienced episodic lightheadedness, confusion, and sweating, usually 2 to 3 hours after eating. She was referred to see you in the endocrinology clinic as an outpatient. History was notable for no personal diabetes history (but diabetes in husband), no family history of hypoglycemia or MEN1 components, and recent weight stability. The exam revealed a BMI of 34 kg/m² and surgical scars and was otherwise normal. General laboratory testing performed in the fasting state at 8:00 AM was normal, including glucose 82 mg/dL, cortisol 12 µg/dL, and hemoglobin A₁c 5.3%.

What are the next best step(s) in diagnostic evaluation? Select all that apply.
A. GTT
B. 72-hour fast
C. Meal tolerance test
D. Food, symptom, and home glucose monitoring diary
E. Venous sample for glucose and β-cell peptides at time of spontaneous hypoglycemia

Answer: C, D, and E

As noted above, an analysis of venous glucose and β-cell peptides at the time of a spontaneous episode of hypoglycemia would be optimal. If this is not practical or safe, provocative testing can be considered. Meal tolerance testing is preferred, as oral glucose is poorly tolerated by postbariatric patients and results do not correlate well with either symptoms or electroencephalogram changes.

The patient was instructed in the use of a home glucose meter to record capillary glucose with symptoms, and completion of a food/activity/symptom log to enable her to identify relationships between specific foods and symptoms. Please note that capillary glucose values should not be used to diagnose hypoglycemia, given that reduced blood flow (as with cold exposure or Raynaud disease) can yield low glucose values not equivalent to central glucose levels. She was given a laboratory slip indicating assays to be checked during a spontaneous episode of hypoglycemia and also scheduled for a mixed-meal tolerance test.

In this case, we were fortunate to be able to “catch” a spontaneous episode. She had a spontaneous hypoglycemic event while at her doctor’s office, 2 hours after eating a donut. Venous samples revealed glucose 43 mg/dL, insulin 12 µU/mL (reference range for laboratory 2.0 to 19.6 µIU/mL), and C-peptide 2.2 ng/mL (1.1 to 4.2 ng/mL). These values are typical of postbariatric hypoglycemia, with modest elevations (inappropriately high) in insulin and C-peptide at the time of hypoglycemia.

What should be your next step(s)? Select all that apply.
A. Imaging of pancreas
B. Start meal plan focused on low glycemic carbohydrates in controlled portions
C. Instruction in use of glucagon emergency kit for family members and medical identification bracelet
D. Add hypoglycemia agent screen to blood samples
E. Inpatient fasting

Answer: B, C, and D

History does not suggest fasting hypoglycemia. In the absence of fasting symptoms and/or biochemical evidence of autonomous insulin secretion, both of which are rare in post-bariatric patients, anatomical imaging is not indicated. Meal planning to reduce glycemic spikes and thus stimulus for insulin secretion is important. Safety measures should include the education of family members about hypoglycemia and use of glucose and glucagon for rescue and a medical identification bracelet indicating hypoglycemia. It would be important to rule out inadvertent or surreptitious use of sulfonylureas or other hypoglycemic agents.

The question of when/how to safely fast to rule out autonomous insulin secretion is often challenging. While post-bariatric hypoglycemia is typically postprandial, recall that 22% of insulinomas present with postprandial hypoglycemia only. Although rare, insulinomas can occur in post-bariatric patients (20), and it is essential to identify these as surgical treatment would be needed. In my experience, not every patient needs a prolonged (72 hour) inpatient diagnostic fast. Rather, the approach needs to be individualized for each patient based on clinical risk. If (1) the patient reports no history of hypoglycemia with fasting, (2) suspicion is low for fasting hypoglycemia or atypical features, or those for whom outpatient testing may not be achieved safely.

The patient saw a dietician and initiated a meal plan focused on choosing low-glycemic-index carbohydrates (30 g maximum per meal, 15 g per snack) and no liquids with meals. The frequency of symptoms was reduced, but some moderate
hypoglycemia (glucose in 40s, not requiring assistance) persisted.

What is the best next step for treatment?
A. Diazoxide
B. Octreotide
C. Acarbose
D. Calcium channel blocker

Answer: C
The disaccharidase inhibitor acarbose is typically the first pharmacologic therapy for postprandial hypoglycemia as it addresses the major pathophysiologic condition of rapid increases in nutrient absorption. Acarbose slows carbohydrate absorption, reducing peak prandial glucose and reducing both insulin and GLP1 responses to meals (21,22). Common side effects include abdominal gas, bloating, and cramping; these can be reduced by gradual increase in dosing and reduction in carbohydrate intake. The patient was started on acarbose 25 mg with each main meal for 1 week; the dose was increased gradually to 100 mg with each main meal. Hypoglycemic episodes were reduced in frequency and severity.

About 1 year later, neuroglycopenia recurred despite compliance with diet and acarbose. Octreotide was started, initially dosed (by injection) before meals and ultimately IM monthly (LAR). She continues to have mild occasional hypoglycemia.

Case 2
The patient is a 44-year-old female who presented with symptoms of shakiness, blurred vision, lip numbness, cold sweats, and anxiety progressively increasing over 1 month after gastric bypass surgery. The patient had progressive weight gain during adult life, particularly after two pregnancies complicated by gestational diabetes, with peak BMI of 44 kg/m². Previous weight loss attempts with commercial weight loss programs (e.g., Jenny Craig and Weight Watchers) were unsuccessful. Evaluation for obesity, hirsutism, and oligomenorrhea led to a diagnosis of polycystic ovarian syndrome. The patient was advised to lose weight with diet and exercise. Metformin was prescribed but discontinued due to symptoms of shakiness and sweating occurring shortly after the first dose. Laboratory testing at the next office visit showed random glucose 88 mg/dL with insulin 50 μU/mL, interpreted as reactive hypoglycemia in association with insulin resistance.

The patient was referred for bariatric surgery due to her severe obesity, hypertension and hyperlipidemia, and underlying insulin resistance. She had an uncomplicated laparoscopic RYGB. While on the recommended postoperative diet, the patient noted symptoms of palpitations, sweating, and lightheadedness, typically after oral intake and occasionally during short walks, and required caloric intake every 3 to 4 hours to prevent symptoms. Capillary glucose levels at the time of symptoms ranged from 30 to 60 mg/dL.

What aspect of this patient’s history is an unusual feature of postbariatric hypoglycemia?
A. Hypoglycemia occurring 2 to 3 hours after meals
B. Hypoglycemia starting 1 month after surgery
C. Symptoms of possible hypoglycemia occurring preoperatively

Answer: B
Hypoglycemia typically begins 1 to 3 years postoperatively, but sometimes as late as 10 years postoperatively! This patient was very atypical in that she had worsening of preexisting hypoglycemia immediately postoperatively. This pattern (within the first 6 months postoperative) should raise concern for an alternative diagnosis.

The hypoglycemic symptoms occurring preoperatively have been identified as a potential risk factor for postbariatric hypoglycemia in a survey study (23,24). As with this patient, it is unclear whether nonspecific symptoms, particularly without neuroglycopenia, occurring preoperatively (but not fully evaluated) truly represented hypoglycemia or not. One study evaluating oral glucose tolerance preoperatively showed that patients who developed hypoglycemia postoperatively had lower BMI, fasting glucose, and nadir glucose during GTT and higher β-cell glucose sensitivity preoperatively than those who did not develop hypoglycemia (25). However, all values were within the normal range, making it impossible to distinguish these patients in a clinical setting. Nevertheless, preoperative risk evaluation should include a detailed query for history of possible hypoglycemia. If positive, additional evaluation should be considered to further define the risk of hypoglycemia.

Returning to this patient, endocrine evaluation revealed no other relevant medical history. The family history was important for obesity in her sister and brother and type 2 diabetes in her maternal grandfather. There was no history of neonatal or adult hypoglycemia, or of pancreatic disease or MEN1 component diseases.

Given the atypical nature of hypoglycemia in this postbariatric patient, an assessment of β-cell peptide secretion and its autonomy was necessary. Although her symptoms were typically occurring after meals and with activity, it is important to remember that 22% of insulinomas present with both fasting and postprandial hypoglycemia (26). Given the prominent exercise component, glucose patterns were assessed after an overnight fast and in response to exercise. The patient developed symptoms after 10 minutes of cycling on a stationary bike, with plasma glucose 56 mg/dL. Cortisol, lactate, and pyruvate responses to exercise were normal. With continued fasting over an additional 4 hours, symptoms of neuroglycopenia developed, with minimum glucose 44 mg/dL.
and inappropriately nonsuppressed insulin (8 μU/mL), C-peptide (1.76 ng/mL), and proinsulin (49 pM) and suppressed β-hydroxybutyrate (0.8 mM). Blood glucose promptly responded to glucagon (1 mg), with increase of glucose of 47 mg/dL at 30 minutes after glucagon.

**What do these data suggest is the underlying cause of the patient’s hypoglycemia?**

A. Postbariatric hypoglycemia syndrome  
B. Autonomous insulin secretion  
C. Inadequate glycogen stores  
D. Exercise-induced hypoglycemia due to MCT1 mutation

**Answer: B**

Hypoglycemia is confirmed by a low venous glucose at the time of neuroglycopenic symptoms. Inadequately suppressed insulin, C-peptide, and proinsulin at the time of hypoglycemia indicate failure of insulin secretion to be appropriately suppressed, thus defining autonomous insulin secretion. In postbariatric hypoglycemia syndrome, insulin secretion is appropriately suppressed with fasting. (Patients with postbariatric hypoglycemia typically do well if they need to fast for any reason, e.g., surgery or diagnostic testing.)

An increase of >25 mg/dL in glucose after glucagon injection indicates residual glycogen stores (despite fasting), suggesting that insulin-like factors are both causing hypoglycemia and promoting glycogen storage.

Exercise-induced hypoglycemia is associated with a mutation in the MCT1 carrier and can be diagnosed by finding insulin secretion in response to exercise, not fasting.

Localization of the presumed insulinoma was ultimately achieved using endoscopic ultrasonography with Optison imaging and computed tomography arteriography. Endoscopic ultrasonography–guided fine needle aspiration identified neoplastic epithelioid cells consistent with a well-differentiated, low-grade (grade 1) neuroendocrine tumor. Surgical resection was performed with a minimally invasive approach. Intraoperative localization was achieved by identification of the reaction to the prior needle aspiration and by intraoperative ultrasound.

Given the patient’s postbypass hormonal milieu and risk for islet hyperplasia, robot-assisted distal pancreatectomy and splenectomy were performed instead of a pancreas-sparing procedure such as central pancreatectomy or enucleation. Pathologic examination showed a 2.1-cm, well-differentiated neuroendocrine tumor, diffusely immunoreactive for insulin, as well as a second well-circumscribed incidental microadenoma (0.28 cm), which was negative for insulin but positive for synaptophysin. The islets in the background nonneoplastic pancreas showed increased islet density in some areas (mean 197 μm) and a few islets >400 μm in size, possibly representing islet hyperplasia; there were no overt abnormalities in islet cell nuclear size or morphology.

Hypoglycemia resolved postoperatively and has not recurred in follow-up of >2 years. For additional details of a series of postbariatric patients with insulinoma and suggested evaluation, please see Mulla et al. (20).

**CONCLUSIONS**

In summary, postbariatric hypoglycemia results from accelerated delivery of undigested nutrients into the proximal intestine, triggering rapid increases in plasma glucose. In the setting of increased prandial incretin hormone secretion (predominantly GLP1), high glucose levels trigger excessive insulin secretion, rapid reductions in glucose levels, and frank hypoglycemia. Hypoglycemia typically occurs 1 to 3 hours after meals and 1 to 3 years after prior surgery. Although some patients can experience hypoglycemia with activity or nocturnal (2:00 to 4:00 AM) hypoglycemia, morning fasting hypoglycemia is not typical. Not all hypoglycemia postbariatric surgery is symptomatic, potentially due to impaired counterregulatory responses accompanying frequent hypoglycemia or interindividual differences (27).

There are many challenges in the diagnostic workup of postbariatric hypoglycemia. As with any hypoglycemic symptom evaluation, the workup should first confirm (with a venous sample) that symptoms are accompanied by true hypoglycemia, and that symptoms resolve with correction of hypoglycemia. If hypoglycemia is confirmed, further workup should be individualized to define patterns/timing/frequency of hypoglycemia and associated insulin secretion patterns. For those individuals with atypical features or fasting hypoglycemia, prolonged fasting to rule out autonomous insulin secretion is required. If autonomous secretion is defined, imaging to localize the suspected insulinoma is required.

Once postbariatric hypoglycemia is defined, therapeutic approaches include medical nutrition therapy to optimize nutrition, vitamin supplementation, and meal plan focused on controlled portions of complex carbohydrates (30 g per meal, 15 g per snack). If this is not adequate, medications can be added sequentially to nutrition therapy, including acarbose, octreotide, and diazoxide. Pancreatic surgery to reduce islet mass is no longer recommended due to (1) recognition that increased islet mass is not the pathophysiologic defect, (2) high morbidity, and (3) high rates of hypoglycemia recurrence (12). Additional therapeutic strategies are in development for this challenging condition.

**REFERENCES**


