Noninsulinoma Pancreatogenous Hypoglycemia Syndrome Following Gastric Bypass Surgery

Kristen A. Scheckel, PA-C

A 28-year-old white woman, KR, presents to primary care with episodic diaphoresis and weakness that occur one to two hours after meals. There is no history of syncope or seizures. The hypoglycemic symptoms abate with intake of oral glucose and do not occur when the patient fasts.

KR underwent Roux-en-Y gastric bypass surgery 12 months ago. At the time, her body weight was 250 lbs and her height, 62 in (BMI, 46). She has lost 60 lbs since surgery (current BMI, 35). KR has no comorbid medical conditions. She denies use of insulin injection or oral hypoglycemic medication, as well as alcohol consumption. There is no history of diarrhea or abdominal pain. Her only medication is a daily multivitamin.

Physical exam reveals a blood pressure of 126/80 mm Hg; pulse, 82 beats/min; respiratory rate, 16 breaths/min; and O_2 saturation, 98%. Heart rate is regular with no murmur. Lungs are clear to auscultation. Abdominal and neurologic exams are unremarkable; musculoskeletal strength and orthostatic vital signs are normal.

The patient is instructed to test her blood sugar with a glucometer and return to the clinic in two weeks. Fingerstick monitoring reveals that her serum glucose level drops into the 40 to 50 mg/dL range approximately one to two hours after meals containing > 45 g of carbohydrate. Her fasting serum glucose readings are in the 80 to 95 mg/dL range.

The patient is presumptively diagnosed with dumping syndrome and receives nutritional counseling; she is instructed to reduce intake of simple carbohydrates and increase the protein content of meals. Despite these dietary modifications, the episodes of hypoglycemia persist.

The patient is then referred to endocrinology. Fasting labwork reveals a serum glucose level of 85 mg/dL; normal adrenocorticotropic hormone (ACTH) and cortisol levels; C-peptide level, 2.46 ng/mL (reference range, 0.80–4.00 ng/mL); and insulin level, 6.4 IU/mL (reference range 2.6–24.9 IU/mL). A 75-g two-hour oral glucose tolerance test (OGTT) reveals peak serum glucose of 180 mg/dL at 30 minutes followed by a nadir serum glucose of 48 mg/dL at 110 minutes, accompanied by hypoglycemic symptoms. The insulin and C-peptide levels are elevated during the entire two-hour test. The serum cortisol level is 22 g/dL when the glucose level is 48 mg/dL. CT of the abdomen, previously ordered by the patient's primary care provider, was unremarkable.

Since there is no laboratory evidence of fasting hypoglycemia and no pancreatic abnormalities are seen on imaging studies, the possibility of insulinoma is excluded from the differential diagnosis. Adrenal insufficiency is excluded based on the normal ACTH and cortisol levels. The possibility of noninsulinoma pancreatogenous hypoglycemia syndrome is considered.

The patient is prescribed verapamil ER 100 mg/d and notes significant reduction in the frequency of hypoglycemic episodes and symptoms. She is scheduled for follow-up in four weeks to assess for any changes in the frequency or severity of her hypoglycemic episodes.

BACKGROUND

Postprandial hypoglycemia is a rare but potentially serious complication of bariatric surgery procedures that divert nutrients into the small bowel.[1,2] The Bariatric Outcomes Longitudinal Database revealed a 0.1% incidence of hypoglycemia in patients who underwent Roux-en-Y gastric bypass surgery.[3]

The most common cause of hypoglycemia following gastric bypass surgery is dumping syndrome, which involves rapid emptying of gastric contents with reactive hypoglycemia due to increased postprandial insulin release. In dumping syndrome, hypoglycemic symptoms—flushing, diaphoresis, weakness, and dizziness—typically occur within two

Kristen A. Scheckel practices at Endocrinology Associates in Denver.

to three hours after meals; patients do not experience the more severe symptoms of neuroglycopenia (eg, cognitive impairment, seizures, and loss of consciousness).[4] The symptoms of dumping syndrome typically improve with reduced intake of simple carbohydrates and increased protein consumption.[1]

Other causes of postprandial hypoglycemia include insulinoma and noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS). Although both diagnoses are rare, they should be considered if no improvement in hypoglycemic symptoms occurs after dietary modification.[1]

Insulinoma is the most common cause of persistent hyperinsulinemic hypoglycemia. It is defined by Whipple's triad: symptomatic hypoglycemia during fasting, a serum glucose level > 50 mg/dL at the time of symptom onset, and relief of symptoms after administration of glucose.[5]

NIPHS is less common than insulinoma. It is characterized by postprandial hypoglycemia due to increased insulin secretion resulting from pancreatic -cell hyperplasia. Hypoglycemia does not typically occur during a 72-hour fast. In addition, pancreatic imaging studies yield normal results in cases of NIPHS. The selective arterial calcium stimulation test is positive in NIPHS.[5] NIPHS is definitively diagnosed by histopathologic examination of the pancreas, which reveals nesidioblastosis.[6]

Nesidioblastosis involves pathologic -cell overgrowth in the pancreas that results in excess insulin secretion.[4] Nesidioblastosis is characterized by pancreatic -cell hypertrophy, islet hyperplasia, and increased -cell mass.[2]

Nesidioblastosis is the leading cause of hyperinsulinemia in newborns and infants (annual incidence, 1 in 50,000 births) but is quite rare in adults, occurring in 0.5% to 7.0% of all those with hyperinsulinism.[7,8] Islet cell hypertrophy—characteristic of nesidioblastosis—is seen in both adults and children, whereas genetic mutations are present only in infants.[7]

Although rare in adults, nesidioblastosis is more common in the setting of gastric bypass than in the general population.[7] As of 2011, there have been 40 cases of nesidioblastosis in adults who received gastric bypass.[2] With the rapid increase in the number of these surgeries performed each year, nesidioblastosis should be considered in the differential diagnosis for patients who experience hypoglycemia following the procedure.[2,7]

HORMONAL MECHANISMS

There are multiple theories regarding the etiology of -cell hyperplasia following bariatric surgery. The specific causes for NIPHS after gastric bypass remain under investigation.[2]

The most common theory is that -cell hyperplasia may occur as a result of the surgical procedure itself and not due to obesity. The rapid delivery of food to the distal ileum after gastric bypass surgery may result in elevated production of incretin hormones (eg, GLP-1 and GIP), which increase -cell proliferation, insulin secretion, and insulin sensitivity.[7]

Roux-en-Y gastric bypass also impairs ghrelin secretion. Ghrelin normally acts to suppress insulin secretion and directly opposes the action of insulin. Reduced levels of ghrelin may increase the likelihood of hypoglycemia. Other hormones that may contribute to the metabolic effects of bariatric surgery include peptide YY, oxyntomodulin, and others as yet unidentified.[5,6]

CLINICAL MANIFESTATIONS

NIPHS is characterized by moderate to severe postprandial hypoglycemia. Symptoms include confusion, diaphoresis, tremulousness, anxiety, weakness, blurred vision, and disorientation, as well as more severe neuroglycopenic symptoms, such as cognitive impairment, seizures, and loss of consciousness.[5]

These symptoms do not typically manifest until several months after gastric bypass surgery. (By contrast, symptoms experienced with dumping syndrome typically manifest shortly after the procedure.) Of note, hypoglycemic symptoms of NIPHS do not typically improve after dietary modifications aimed at reducing carbohydrate intake.[2]

DIAGNOSIS

Diagnosis of NIPHS is based on hypoglycemic/neuroglycopenic signs and symptoms without fasting hypoglycemia; endogenous hyperinsulinemia in the presence of hypoglycemia; negative localization studies for insulinoma (using triple-phase spiral CT); and positive selective arterial calcium stimulation test.[4,6]

If fasting hypoglycemia is reported or suspected, the patient should be evaluated for insulinoma using a 72-hour fast. During it, glucose, insulin, C-peptide, and pro-insulin levels should be tested every six hours; results will be normal in patients with NIPHS.[5]

The use of OGTT is controversial, as patients can experience

variable degrees of postprandial hyperinsulinism and symptomatic hypoglycemia during the test. There are no guidelines on whether to perform OGTT in the work-up for NIPHS. In research protocols, it is common to perform a five-hour OGTT; subjects consume a mixed meal containing 50 g of carbohydrates, then their glucose, insulin, and C-peptide levels are tested every 30 to 60 minutes (or sooner if hypoglycemic symptoms occur).

Elevated insulin and C-peptide levels in the setting of hypoglycemia are characteristic findings in patients with NIPHS.[5,9] In the setting of hypoglycemia, a cortisol level > 20 g/dL is considered an appropriate adrenal response and excludes adrenal insufficiency. Triple-phase CT of the abdomen should be performed to rule out insulinoma if strongly suspected and if work-up for NIPHS is negative.[5]

The selective arterial calcium stimulation test is employed to confirm the diagnosis of NIPHS and to guide the extent of pancreatic resection, in an effort to minimize postoperative complications of insulin-dependent diabetes and exocrine insufficiency. In this procedure, the splenic, gastroduodenal, superior mesenteric, and hepatic arteries that supply the pancreas are selectively injected with calcium gluconate. After injection of calcium, the insulin level is measured within each artery.[4,5,7] The selective arterial calcium stimulation test can also be used to localize an insulinoma. NIPHS is distinguished from insulinoma by a diffuse increase in insulin secreted from multiple segments of the arteries that supply the pancreas, following calcium stimulation.[4,5,7]

TREATMENT

There is no consensus on treatment of NIPHS in postbariatric surgery patients, and no "gold standard" exists. Pharmacologic treatment is recommended prior to surgical intervention in patients who present with symptomatic hypoglycemia without loss of consciousness or seizures.[1]

Pharmacologic treatments include calcium channel blockers (eg, verapamil or nifedipine), the -cell inhibitor diazoxide, the secretory inhibitor octreotide, and -glucosidase inhibitors.[1] In one hospital group, patients were initially treated with verapamil ER 100 mg/d.[5] If patients did not respond to this therapy or developed adverse effects, diazoxide was added (starting dose, 25 mg tid, titrated to 75 mg tid).[5] If this combination did not produce results, octreotide (dose ranging from 25 g/d to 50 g tid, subcutaneously) was added. Acarbose can also be added, with the typical starting dose of 50 mg tid.[1]

Distal or subtotal pancreatectomy to debulk the hypertrophic islets is the most common surgical method used in patients with severe hypoglycemia that is refractory to medical management.[2,5] The extent of pancreatic resection is guided by calcium angiography and typically ranges from 80% to 95%.[7] Smaller pancreatic resection is associated with higher risk for persistent postoperative hypoglycemia.[5] Complications associated with pancreatectomy include insulin-dependent diabetes and exocrine insufficiency.[5]

It is not uncommon for patients to experience recurrent symptoms after subtotal pancreatectomy, but the symptoms are typically easier to manage pharmacologically than they were preoperatively. Occasionally, a second surgery with 95% to complete pancreatectomy is employed if recurrent hypoglycemia develops that is refractory to medical management.[5]

Reversal of Roux-en-Y bypass surgery has been described as an attempted treatment method in several case reports of patients with NIPHS. In at least one patient, hyperinsulinemic hypoglycemia persisted after Roux-en-Y gastric bypass reversal.[2] Adjustable gastric band placement was recently reported to reverse hypoglycemic symptoms and maintain weight loss, due to restricted gastric emptying.[2] Conversion of Roux-en-Y gastric banding to gastric sleeve may also be employed to restore normal gastrointestinal continuity and resolve hypoglycemia, though limited data is available regarding the efficacy of this procedure.[2]

Close monitoring is necessary in patients treated with pharmacologic therapy to ensure that symptoms are well controlled and that surgery is not necessary.[1]

SUMMARY AND CONCLUSION

Symptomatic hypoglycemia is a potential complication associated with gastric bypass surgery and is most commonly caused by dumping syndrome. It is important to consider other causes of postprandial hypoglycemia, such as insulinoma and NIPHS, in patients who continue to experience hypoglycemia despite making dietary modifications.[1,4]

NIPHS is a rare and poorly understood complication of gastric bypass surgery involving pathologic -cell overgrowth, leading to hyperinsulinemia and potentially severe hypoglycemia.[6] Some patients may present with complete

relief of symptoms with pharmacologic treatment, while others will need surgical treatment with subtotal pancreatectomy.[1]

The findings of increased levels of GLP-1 hormone in patients who have received gastric bypass surgery and the fact that only a very small subset of gastric bypass patients develop NIPHS with histologic features of nesidioblastosis are subjects for further research. Further understanding of the hormonal factors involved in the pathogenesis of NIPHS and adult-onset nesidioblastosis following gastric bypass surgery could lead to novel drug development to treat diabetes.[6] **CR**

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