Carol Rees Parrish, M.S., R.D., Series Editor

Hyperinsulinemic Hypoglycemia After Gastric Bypass Surgery

Jennifer L. Kirby

Kelly O'Donnell

Hypoglycemia after Roux-en-Y gastric bypass is a rare, yet challenging condition. Patients typically present with post-prandial hypoglycemia 1-5 years after their surgery, often after weight stabilization. Most concerning are the subset of patients who present with symptoms of neuroglycopenia. Hypoglycemia in these patients is felt to be due to an altered GLP-1 response in the post-prandial period. Treatment options include dietary interventions such as limitation of carbohydrate intake, pharmacotherapy aimed at reducing post-prandial glucose excursion and in more recalcitrant cases, surgical reversion of the bypass. However, the optimal treatment of these patients has not been well studied and the underlying etiology requires further research.

REPRESENTATIVE CASE

A 42 year old female presents with one year of flushing, shaking and diaphoresis. These episodes have been increasing in frequency, occur approximately 1.5-2 hours after meals and improve with food. She has a history of obesity and underwent Roux-en-Y gastric bypass (RGBP) five years earlier. Twenty months after her surgery, she had lost 120 pounds and her weight stabilized. Self-monitoring with capillary blood glucose now reveals values measuring <60 mg/dL, with the lowest measuring 33 mg/dL, all associated with symptoms. Symptoms resolve with carbohydrate intake. Her episodes have continued to increase in frequency and of late, include a syncopal episode.

Jennifer L. Kirby, MD-PhD[1] Kelly O'Donnell, MS, RD, CNSC[2] [1]Division of Endocrinology and Metabolism, Department of Medicine, [2]Surgery Nutrition Support, University of Virginia Health System, Charlottesville, VA

INTRODUCTION

Hyperinsulinemic hypoglycemia after RGBP was first described in 2005 by two independent groups.[1,2] In the 10 years since, numerous articles have been written about this entity and although much has been learned, our understanding of the etiology and optimum treatment has not been fully elucidated. Initial reports suggested a role for increased β-cell mass or nesidioblastosis.[1,3] However, these findings were not universally supported.[4] Subsequent studies have shown that in RGBP patients, the rapid passage of nutrients directly into the intestine results in a rapid rise of serum glucose with higher peak values and lower nadirs compared to controls.[5] Additionally, RGBP patients have increased post-meal insulin and GLP- 1 responses. Studies involving patients with hypoglycemia suggest that this response is exaggerated and provide evidence for a prominent role of GLP-1.[6] Some authors have proposed that hyperinsulinemic hypoglycemia after RGBP is due to dumping syndrome, which occurs

Table 1. Symptoms of Hypoglycemia

Autonomic	Neuroglycopenic
♦ Diaphoresis	♦ Confusion or altered mentation
♦ Paresthesias	♦ Blurred/double vision
♦ Tremor	♦ Fatigue or weakness
♦ Hunger	♦ Mood disturbance/emotional lability
♦ Palpitations	♦ Presyncopal symptoms/syncope
♦ Anxiety	♦ Coma

due to rapid passage of nutrients from the stomach remnant into the proximal small intestine.[7] Regardless of mechanism, a small subset of these patients develop severe neuroglycopenic symptoms (see Table 1) that can result in seizure, syncope and trauma such as a motor vehicle collision.[2,3] Often these patients are refractory to conservative therapies with dietary changes and pharmacotherapy. Many have undergone more invasive therapies, such as gastrostomy tube placement, partial/full pancreatectomy or reversal of the bypass. The goal of this paper is to provide a practical approach to the evaluation and management of the patient who presents with hypoglycemia after RGBP.

DIAGNOSIS

Most patients with hyperinsulinemic hypoglycemia after RGBP present within 1-5 years after surgery, but it has been observed in patients within months post-operatively and as long as 20+ years later. The typical patient develops hypoglycemia 1-3 hours after ingestion of a carbohydrate-containing meal and hypoglycemia is absent in the fasting state. Per Endocrine Society guidelines,[8] evaluation should proceed only after Whipple's triad has been satisfied (development of symptoms typical of hypoglycemia, low serum glucose at the time of symptoms and relief of symptoms with the administration of glucose).

The symptoms of hypoglycemia can be divided into autonomic and neuroglycopenic symptoms (see Table 1). A detailed history of the symptoms of hypoglycemia should be obtained to identify patients who have neuroglycopenic symptoms as these are the most concerning given the potential risk for harm. A reasonable approach to establish the diagnosis of hyperinsulinemic hypoglycemia would be to obtain serum glucose, insulin, and C-peptide levels in addition to a sulfonylurea screen at the time of hypoglycemia. The utility of other studies in the assessment of the patient with post-RGBP hypoglycemia is not clear. Oral glucose tolerance tests are not recommended to diagnose hypoglycemia in any setting.[8] Mixed meal testing has been used in research studies, but not all patients with a history of hypoglycemia after RGBP will develop hypoglycemia in this setting.[6,9-11] More recently, continuous glucose monitoring (CGM) has shown promise not only for diagnosis, but also for monitoring response to treatment. Notably, results should be viewed with caution as the accuracy of CGM in the hypoglycemic range is poor.[12,13] The clinical history, time course with regard to onset after surgery, and symptoms should steer the clinician towards a diagnosis of post-gastric bypass hypoglycemia. It is unclear what role more detailed studies, such as 72-hour fast, radiologic imaging or selective arterial calcium stimulation play in evaluation. However, atypical symptoms in these patients (such as fasting or overnight hypoglycemia) should be fully explained with a thorough evaluation.[8] Rarely, hypoglycemia after RGBP has been due to insulinoma.[1] See Table 2 for suggested guidelines for the initial evaluation.

INTERVENTION

Dietary Modification

Dietary intervention is recommended as the first treatment option for patients diagnosed with hypoglycemia after RGBP. Several different strategies have have been published, but all target reducing carbohydrate intake to avoid an insulin surge (summarized in Table 3). Kellogg et al.[5] treated 12 patients with symptoms suggestive of hyperinsulinemic hypoglycemia with a

Table 2. Suggested Guidelines for Initial Evaluation

Patient Identification	Lab Evaluation	Provocative Testing	Other Diagnostic Options
◆ Document Whipple's triad ◆ Assess for neuroglycopenic symptoms ◆ Assess for atypical symptoms (e.g., fasting hypoglycemia)	◆ Obtained during hypoglycemic event: ▪ Serum glucose ▪ Insulin ▪ c-peptide ▪ sulfonylurea screen	◆ Mixed meal tolerance test can be used to confirm diagnosis ◆ Avoid oral glucose tolerance test	◆ Continuous glucose monitoring ◆ 72-hour fast for atypical symptoms

high carbohydrate (79%) meal on day 1 of the study followed by a low (2%) carbohydrate meal on day 2. The meals contained the same amount of calories. After the high carbohydrate meal, serum insulin levels peaked at 30-90 minutes, while the mean glucose nadir (44 mg/dL) occurred at 90-120 minutes. After the low carbohydrate meal, there was only a modest rise in plasma insulin with very little change in glucose levels. After one month of a low carbohydrate diet, 25% of patients reported complete resolution of symptoms while another 25% had improvement in major symptoms, 33% had improvement in minor symptoms and 17% experienced no improvement at all. Botros et al.[14] found that when patients with hyperinsulinemic hypoglycemia consumed a meal containing 30 grams of carbohydrate, none of them experienced hypoglycemia. Based on these results, the authors suggested consuming three meals per day containing 30 grams carbohydrate plus three snacks per day, each containing 15-30 grams carbohydrate while avoiding simple sugars. Because this study occurred in a supervised clinical setting, results and compliance may be altered in real world practice. Also, only 30-gram carbohydrate meals were tested and it may be possible that some patients can tolerate a more liberal carbohydrate allowance. Five of six gastric bypass patients had improvement in symptoms of hyperinsulinemic hypoglycemia with diet modification consisting of three small meals plus 2-3 small snacks with 60 grams of protein daily.[16] High carbohydrate, high fat foods were eliminated as well as sugar-containing fluids.

Pharmacotherapy

When dietary modification fails, pharmacotherapy is often employed for treatment. Several agents including acarbose, calcium-channel blockers, diazoxide, octreotide and GLP-1 receptor agonists have been effective in case reports and case series either alone or in combination (see Table 3). To date, these medications have not been rigorously studied for treatment of hyperinsulinemic hypoglycemia after RGBP and are not FDA-approved for this reason. However, patients may clearly benefit from a trial of therapy, particularly when having severe and debilitating symptoms associated with neuroglycopenia. A reasonable approach would be to try each agent and assess effectiveness, leaving in place those agents that prove beneficial and discontinuing those with either intolerable side effects or lack of efficacy. Combinations of agents that target different mechanisms have also shown benefit (e.g., acarbose with calcium-channel blocker).[19]

Partial or Full Pancreatectomy

Initial reports of nesidioblastosis as a cause of hyperinsulinemic hypoglycemia after RGBP led to many patients being treated with partial or full pancreatectomy. Recently, pancreatectomy has fallen out of favor, likely due to studies providing an alternative mechanism to nesidioblastosis as the underlying cause as well as the significant associated morbidity. A recent review of the literature noted that 34 out of 51 patients (67%) had resolution of symptoms after pancreatic resection.[27] However, follow-up in these studies was

short; longer-term follow-up has shown that some patients have a return of symptoms farther out from surgery.[28] In addition, the risk of developing diabetes and pancreatic exocrine dysfunction increased with more aggressive resection.[29]

Gastrostomy Tube Placement

In 2010, McLaughlin et al. incidentally noted improvement in neuroglycopenic hypoglycemic symptoms after placement of a gastrostomy tube (G tube) into the remnant stomach of a patient with a small bowel obstruction.[7] To formally assess the reason for the improvement, the patient was readmitted to the hospital and given a can of liquid formula by mouth followed by overnight fasting and administration of the same liquid formula through the G tube. Feeding by mouth versus G tube caused symptomatic hypoglycemia at 90-120 minutes (60 mg/dL vs 80 mg/dL) and insulin concentrations that were eight times higher, respectively. The authors concluded that the results were inconsistent with β-cell hyperplasia or increased β-cell activity as a cause of the hypoglycemia. Rather, hyperinsulinemia was a result of nutrients delivered through the bypassed GI tract, but not through the remnant stomach, perhaps due to altered incretin responses. In another study, a G tube was placed in the gastric remnant of 5 patients who were refractory to medical and diet management of their hyperinsulinemic hypoglycemia.[15] The patients received 3 bolus feedings per day of a standard formula providing a total of 450 calories and experienced no symptoms of hypoglycemia. All 5 patients had remission of hypoglycemia after placement of the G tube. However, successful resolution of hypoglycemia with G tube placement is not universal.[17]

Gastric Bypass Reversal

Several groups have now shown successful remission of hypoglycemia with reversal of gastric bypass with or without modified sleeve gastrectomy. In the review by Mala, 13 out of 17 patients (76%) had resolution of symptoms and weight regain was a common outcome.[27] In patients with reversal without modified sleeve gastrectomy, weight regain can be an issue.

TREATMENT APPROACH

When approaching a patient with symptoms suggestive of hypoglycemia after gastric bypass, it is important to document evidence of Whipple's triad. In particular, the provider should assess for symptoms of neuroglycopenia, which place the patient at risk for severe adverse events, such as seizure and death. In patients with documented hypoglycemia, it is reasonable to obtain serum glucose, insulin, and c-peptide levels with a sulfonylurea screen. Provocative testing, such as a mixed meal tolerance test, can be used as a method to confirm the diagnosis. In cases where the history is inconsistent with typical hyperinsulinemic hypoglycemia after RGBP (e.g., fasting or overnight hypoglycemia), further diagnostic

Table 3. Nutritional Approaches for Hypoglycemia After Roux-en-Y Gastric Bypass

Author	Dietary Interventions
Kellogg et al.[5]	Low carbohydrate meals: 2% carbohydrate, 74% fat, 24% protein
Botros et al.[14]	3 meals containing 30 grams carbohydrate plus 3 snacks each with 15-30 grams carbohydrate combined with 1.5 gram protein/kg and 650-800 calories from fat per day
Campos et al.[15]	Minimize simple carbohydrates and increase fiber and protein
Mordes and Alonso[16]	3 meals plus 2-3 small snacks, 60 grams protein, eliminate high fat and high carbohydrate foods and sugar-filled beverages
Rao et al.[17]	Small meals every 4 hours, high in protein and complex carbohydrates
	Nutrition Support Interventions
O'Donnell[18]	Gastrostomy tube placement into the remnant stomach (bypassed segment) should be considered after failed dietary interventions. Once the patient has established tolerance to continuous tube feedings, nocturnal or bolus feeds may be attempted.

Table 4. Pharmacotherapy for Hypoglycemia After Roux-en-Y Gastric Bypass

Drug	Dose	Route	References
Acarbose	50-100 mg TID with meals*	Oral	Moreira et al.[19] Hanaire et al.[20] Valderas et al.[11]
Diazoxide	50 mg BID	Oral	Spanakis and Gragnoli [21] Gonzalez-Gonzalez et al.[22]
Octreotide	100 mcg BID	SQ	Rabiee et al.[23] Myint et al.[24]
Calcium-channel blockers (e.g. verapamil, nifedipine)	80 mg BID	Oral	Moreira et al.[18] Guseva et al.[25]
Liraglutide (GLP-1 receptor agonist)	1.2-1.8 mg daily	SQ	Abrahamson et al.[26]

*up to 6 times per day
BID = two times per day; TID = three times per day; SQ = subcutaneous

testing and imaging are warranted as indicated.[8]

Initial therapy should be directed at dietary modification to reduce the content of total carbohydrate in the patient's diet, ideally targeting for 4-6 small meals per day containing 30 grams or less per meal. Elimination of simple sugars is critical. A journal that includes dietary information, blood glucose values and symptoms can be helpful to elucidate particular triggers to guide dietary interventions. If dietary changes are unsuccessful at reducing/eliminating hypoglycemic episodes, pharmacologic agents (listed in Table 4) can be used either alone or in combination. Given that there are no trials comparing these medications, a trial of each agent to assess for benefit may be attempted prior to proceeding with more invasive therapies. Certainly cost and tolerability will play a role in the ability of patients to try these agents. Although it is unclear what utility continuous glucose monitoring (CGM) has in the diagnosis of hyperinsulinemic hypoglycemia, CGM can be useful for patients who have neuroglycopenic symptoms for monitoring to prevent severe episodes and to assess responses to therapy. Again, cost may be a barrier as this is not a traditional use for CGM and may not be covered by many insurance plans.

Surgical procedures such as placement of a gastrostomy tube into the gastric remnant and reversal of the gastric bypass with or without gastrectomy should be used only if more conservative therapies have been tried and failed. In addition, involvement of providers with experience treating these patients should be sought, including dietitians, endocrinologists and bariatric surgeons. ■

CONCLUSION

Hyperinsulinemic hypoglycemia after gastric bypass, particularly with neuroglycopenia, is a rare and difficult entity to treat. Although our understanding of the pathophysiology underlying this entity has advanced in the 10 years since it was initially described, there are no evidenced-based guidelines for the diagnosis and treatment at this time. Further research regarding the underlying mechanism driving hyperinsulinemia in these patients is needed and will hopefully provide better therapeutic options. Early identification of patients with neuroglycopenia is warranted. These patients may benefit from systematic intervention from dietary changes on up to surgical revision of the bypass in some. ■

References

1. Service GJ, Thompson GB, Service FJ, et al: Hyperinsulinemic Hypoglycemia with Nesidioblastosis after Gastric-Bypass Surgery. N Engl J Med 2005;353:249-254.
2. 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.
3. 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.
4. Meier JJ, Butler AE, Galasso R, et al: Hyperinsulinemic Hypoglycemia After Gastric Bypass Surgery Is Not Accompanied by Islet Hyperplasia or Increased β-cell Turnover. Diabetes Care 2006;29:1554-1559.
5. Kellogg TA, Bantle JP, Leslie DB, et al: Postgastric bypass hyperinsulinemic hypoglycemia syndrome: characterization and response to a modified diet. Surg Obes Relat Dis 2008;4:492-499.
6. Salehi M, Gastaldelli A, D'Alessio DA: Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. Gastroenterology 2014;146:669-680.
7. McLaughlin T, Peck M, Holst J, et al: Reversible Hyperinsulinemic Hypoglycemia after Gastric Bypass: A Consequence of Altered Nutrient Delivery. J Clin Endocrinol Metab 2010;92:1851-1855.
8. Cryer PE, Axelrod L, Grossman AB, et al: Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009;94:709-728.
9. Salehi M, Prigeon RL, D'Alessio DA: Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. Diabetes 2011;60:2308-2314.
10. Salehi M, Gastaldelli A, D'Alessio DA: Altered islet function and insulin clearance cause hyperinsulinemia in gastric bypass patients with symptoms of postprandial hypoglycemia. J Clin Endocrinol Metab 2014;99:2008-2017.
11. Valderas JP, Ahuad J, Rubio L, et al: Acarbose Improves Hypoglycemia Following Gastric Bypass Surgery Without Increasing Glucagon-Like Peptide 1 Levels. Obes Surg 2012;22:582-586.
12. Halperin F, Patti ME, Skow M, et al: Continuous glucose monitoring for evaluation of glycemic excursions after gastric bypass. J Obes 2011;Article ID 869536 doi:10.1155:2011/869536
13. Kefurt R, Langer FB, Schindler K, et al: Hypoglycemia after Roux-en-Y gastric bypass: detection rates of continuous glucose monitoring (CGM) versus mixed meal test. Surg Obes Relat Dis 2015;11:564-572.
14. Botros N, Rijnaarts I, Brandts H, et al: Effect of carbohydrate restriction in patients with hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass. Obes Surg 2014;24:1850-1855.
15. Campos GM, Ziemelis BS, Paparodis MD, et al: Laparoscopic reversal of Roux-en-Y gastric bypass: Technique and utility for treatment of endocrine complications. Surg Obes Relat Dis 2014;10:36-43.
16. Mordes JP, Alonso LC: Evaluation, Medical Therapy and Course of Adult Persistent Hyperinsulinemic Hypoglycemia after Roux-en-Y Gastric Bypass Surgery: A Case Series. Endocr Pract 2015;21:237-246.
17. Rao BB, Click B, Eid G, et al: Management of Refractory Noninsulinoma Pancreatogenous Hypoglycemia Syndrome with Gastric Bypass Reversal: A Case Report and Review of the Literature. Case Rep Endocrinol 2015;2015:384526.
18. O'Donnell K: Managing Hyperinsulinemic Hypoglycemia with Enteral Feeding in a Gastric Bypass Patient. Support Line 2015;37:3-5.
19. Moreira RO, Moreira RBM, Machado NAM, et al: Post-prandial Hypoglycemia after Bariatric Surgery: Pharmacologic Treatment with Verapamil And Acarbose. Obes Surg 2008;18:1618-1621.
20. Hanaire H, Dubet A, Chauveau M-E, 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.
21. Spanakis E, Gragnoli C: Successful Medical Management of Status Post-Roux-en-Y-Gastric-Bypass Hyperinsulinemic Hypoglycemia. Obes Surg 2009;19:1333-1334.
22. Gonzalez-Gonzalez A, Delgado M, Fraga-Fuentes MD: Use of diazoxide in management of severe postprandial hypoglycemia in patient after Roux-en-Y gastric bypass. Surg Obes Relat Dis 2013;9:e18-e19.
23. Rabiee A, Magruder BA, Salas-Carrillo R, et al: Hyperinsulinemic Hypoglycemia After Roux-en-Y Gastric Bypass: Unraveling the Role of Gut Hormonal and Pancreatic Endocrine Dysfunction. J Surg Res 2011;167:199-205.
24. Myint KS, Greenfield JR, Farooqi IS, et al: Prolonged successful therapy for hyperinsulinemic hypoglycaemia after gastric bypass: the pathophysiological role of GLP1 and its response to a somatostatin analogue. Eur J Endocrinol 2012;166:951-955.
25. Guseva N, Phillips D, Mordes JP: Successful treatment of persistent hyperinsulinemic hypoglycemia with nifedipine in an adult patient. Endocr Pract 2010;16:107-111.
26. Abrahamson N, Engström BE, Sundbom M, et al: GLP1 analogs as treatment of postprandial hypoglycemia following gastric bypass surgery: a potential new indication? Eu J Endocrinol 2013;169:885-889.
27. Mala T: Postprandial hyperinsulinemic hypoglycemia after gastric bypass surgical treatment. Surg Obes Relat Dis 2014;10:1220-1225.
28. Vanderveen KA, Grant CS, Thompson GB, et al: Outcomes and quality of life after partial pancreatectomy for noninsulinoma pancreatogenous hypoglycemia from diffuse islet cell disease. Surgery 2010;148:1237-1245.
29. Ritz P, Hanaire H: Post-bypass hypoglycaemia: A review of current findings. Diabetes Metab 2011;37:274-281.

PRACTICAL GASTROENTEROLOGY