

In Brief

Severe hypoglycemia characterized by neuroglycopenic symptoms is a recently described and relatively uncommon complication of gastric bypass surgery. It occurs several months to years after surgery and may be distinct from the more commonly encountered dumping syndrome that occurs early in the postoperative course and usually improves with time. Nesidioblastosis has been proposed as a possible underlying mechanism for late postoperative hypoglycemia. This syndrome is distinct from noninsulinoma pancreatogenous hypoglycemia and likely has a multifactorial etiology. It responds variably to nutrition and pharmacological interventions. Partial pancreatectomy and reversal of the bypass have sometimes been used to ameliorate symptoms.

Hypoglycemia After Gastric Bypass Surgery

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Obesity rates are increasing annually, making obesity and its related conditions a major public health problem. Lifestyle measures have had limited success in the management of morbid obesity, and bariatric surgery remains the only intervention that results in significant, sustained weight loss and improvement or resolution of comorbidities such as type 2 diabetes.^{1,2} Furthermore, bariatric procedures have been shown to decrease overall mortality in the obese population in longitudinal, observational studies.^{3,4} The rising popularity of bariatric procedures is therefore not surprising.

Roux-en-Y gastric bypass (RYGB) surgery is the most popular procedure used to treat medically complicated obesity,⁵ and the last decade has witnessed a tremendous increase in the number of these procedures performed.⁶ This has increased the frequency of complications associated with this procedure.

Hyperinsulinemic hypoglycemia has been recognized relatively recently as a complication of gastric bypass surgery.^{7,8} Several years after this phenomenon was first described, there remain significant gaps in our experience and understanding of the pathophysiology of this uncommon disorder.

Etiology of Hypoglycemia in Patients With Gastric Bypass Surgery

Nonspecific postprandial symptoms attributable to hypoglycemia are rather common in patients with a previous gastric bypass surgery. Indeed, many

hypoglycemia symptoms are common and not specific to hypoglycemia (e.g., tremor, tachycardia, and diaphoresis). However, the diagnosis of a true hypoglycemic disorder requires a low plasma glucose (< 50–55 mg/dl) in the presence of symptoms compatible with neuroglycopenia that are ameliorated by correction of the low glucose (Whipple's triad).

Postprandial hypoglycemia can occur in patients with gastric bypass surgery in the context of the dumping syndrome, although most of the associated symptoms are likely vascular in origin.⁹ Dumping can occur postoperatively in up to half of gastric bypass patients with ingestion of simple sugars.¹⁰ Early dumping, a result of rapid emptying of food into the jejunum because of the surgically altered anatomy, is characterized by vasomotor symptoms (flushing, tachycardia), abdominal pain, and diarrhea.¹¹ Late dumping, a form of "reactive hypoglycemia," occurs 1–3 hours after meal ingestion and is a consequence of the brisk insulin response to hyperglycemia resulting from rapid absorption of simple sugars from the proximal small intestine. These patients present with dizziness, fatigue, weakness, and diaphoresis, but these symptoms often resolve spontaneously and neuroglycopenic symptoms may not be prominent.

Most patients with dumping respond to nutrition modification, comprising frequent, small, low-carbohydrate meals. Pharmacological therapy is sometimes necessary.

Acarbose and somatostatin have been empirically associated with improvement of symptoms in some patients, but the primary modality of treatment of these patients is still nutrition intervention. Pharmacotherapy is to be used as an add-on intervention only. Use of acarbose in patients who are not compliant with nutrition recommendations can be expected to have significant gastrointestinal side effects. There are also case reports of amelioration of dumping after institution of continuous enteral feeding or takedown of RYGB,⁹ although these approaches are reserved for cases that are truly refractory to conservative management.

Although dumping syndrome has long been recognized as a common complication of gastric bypass, more severe postprandial hypoglycemia was first described more recently by Service et al. in 2005.⁸ In contrast to dumping, which is noted soon after the surgery and improves with time, hyperinsulinemic hypoglycemia presents several months to years (usually > 1 year) after gastric bypass surgery. The hallmark of this rare syndrome is severe postprandial neuroglycopenia, which is characteristically absent in dumping. Pancreatic nesidioblastosis (islet cell enlargement, β -cells budding from ductal epithelium, and islets in apposition to ducts) has been proposed as the underlying mechanism for this disorder,^{7,8,12,13} but this remains controversial, as discussed in more detail later in this article.

Post-RYGB hypoglycemia has been more commonly seen in females and is distinct from noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS), the other form of endogenous hyperinsulinemic hypoglycemia. NIPHS also results in postprandial hypoglycemia and is characterized by nesidioblastosis, but it is seen in patients who have not had a gastric bypass procedure.¹⁴

Rarely, an insulinoma (insulin-producing islet cell tumor) may be responsible for hypoglycemia in a patient who has had gastric bypass surgery.^{15,16} Although this typically causes fasting hypoglycemia, postprandial hypoglycemia may be reported in ~ 10% of patients with insulinoma.¹⁷

The distinction between dumping and organic hyperinsulinism is often difficult to make because the severity of symptoms as reported by the patient

may be the sole differentiator from a historical point of view. A delayed onset of symptoms after the surgery, severe hypoglycemia refractory to lifestyle interventions, and the absence of vasomotor symptoms of dumping would suggest the need for appropriate evaluation as detailed later in this article.

Diagnosis of Hyperinsulinemic Hypoglycemia

In addition to fulfillment of the Whipple's triad, theoretically, confirmation of hyperinsulinemic hypoglycemia requires a concomitantly elevated insulin (> 3 μ U/ml) and C-peptide (> 0.6 ng/ml) and a negative oral hypoglycemic agent screen.¹⁸ However, applying fasting criteria for the diagnosis of hyperinsulinemic hypoglycemia¹⁹ in the postprandial period is problematic given the biological half-life of C-peptide of ~ 30 minutes. C-peptide and insulin may still be detectable after meal ingestion even if insulin secretion is appropriately suppressed at the time of postprandial hypoglycemia.

Normative values for the postprandial period developed in asymptomatic patients with RYGB are urgently required. However, obtaining a blood sample for analysis at the time of neuroglycopenic symptoms can be logistically challenging. Provocative testing, including an oral glucose tolerance test (OGTT) and mixed-meal studies have therefore been suggested to induce hypoglycemia and the symptoms thereof.

The OGTT, historically used as the diagnostic test for the so-called "reactive hypoglycemia" in patients presenting with postprandial autonomic symptoms reminiscent of a hypoglycemic disorder, has lost favor through the years. At least 10% of normal people have a positive OGTT (nadir plasma glucose < 50 mg/dl).²⁰ Another study reported the absence of electroencephalographic evidence of hypoglycemia in patients with nadir plasma glucose < 50 mg/dl with an OGTT.²¹ In a study of gastric bypass patients with hypoglycemia, the frequency of a positive OGTT was equally distributed among the normal and hypoglycemic subjects.²²

A liquid mixed-meal test is likely fraught with the same pitfalls as the OGTT in gastric bypass patients given the rapid rate of absorption of the liquid formulation. One study reported

asymptomatic hyperinsulinemic hypoglycemia in > 30% of patients who had a gastric bypass without any reported neuroglycopenia.²³ Moreover, such testing is extremely unpleasant for patients with RYGB and should be avoided.

Although continuous glucose monitoring can detect low interstitial fluid glucose at the time of symptoms,^{24,25} confirmatory laboratory testing with documentation of a low venous blood glucose is still required for the diagnosis of hyperinsulinemic hypoglycemia.

Once biochemical testing confirms hyperinsulinemic hypoglycemia, imaging studies, including triple-phase spiral computed tomography and transabdominal ultrasound of the pancreas, should be undertaken to screen for an insulinoma. Postprandial hypoglycemia could be an unusual presentation of an insulinoma, and there are case reports of it being misdiagnosed as dumping syndrome in patients with previous gastric bypass surgery.¹⁷ Endoscopic ultrasonography is not technically feasible in the presence of the altered gut anatomy in these patients.⁸ The selective arterial calcium-stimulation test is the last step in the evaluation of these patients when the imaging studies are negative and symptom severity warrants surgical treatment.

Incidence of Hyperinsulinemic Hypoglycemia in Patients With Gastric Bypass Surgery

Service et al.,⁸ the first to describe hyperinsulinemic hypoglycemia in gastric bypass patients, reported six patients with refractory postprandial neuroglycopenia 6 months to 8 years after bypass surgery. All had endogenous hyperinsulinemic hypoglycemia, and, with the exception of one patient, there was no radiological evidence of an insulinoma. Selective arterial calcium-stimulation testing was positive in all and led to gradient-guided partial pancreatic resection. All the pancreata revealed nesidioblastosis, and multiple insulinomas were described in one specimen. Surgery resulted in amelioration of hypoglycemic symptoms.

Since this initial report, the condition has come to be widely recognized and reported,^{12,13,26,27} but its true incidence is not really known. Nevertheless, it does seem infrequent in proportion to the number of gastric bypass surgeries performed.

Marsk et al.²⁸ recently reported on the incidence of hypoglycemia after gastric bypass in a Swedish nationwide cohort study spanning 21 years. The authors used the Swedish national registry to identify 5,040 patients who underwent gastric bypass surgery between 1986 and 2006. Each of these patients was compared to 10 age- and sex-matched participants from the general population. The authors studied the rates of hospitalization for hypoglycemia and other related diagnoses, including confusion, syncope, epilepsy, and seizures. The risk for hypoglycemia and related diagnoses was > 2- to 7-fold higher in the gastric bypass patients. The absolute risk, however, was low at 0.2%. This might be an underestimation of the incidence of this disorder because outpatient hypoglycemic episodes were excluded from the analysis. Nevertheless, the study does point to a rather low incidence of the problem.

Clearly, long-term prospective studies of patients who have had gastric bypass surgery are required to assess the frequency, spectrum, and course of this intriguing complication.

Mechanisms Causing Hypoglycemia After Gastric Bypass

There is significant controversy and debate about the pathophysiology of hypoglycemia after gastric bypass surgery. Several years after this phenomenon was first reported, it remains incompletely understood. The proposed mechanisms include expansion of β -cell mass, enhanced β -cell function, and causes not related to the β -cell.

Expansion in β -cell mass

Service et al.⁸ were the first to propose this mechanism for postprandial hypoglycemia in gastric bypass patients. All six patients in their series underwent gradient-guided partial pancreatic resection because of the severity of their hypoglycemia symptoms. The resected pancreata showed β -cell hypertrophy and nesidioblastosis.

These authors additionally described that 40% (6 of 15) of the total cases of nesidioblastosis seen at around the same time occurred in gastric bypass patients, while < 0.1% of the general population underwent this surgery.²⁹ They therefore concluded that gastric bypass can somehow result in β -cell expansion and cause serious hypoglycemia.

This hypothesis was supported by the findings of Patti et al.,⁷ who also found islet hyperplasia in the resected pancreata of the patients with hyperinsulinemic hypoglycemia after gastric bypass surgery.

One of the proposed theories behind β -cell expansion is the adaptive islet hypertrophy characteristic of obesity. Reduced caloric intake postoperatively could potentially lead to hypoglycemia resulting from unopposed action of the hyperplastic islets. This theory, however, does not explain the lag time of months to years between the bypass surgery and development of hypoglycemia.¹⁴ Moreover, insulin action is restored to normal shortly after bariatric surgery,³⁰ long before severe neuroglycopenia develops in a small group of patients. Furthermore, Service et al.⁸ showed normal-sized islets in obese control subjects who did not undergo gastric bypass, and nesidioblastosis and hypoglycemia has not been described in nonsurgical weight loss groups. Islet cell hyperplasia, therefore, seems to be a result of the gastric bypass and develops over time after the surgery.

The flaws in the nesidioblastosis-centric view of hypoglycemia after gastric bypass have become apparent through the years. Partial pancreatic resection does not always cure severe hypoglycemia in these patients,⁷ pointing to alternate etiologies. Moreover, Meier et al.³¹ did not find any increase in β -cell mass (as estimated by fractional β -cell area) in the gastric bypass patients initially reported by Service et al., when compared to autopsy specimens from BMI-matched and lean controls. On the other hand, they found a close positive correlation between preoperative BMI and increased β -cell nuclear size, possibly a marker of cellular hyperfunction. Certainly, postmortem changes in pancreatic specimens could diminish the reliability of these observations.

In support of the observations by Service et al., Cummings³² hypothesized that an increase in glucagon-like peptide-1 (GLP-1) concentration may be responsible for the islet cell expansion. Elevated GLP-1 is commonly seen in the postprandial phase of patients with gastric surgery. Moreover, GLP-1 promotes islet cell growth and inhibits apoptosis in diabetic rodents *in vitro*.³³ Despite that, 2-year studies in rats and mice using the GLP-1 receptor agonist exenatide at doses > 100

times those given to humans did not report any pathological changes in the islets.³⁴ Additionally, a 9-year study of the same agent in healthy cynomolgus monkeys employing doses > 400 times those used in humans showed a minimal increase in islet cellularity without any change in size.³⁴ These observations, coupled with the absence of severe hypoglycemia or nesidioblastosis reports with years of GLP-1 therapies in patients with type 2 diabetes, call the hypothesis proposed by Cummings into question.

In summary, aside from the rare occurrence of an insulinoma, there is insufficient evidence to implicate a β -cell anatomical pathology for hyperinsulinemic hypoglycemia in gastric bypass patients. The link between the two, if it exists, is best considered multifactorial and not mediated by a single factor such as GLP-1. Hypoglycemia after gastric bypass therefore has also been viewed as a result of altered β -cell function, as discussed next.

Enhanced β -cell function and dysregulated insulin secretion

High incretin levels have long been reported in other types of gastric surgeries,^{35,36} and it has been hypothesized that elevated incretin levels may contribute to hypoglycemia in patients with gastric bypass surgery without causing β -cell hyperplasia *per se*. Goldfine et al.²³ have shown that GLP-1 levels in the fasting state and after a liquid meal are higher in gastric bypass patients with neuroglycopenia than in bypass patients who are asymptomatic.

As intriguing as these observations are, they do not establish a cause-and-effect relationship between GLP-1 and hypoglycemia after gastric bypass. Elevated GLP-1 levels noted right after the gastric bypass surgery may simply reflect rapid transit of meals to the small intestine and do not explain the lag time of years before development of hyperinsulinemic hypoglycemia.

Possible mechanisms not related to β -cells

Ghrelin suppresses insulin secretion, opposes its action, and stimulates counterregulatory hormones.³⁷ Its secretion is decreased after gastric bypass surgery, which may contribute to hypoglycemia.³⁸

In sum, it is unclear why severe hypoglycemia occurs in a small pro-

portion of patients who have had a gastric bypass. In addition to the above offenders, other potential contributors include sustained weight loss, complex anatomical changes including bypass of the duodenum, and increased levels of circulating bile acids.³⁹ This hypoglycemia is most likely a combination of the above-noted anatomic, hormonal, and metabolic changes. Finally, it also remains to be seen whether this is an extreme physiological response or is a result of an unrecognized genetic predisposition.⁴⁰

Management of Hypoglycemia After Gastric Bypass

Management of hypoglycemia after gastric bypass is complex and requires a multidisciplinary approach involving a varying combination of nutrition changes, medications, and surgery.

Unlike dumping syndrome, hypoglycemia after gastric bypass generally responds suboptimally to carbohydrate restriction alone, but some investigators have reported good results with this strategy with or without the use of pharmacological agents.^{26,27} There have been case reports of variable success with medications, including the α -glucosidase inhibitor acarbose, octreotide, verapamil, and diazoxide. However, it was not clearly established that all of these patients had hyperinsulinemic hypoglycemia as opposed to dumping syndrome.^{41–45} Continuous glucose monitoring can be a useful tool in management and can help ensure timely corrective measures for hypoglycemia prevention.⁴⁶

Data evaluating the efficacy of surgery in managing hypoglycemia after gastric bypass are limited to case reports and case series. Some patients with severe symptoms and a positive selective arterial calcium-stimulated test have responded well to partial pancreatectomy, with resolution or significant improvement in hypoglycemia.⁴⁷ The extent of surgery is dictated by the results of the calcium stimulation test. In extreme cases, reversal of the bypass may be required because feeding into the bypassed stomach has been shown to prevent hypoglycemia.^{48,49}

Conclusion

Severe postprandial hypoglycemia has been recently described in a small proportion of gastric bypass patients. In contrast to dumping syndrome, this condition presents months to years

after surgery and has a more dramatic presentation comprising neuroglycopenic symptoms. Although reminiscent of NIPHS, this hypoglycemia appears to be a distinct condition.

The complex pathophysiology of this rare syndrome remains poorly understood, and it is likely multifactorial in etiology. It responds variably to nutrition changes and pharmacological therapy, and partial pancreatectomy or reversal of the gastric bypass may be required for severe cases.

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