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Hypoglycemia complicating bariatric surgery: incidence and mechanisms

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Abstract

Purpose of review—Discuss the clinical scope and frequency of hypoglycemia following bariatric surgery, and possible mechanisms mediating this potentially life-threatening complication.

Recent findings—Consequent to the rise in severe obesity, bariatric surgery is being performed with ever increasing frequency. Although data continue to accumulate supporting the myriad metabolic and other health benefits of bariatric surgery, there are also concerns regarding the mounting reports of severe hypoglycemia. The problem is particularly significant following gastric bypass, with the first concerns raised in 2005 following a case series reported from the Mayo Clinic. A Swedish nationwide cohort study recently estimated the frequency of this complication suggesting it was less than 1%. Hypotheses regarding the mechanism(s) by which hypoglycemia arise following gastric bypass range from beta cell expansion to altered beta cell function as well as non-beta cell factors.

Summary—Regardless of the incidence, the severity of hypoglycemia for select patients following gastric bypass necessitates that we strive to gain a better understanding of the underlying mechanisms. With such knowledge, those patients at greater risk for this complication might be identified pre-operatively, and decisions regarding their surgical management optimized to reduce this risk.

Keywords

Bariatric surgery; dumping syndrome; gastric bypass; hypoglycemia; hyperinsulinism; incretin; insulin sensitivity; obesity

Introduction

Obesity rates have reached pandemic levels globally [1], and in the United States the prevalence of severe obesity (body mass index (BMI) > 40 kg/m^2) has increased over 50% from 2000 to 2005 [2]. With the relatively poor efficacy of lifestyle change and the availability of only one FDA-approved pharmacotherapeutic weight-loss agent for long-term use, bariatric surgery represents the most effective option for major, durable weight loss [3, 4]. Furthermore, as evidence accumulates supporting the beneficial impacts of bariatric surgery on obesity-associated co-morbidities, particularly type 2 diabetes (as reviewed in this issue by Puruini *et al*), it comes as no surprise that increasing numbers of patients are seeking these procedures. The absolute growth rate for bariatric surgery worldwide has

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continued to increase, and over 220,000 procedures were performed in the United States in 2008 [5].

Despite the favorable effects of bariatric surgery on obesity-associated morbidity and overall mortality [6], there has been mounting concern about severe hypoglycemia associated with Roux-en-Y gastric bypass surgery, which was initially reported among 6 patients in 2005 by Service *et al* [7]. These patients experienced postprandial hyperinsulinemic hypoglycemia with neuroglycopenic symptoms (altered mental status, loss of consciousness, seizures), that developed months to years following surgery, and in all cases required at least partial pancreatectomy. The pathologic findings suggested hyperplasia of pancreatic islets consistent with nesidioblastosis. Only a few months later another series of 3 patients with a very similar clinical presentation and pathology was reported by Patti *et al* [8]. These two reports introduced this new serious adverse effect of gastric bypass surgery, yet at the same time provocatively suggested a novel mechanism by which the procedure could lead to resolution of type 2 diabetes in some patients [9].

Post-bariatric surgery hypoglycemia: a spectrum

Following the initial publications from Service *et al* [7] and Patti *et al* [8], other case reports describing similar patients followed quickly, though symptoms, methods of evaluation, and management were variable, suggesting a spectrum in severity [10-17]. One issue complicating the characterization of post-gastric bypass hypoglycemia is that patients who have undergone bariatric surgery typically experience numerous post-prandial symptoms including the “dumping syndrome”, which may part of a continuum of post-gastric bypass hypoglycemia [18, 19]. Classically, dumping syndrome results from food reaching the small intestine too rapidly; this occurs due to the altered anatomy following gastric bypass as well as other gastrointestinal surgeries. Early symptoms include abdominal pain, bloating, and diarrhea, as well as vasomotor symptoms such as flushing, hypotension, and tachycardia. Hypoglycemia has been ascribed as a late sign of dumping occurring 1-3 hours after meals, and is typically responsive to dietary modification encompassing frequent small, low carbohydrate meals. Medical therapy is needed for some patients: alpha-glycosidase inhibitors (acarbose) to reduce carbohydrate absorption; somatostatin analogs to reduce gastric emptying, inhibit gastrointestinal hormones, and inhibit insulin secretion; diazoxide to inhibit calcium-induced insulin release [19]. More difficult cases rarely require surgical intervention or continuous enteral feeding. In contrast, post-gastric bypass hypoglycemia appears to be more severe. Two years after their initial report, the Mayo experience had expanded to 37 patients with a majority requiring partial pancreatic resection [20].

A simple diagnostic test to distinguish severe post-gastric bypass hypoglycemia would certainly help clinicians dealing with this disorder. Application of Whipple's triad, namely establishing (1) symptoms of hypoglycemia (2) low plasma glucose (< 55mg/dl) at the time of symptoms (3) relief of symptoms with the correction of low glucose, as well as concomitant measurement of serum insulin (>3μU/ml), C-peptide (0.6ng/ml), and a negative sulfonylurea screen, is a requisite starting point though perhaps not so simple [21]. For instance, requiring a patient to come to a lab when symptoms occur is difficult. Thus, some suggested provocative tests, such as the oral glucose tolerance test (OGTT), to induce symptoms and signs. The OGTT had historically been used for non-surgical patients who experienced postprandial autonomic symptoms to diagnose so-called reactive hypoglycemia, which was felt to result from a disparity between glucose appearance in the circulation and insulin secretion. And yet this test was found to be positive (glucose nadir <50 mg/dl) in at least 10% of normal people [22]. Interestingly, asymptomatic hyperinsulinemic hypoglycemia following OGTT was noted in approximately 3-4% of patients who underwent laparoscopic adjustable gastric banding, a procedure which does not alter

gastrointestinal anatomy [23]. Furthermore, in one study of post-gastric bypass patients with and without hypoglycemia (n=9 per group), a glucose nadir <50 mg/dl occurred with the same frequency following an OGTT (33%, or 3/9 patients in each group) [24]. In another study, asymptomatic hyperinsulinemic hypoglycemia following a liquid mixed meal test also occurred in over 30% of post-gastric bypass control subjects without a history of neuroglycopenia [25], hence the same issues relevant to the OGTT have been suggested to apply to this test as well [20]. Continuous glucose monitoring may help document low glucose episodes in free-living conditions [26], but patients would still need to present to a lab for measurement of the other circulating parameters to confirm the diagnosis.

It is likely, based on the patients reported to date, that postprandial hypoglycemia occurs with a range of severity in post-gastric bypass patients. At one end of the spectrum are the relatively mild “dumping syndrome” cases that lack the neuroglycopenic symptoms and that can be managed largely via dietary modification. At the other end of the spectrum are the patients who present with severe, refractory postprandial hyperinsulinemic hypoglycemia associated with neuroglycopenic symptomatology. Establishing the precise incidence of these diagnoses post-gastric bypass would certainly help shed more light on the scope of this problem.

Incidence of post-bariatric surgery hypoglycemia

The rapidity with which post-gastric bypass hypoglycemia cases came to light following the initial 2005 report along with the increasing use of bariatric surgery lead some to fear that this complication may not be rare. Recognition that the frequency of asymptomatic hypoglycemia in this population may be over 30% [24, 25], and that there is a range in severity as suggested by the case literature, underscores the critical need to get a better handle on the true incidence of this complication [10-17].

A recently published paper has taken the approach of analyzing a nationwide cohort to establish the incidence of the most severe post-bariatric surgery hypoglycemia. Marsk *et al* used national patient registries in Sweden to identify a cohort of 5,040 patients that underwent Roux-en-Y gastric bypass surgery, 4,366 patients that underwent vertical banded gastroplasty, and 2,917 patients that underwent gastric banding between 1986 and 2006, and then compared each case to 10 non-surgical controls matched for age and gender (total123,230) [27]. They established rates of inpatient hospitalization for hypoglycemia as well as the potentially related diagnoses including confusion, syncope, epilepsy, and seizures both before and after surgery (or before and after study inclusion date for the control population).

The authors found that the frequency of hypoglycemia or related diagnoses in the surgical cohort pre-operatively did not differ from the frequency in the general population. This finding was important, as it rejected the notion that post-gastric bypass patients with severe hypoglycemia had pre-existing hypoglycemia partially masked by their severe insulin resistance pre-operatively. Further, they found no increase in hypoglycemia or related diagnoses in the patients who underwent the purely restrictive vertical banded gastroplasty or gastric banding post-operatively. As noted in the accompanying editorial, this finding suggested that the exclusion of the proximal gut and more rapid delivery of nutrients to the distal small intestine that characterizes gastric bypass are likely critical for the expression of severe hypoglycemia [28]. Among the gastric bypass cohort, the increased risk for hypoglycemia and related diagnoses following surgery increased significantly by over 2- to 7-fold, and this was true whether or not individuals with pre-existing diabetes were included in the analyses. Importantly, the absolute risk was still low, with approximately 0.2% of the

post-gastric bypass population hospitalized for hypoglycemia (1% for all related diagnoses), compared to 0.04% of the general population [27].

Clearly the findings of Marsk *et al* [27] suggest the risk of severe hypoglycemia following gastric bypass increases significantly, but with a reassuringly low overall incidence. Still, this study may underestimate of the problem as a whole, since less severe hypoglycemia would likely be evaluated in the outpatient, rather than inpatient setting. Ultimately, prospective longitudinal cohort studies of gastric bypass patients that are well-characterized metabolically at baseline and followed over time after surgery will be required to gain a better insight into the range of severity and frequency of the complication.

Possible mechanisms mediating post-gastric bypass hypoglycemia

Perhaps not surprising given the span of hypoglycemia complicating gastric bypass as well as the possibility that the incidence could vary for the less to more severe manifestations, there is controversy surrounding the disorder's underlying pathophysiology. Suggested mechanisms have ranged from expansion of beta cell mass, to alterations in beta cell function, and non-beta cell related factors, or possibly a combination of mechanisms [20, 28].

Alterations in beta cell mass

The pancreatic pathology reported in both of the series of patients first detailed by Service *et al* and Patti *et al* in 2005 was described as consistent with nesidioblastosis, due to the findings of enlarged islets, hypertrophic beta cells, and ductoinsular complexes (the presence of islet cells within or adjacent to ducts) [7, 8]. Patti *et al* also reported increased Ki67 staining in ductal cells suggestive of beta cell proliferation [8]. Some have suggested that hypertrophic islets could have been present pre-surgically due to bariatric surgery patients' obesity, and that this may have predisposed them to hypoglycemia [23, 29]. This argument would suggest that the increased beta cell mass of obese patients undergoing surgery does not properly adapt to the drop in food intake after surgery which is then followed quickly by major weight loss. There are two flaws to this theory. First, reported patients did not experience their neuroglycopenic symptoms immediately as would be expected based on this proposed mechanism (except in the case of rare patients with insulinoma [7, 30]), but rather months and typically years later. In fact, Marsk *et al* reported a median time from surgery to symptoms of 2.7 years in their population [27]. Second, obese patients undergoing purely restrictive bariatric surgery procedures, such as vertical banded gastroplasty or gastric banding, would also be expected to have hypertrophied islets that could be equally maladaptive to the decreased food intake and weight loss following these procedures, and yet the severe, hyperinsulinemic hypoglycemia has not been reported in this population. Furthermore, Marsk *et al* confirmed there were no differences in the incidence of hypoglycemia post-operatively for these patients compared to the control population [27].

A more cogent argument regarding presence or absence of islet hyperplasia relates to the selection of control pancreatic specimens. It should be noted that control pancreata for comparison in the initial case series from Service *et al* came from surgical specimens from less obese (compared to the preoperative BMI of cases) individuals without endocrine disease [7]. When the same patients were examined by a separate group and compared to both obese (n=31) and lean (n=16) control samples, the finding of increased islet hyperplasia and increased beta cell turnover did not hold up, though the nuclear diameter of the beta cells was found to be enlarged which was suggested to indicate increased secretory activity [31]. However, this study has not laid to rest the question of whether or not gastric bypass leads to islet hypertrophy. The obese and lean control samples came from autopsy specimens, and concerns about quality given the potential for post-mortem changes have

also been raised. In follow-up to the initial series from the Mayo, Rumilla *et al* measured islet growth factor expression in 36 cases of nesidioblastosis (27 post-gastric bypass) compared to 52 surgical specimens from patients with benign exocrine tumors reasonably matched for post-operative BMI but slightly older age [32]. Islets were reported to be more hypertrophied and irregular with enlarged cell nuclei among nesidioblastosis cases *vs.* controls. Increased expression of insulin-like growth factor 2, insulin-like growth factor 1 receptor-α, and transforming growth factor-β receptor 3 was found, and some of these factors have been implicated in beta cell proliferation, at least in animal models [32]. Given the difficulty of obtaining pancreatic specimens appropriately matched for possible confounding elements, the question of islet morphology in post-gastric bypass hypoglycemia will likely remain a subject of debate.

Alterations in beta cell function

Two observations suggest that mechanisms beyond a pure anatomical cause for post-gastric bypass hypoglycemia exist. First, reduction in beta cell mass arising from partial pancreatectomy does not always cure the hypoglycemia [28]. Second, the severity of nesidioblastosis does not correlate with duration of the post-gastric bypass period [32]. Hence, a functional defect may well underlie post-gastric bypass hypoglycemia. Glucagon-like peptide 1 (GLP-1) was suggested as a possible candidate for this role from the start [7-9]. Not only does GLP-1 contribute to beta cell proliferation at least in rodent models [33], but it mediates the augmentation of insulin secretion with oral glucose (the incretin effect), and has additional impacts on beta cell response to glucose [34]. Patients that have undergone gastric bypass have an augmented GLP-1 response to meals [35], but Goldfine *et al* in one of the most comprehensive mechanistic studies to date, demonstrated that this response was even greater in gastric bypass patients with neuroglycopenic symptoms compared to gastric bypass patients matched for duration post-surgery without hypoglycemia, or to non-surgical pre- or post-operative weight-matched controls [25]. Consistent with their higher GLP-1 levels, the post-gastric bypass hypoglycemic patients also had higher insulin and C-peptide levels, though a subsequent study demonstrated that glucose and insulin regulation was not different among post-gastric bypass patients with or without hypoglycemia using the OGTT (GLP-1 was not measured) [24]. Whether GLP-1 plays a causative role or is simply a marker of the phenomenon remains to be determined.

Non-beta cell mechanisms

Other factors have also been suggested to potentially play a role in mediating post-gastric bypass hypoglycemia, such as decreased levels of the appetite-stimulating and insulin counter-regulatory gastrointestinal hormone, ghrelin or alterations in other counter-regulatory hormones. Goldfine *et al* measured ghrelin, as well as peptide YY, gastric inhibitory peptide (GIP), glucagon, adiponectin, and leptin, but reported no differences in these hormones between gastric bypass patients with and without hypoglycemia [25].

Given the presence of altered anatomy following gastric bypass such that the proximal gut is excluded from continuity with nutrients, the possibility that some unknown factor produced by this tissue may contribute to glucose homeostasis has been raised [36]. For most patients with type 2 diabetes, such a factor could lead to the rapid and dramatic resolution of the disease, but in some cases it may cause hypoglycemia. A recent publication lending support to this theory described a case of post-gastric bypass hypoglycemia that was completely ameliorated by feeding via G-tube through the bypassed gut [37]. Identical liquid mixed meals (Ensure) were provided via both oral and G-tube routes, and with oral ingestion, significantly higher levels of glucose, insulin, GLP-1, as well as GIP and glucagon were found that were not seen with G-tube feeding. The authors suggest that the altered nutrient flow with gastric bypass causes the exaggerated incretin response and hence hypoglycemia,

rather than some impact of gastric bypass to permanently alter pancreatic islets. Still, other as yet unknown factors could play a role, and furthermore, anatomic changes could still contribute, given that prior reports of reversal of gastric bypass did not result in resolution of hypoglycemic symptoms universally [8].

Conclusion

Why some patients experience severe, hyperinsulinemic hypoglycemia as a long-term complication of their gastric bypass surgery remains to be fully understood. These patients could represent an extreme of the altered physiology that accompanies the surgery, which in most cases brings metabolic benefit. They may also have some kind of underlying genetic predisposition whose phenotype is not apparent in the preoperative state but which becomes apparent over time post-operatively. Regardless of the mechanism, the manifestations are severe. Improved understanding of this complication of gastric bypass will promote the ability to pre-operatively identify patients at risk for the complication, hence optimizing the patient's ability to make informed decisions about their surgical options.

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Key Points

- There is a broad spectrum of post-prandial symptomatology following gastric bypass, but establishing the presence of severe, hyperinsulinemic hypoglycemia requires: (1) symptoms of hypoglycemia; (2) low plasma glucose at the time of symptoms (as well as concomitant measurement of elevated serum insulin, C-peptide, and negative sulfonylurea screen); (3) relief of symptoms with the correction of low glucose.
- Severe hypoglycemia post-gastric bypass is rare overall, but the risk is still 2 to 7-fold higher compared to non-surgical populations or to patients who have undergone purely restrictive gastric banding or gastroplasty.
- Mechanisms remain poorly understood and may be multifactorial, with hypotheses ranging from alterations in beta cell mass and/or function, or non-beta cell factors.