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ASMBS Position Statement on Postprandial Hyperinsulinemic Hypoglycemia after Bariatric Surgery

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The following position statement is issued by the American Society for Metabolic and Bariatric Surgery (ASMBS) for the purpose of enhancing quality of care in metabolic and bariatric surgery. In this statement, suggestions for management are presented that are derived from available knowledge, peer-reviewed scientific literature, and expert opinion. This was accomplished by performing a systematic review of currently available literature regarding postprandial hyperinsulinemic hypoglycemia after bariatric surgery. The intent of issuing such a statement is to provide objective information regarding postprandial hyperinsulinemic hypoglycemia after bariatric surgery. The statement may be revised in the future should additional evidence become available.

The issue

Obesity is a major global and national health concern that is associated with significant disability and mortality [1]. Worldwide, it is estimated that the prevalence of obesity has doubled since 1980, affecting more than 1.9 billion adults [2]. More than one third of U.S. adult men and women are obese [3]. Bariatric surgery has been shown to be the most effective and durable treatment of severe obesity and leads to significant improvement of obesity-related co-morbid conditions [4–6].

Postprandial hyperinsulinemic hypoglycemia after bariatric surgery is an uncommon and rarely reported metabolic complication of weight loss surgery, most commonly associated with Roux-en-Y gastric bypass (RYGB). It is distinguished from fasting hypoglycemia in that it occurs after a meal [7,8], along with biochemical detection of postprandial hyperinsulinemia and hypoglycemia. Postprandial hyperinsulinemic hypoglycemia should be suspected when postprandial neuroglycopenic symptoms occur after bariatric surgery. These are a variable constellation ranging from confusion, altered levels of consciousness, reduced cognition, weakness, fatigue, warm sensation, slurred speech, and visual disturbances—in the setting of documented low blood glucose levels. Importantly, persistent or unrecognized hypoglycemia can progress to severe symptoms such as hypoglycemia unawareness, loss of consciousness, seizures, coma, and even death [9].

Postprandial hyperinsulinemic hypoglycemia after bariatric surgery was initially described in 6 patients who underwent RYGB for severe obesity [7]. In that series, onset of symptoms was noted between 6 months and 8 years after bariatric surgery. It was initially thought to be due to endogenous hyperinsulinemia from increased beta-cell mass hyperfunctioning islet cells; however, most experts now agree that the factors responsible for recalcitrant symptoms of hyperinsulinemic hypoglycemia after

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bariatric surgery are related to the anatomic changes that occur with surgery resulting in alterations in glucose kinetics, changes in multiple glucose regulatory mechanisms, as well as gastrointestinal and pancreatic hormone levels involved in glucose homeostasis, and not from an inherent change in pancreatic beta-cell mass related to RYGB [10].

Since its initial recognition, the number of reported cases of postprandial hyperinsulinemic hypoglycemia after gastric bypass surgery have increased with the number of bariatric operations performed [7,8,11,12]. RYGB has been the most common bariatric operation performed worldwide; although recently, it has been superseded by the sleeve gastrectomy (SG) [13]. Postprandial hyperinsulinemic hypoglycemia has been most often associated with RYGB. However, it has been observed after other operations, such as the duodenal switch, in which nutrients are directly delivered to the mid or distal small intestine. Although less common, there have also been reports of hypoglycemia after the SG [14–18].

With growing case reports, there have been increasing awareness and recognition of postprandial hyperinsulinemic hypoglycemia after bariatric surgery. Incidence of hypoglycemia after bariatric surgery is low, but the actual incidence is unknown. In a nationwide population-based Swedish study of more than 5000 patients over 2 decades, Marsk et al. reported a prevalence of hypoglycemia of .2% [19]. Increased risk of hypoglycemia was not seen in patients undergoing vertical banded gastroplasty or laparoscopic adjustable gastric banding. In their study, the mean time from surgery to symptoms was 2.7 years. This is consistent with other studies that found most patients with postbariatric surgery postprandial hyperinsulinemic hypoglycemia presented between 2 and 4 years after their operation [11]. In a review of 3082 patients undergoing bariatric surgery over the course of 42 years, Kellogg et al. found a prevalence of .36% of postgastric bypass hypoglycemia [20]. Most patients in their study presented with hypoglycemic symptoms 1 to 2 years after surgery, and nearly all patients presented within 4 years, postoperatively.

Data from the Bariatric Outcomes Longitudinal Database (BOLD) suggest that the incidence of postprandial hyperinsulinemic hypoglycemia after bariatric surgery may be even lower [17]. Of 145,000 patients, the incidence of self-reported post-RYGB hypoglycemia was found to be .1% among all patients, and .02% in patients not taking diabetic medications. This study was limited by self-reporting and may underestimate the actual number. Others have suggested that far more patients, perhaps as many as one third, may develop some level of hypoglycemia after mixed meals, but may not seek medical attention [21]. In fact, a questionnaire-based study of 450 patients suggested that as many as 34% of patients had some suspicion for postprandial hypoglycemic symptoms based on responses to directed questions [15]. Nonetheless, though the true prevalence of postprandial hyperinsulinemic hypoglycemia after bariatric surgery is unknown, it is clear that the vast majority of patients undergoing RYGB do not suffer from it.

Presentation and diagnosis

Postprandial hyperinsulinemic hypoglycemia after RYGB surgery has historically been referred to as "late dumping syndrome" [20–22]. This is distinct from the entity commonly referred to as "dumping syndrome," which is common after RYGB and generally occurs within minutes to 1 hour of the ingestion of high-calorie-dense foods (particularly refined sugars and fats) leading to the release of gut hormones and the rapid entry of water into the intestinal lumen. Symptoms of postprandial hyperinsulinemic hypoglycemia may develop months to years after surgery, and typically present 1 to 3 hours after a refined carbohydrate rich meal [23]. Symptoms can be nonspecific and include a broad spectrum of presentations related to Whipple's triad for hypoglycemia: (1) symptomatic hypoglycemia, (2) documented low plasma glucose level, and (3) resolution of symptoms after glucose administration. Specific symptoms of hypoglycemia are categorized as autonomic or neuroglycopenic. Autonomic symptoms include anxiety, sweating, tremors, and palpitations. Neuroglycopenic symptoms include confusion, weakness, light-headedness, dizziness, blurred vision, disorientation, and eventually loss of consciousness [20].

There is no single agreed-upon criterion for the diagnosis of postprandial hyperinsulinemic hypoglycemia after bariatric surgery, and it represents variable self-reported postprandial symptoms, documented low plasma glucose levels, ICD codes reflecting low plasma glucose or neuroglycopenic symptoms. There is no consensus for a plasma glucose level that defines hypoglycemia, making interpretation of reports difficult. However, a detailed history and high level of suspicion are necessary to diagnose postprandial hypoglycemia. A patient journal, with particular attention to dietary history, specific hypoglycemic symptoms and their temporal relationship, is imperative in arriving at the diagnosis. Patients who present with atypical symptoms or symptoms that are not associated with food intake should undergo further workup to identify other potential causes for hypoglycemia. An insulinoma must be ruled out in patients with fasting hypoglycemia. It can be confirmed by performing a 72-hour fasting test and diagnostic imaging, including computed tomography and magnetic resonance imaging [24]. If these tests fail to identify a focal pancreatic lesion, further invasive testing can be performed by endoscopic ultrasound or selective arterial calcium stimulation testing, in which hepatic vein insulin levels are measured after focal injection of calcium. Whereas an insulinoma can be localized to the gastroduodenal, superior mesenteric, or splenic artery distribution, a patient with postprandial hyperinsulinemic hypoglycemia

would be expected to have diffuse stimulation of insulin production [24].

Up to 50% of post-RYGB patients will have some level of postprandial decreased glucose levels, but remain asymptomatic. To make a definitive diagnosis of postprandial hyperinsulinemic hypoglycemia, a patient must have both symptoms and laboratory values that support the diagnosis [21]. Multiple scoring systems have been established to aid in the diagnosis of either dumping syndrome and/or hypoglycemia. The Sigstad Dumping Score was initially created for patients who had undergone partial gastrectomy for peptic ulcer disease and later adapted for RYGB patients. Whereas other scoring systems exist, none has been formally validated for bariatric surgery patients [22].

Based on early case reports, postprandial hyperinsulinemic hypoglycemia after RYGB is a constellation of postprandial hypoglycemia with neuroglycopenia more than 1-year postoperatively, spontaneous correction of hypoglycemia, normal fasting glucose and insulin, and hyperinsulinemia at the time of hypoglycemia with plasma glucose <50 mg/dL and serum insulin >50 μU/ml (with the corresponding increase in C-peptide) [25]. Laboratory testing is an essential component in confirming the diagnosis of postprandial hypoglycemia. There is not a single standardized test or model, but several methods, including provocative tests, have been used. Hypoglycemia itself is defined by the American Diabetes Association as blood glucose level of <70 mg/dL. However, in patients after bariatric surgery, levels of <60 mg/dL or <50 mg/dL are often used as the threshold to define hypoglycemia [11,20,26,27].

To diagnose postprandial hyperinsulinemic hypoglycemia, at least 2 peripheral blood draws are required including a baseline glucose level and a postprandial glucose level. Finger stick glucose measurements are variable and not sufficiently consistent [28]. Alternatively, continuous glucose monitoring over the course of 3 days is more sensitive and allows for glucose monitoring while patients are eating as they would normally [24]. A pattern of hyperglycemia within 30 minutes of a high glucose meal, followed by significant hypoglycemia is highly suggestive of the diagnosis [20]. Typically, patients have a spontaneous return to euglycemia after the hypoglycemic episode.

Provocative testing such as the oral glucose tolerance test (oGTT), have been used in RYGB patients since the 1980s [29]. It is performed with serial serum glucose measurements at intervals up to 120–240 minutes after administration of 75–100 grams of glucose [22]. However, up to 70% of RYGB patients were found to have a glucose level <60 mg/dL during testing, and differences between symptomatic and asymptomatic patients were small, making the oGTT less useful in confirming the diagnosis [30,31]. The mixed meal tolerance test is a preferred provocative test, in which a standardized meal of carbohydrates, protein, and fat is given. Glucose and insulin levels are determined during the fasting state and at 30-minute intervals after the mixed meal. A positive mixed meal tolerance test found normal fasting glucose levels, hyperinsulinemia before hypoglycemia, hypoglycemia with plasma glucose levels <50–60 mg/dL, and symptoms of hypoglycemia.

Although securing the diagnosis can be challenging, postprandial hyperinsulinemic hypoglycemia after bariatric surgery requires (1) symptoms occurring >1 year after surgery, (2) normal fasting glucose and insulin levels, (3) correlation of symptoms with hypoglycemia, followed by spontaneous resolution of hypoglycemia, and (4) a positive provocative test.

Pathophysiology

Post-RYGB postprandial hyperinsulinemic hypoglycemia is most likely due to multifactorial alterations in hormonal and glycemic patterns that have not yet been fully elucidated. Potential mechanisms that have been suggested to explain the biochemical and clinical findings include (1) an increase in levels of incretins—gut-derived hormones that augment insulin response to nutrients, mainly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, also known as gastric inhibitory peptide; (2) enhanced β-cell sensitivity to GLP-1; (3) failure of reduction of islet cell mass or function in the obese state after surgery; (4) increased insulin sensitivity after weight loss; (5) inappropriate hypersecretion of insulin; and (6) abnormal counter-regulatory hormonal response to hypoglycemia [14,24,32–35]. For example, evidence suggests that changes in postprandial glucagon levels fail to play a role in postprandial hypoglycemia. Although some have hypothesized that a lack of glucagon response to profound hypoglycemia could be attributed to glucagonostatic effects of elevated GLP-1 levels and that the disruption of this physiologic feedback mechanism could contribute to hypoglycemia [32,35], others have found a paradoxical increase in glucagon levels during oGTT after RYGB [36]. Others have also documented no impairment in postprandial glucagon levels in the setting of hyperinsulinemic hypoglycemia and no inherent inappropriate glucagon to insulin secretion [37].

In the initial description of the condition, histopathologic examination of specimens from several patients undergoing partial pancreatectomy for postprandial hypoglycemia were proposed to have characteristics of nesidioblastosis-defined as β-cell hypertrophy and hyperfunction, islet cell hyperplasia, and neoformation of islets of Langerhans from pancreatic duct epithelium [7,32,35]. It was further suggested that this finding is consistent with prolonged hypersecretion of GLP-1. However, experimental evidence has failed to show a direct link between GLP-1 secretion and histologic findings of nesidioblastosis. Moreover, removal of islet cell mass by partial pancreatectomy often fails to

entirely resolve hypoglycemia [38]. In addition, examination of the same pancreatic specimens from the original study of Service et al. [7], conducted by Meier et al. [10], found that the patients in the original publication did not have increased islet cell hyperplasia, greater β-cell turnover, or greater relative β-cell area. Rather, studies found that β-cell nuclear diameter increased with body mass index, and these changes along with β-cell hyperfunction persisted in post-RYGB hypoglycemia patients compared to body mass index-matched controls [10,39]. A proposed mechanism, based on these findings, is β-cell hyperfunction in the obese state, which persists despite weight loss after bariatric surgery.

Postprandial hyperinsulinemic hypoglycemia is more often seen in patients who undergo RYGB, compared with patients who have undergone the duodenal switch or SG. It has not been reported after the vertical banded gastroplasty or laparoscopic adjustable gastric banding. The rapid passage of food from the gastric pouch into the small intestine triggers a sharp and excessive rise in glucose, and a matching increase in insulin secretion. GLP-1, a peptide released by intestinal L-cells in response to food, stimulates insulin secretion in a glucose-dependent manner. The postprandial increase in GLP-1 is thought to play a major role in the improvement in diabetes commonly observed after RYGB [40]. This same mechanism may also contribute to "reactive hypoglycemia" or postprandial hyperinsulinemic hypoglycemia [41]. In fact, postprandial GLP-1 levels have been shown to be higher and to elicit an exaggerated insulin response in those patients with hyperinsulinemic hypoglycemia and neuroglycopenic symptoms, compared to asymptomatic patients [12,26,32].

Salehi et al. compared matched controls to RYGB surgical patients with and without symptomatic hypoglycemia [26]. Their data suggested a GLP-1 effect on insulin secretion in symptomatic and asymptomatic RYGB patients that was absent in the nonoperative controls. In other studies, the same group found that after a mixed meal test, the rate of glucose appearance in the portal and systemic circulation was significantly higher in the RYGB groups, compared with controls. The rate was even higher in patients with symptomatic hypoglycemia, compared with asymptomatic patients [42]. In addition, inappropriate insulin secretion in late stages after the meal combined with reduced insulin clearance was observed in the patients with postprandial hyperinsulinemic hypoglycemia. The putative role of GLP-1 was further suggested by studies showing correction of hypoglycemia after gastric bypass by the administration of exendin (9-39), a GLP-1 receptor antagonist [43]. However, other studies suggest that GLP-1 agonists may have a beneficial role in correction of hypoglycemia, suggesting that the role of GLP-1 in post-RYGB hypoglycemia is likely complex and not fully understood [44].

The physiologic counter-regulatory mechanism in response to hypoglycemia may also be disrupted in post-RYGB hypoglycemic patients. Kamvissi et al. proposed an anti-incretin theory suggesting that nutrient passage through the gastrointestinal tract after RYGB may also activate negative feedback mechanisms to balance the effects of incretins and to prevent postprandial hypoglycemia [45]. The failure of these counter-regulatory mechanisms may accentuate hyperinsulinemic hypoglycemia. For example, in post-RYGB patients with hypoglycemia the inadequate production of glucagon by α -cells fails to increase glucose levels in response to hypoglycemia, whereas the GLP-1 receptor antagonist, exendin (9-39), has been shown to increase glucagon concentration [42,43].

Treatment

Management of postprandial hyperinsulinemic hypoglycemia is made challenging due to its variable clinical presentation and a pathophysiology not yet fully elucidated. Several therapeutic options have been described for hyperinsulinemic hypoglycemia after RYGB. Described therapies have included dietary modifications, medical management, gastrostomy tube placement, gastric pouch restriction, reversal of RYGB, conversion to SG and pancreatectomy [34,48–51].

Dietary modification

The vast majority of patients present with mild to moderate disease and can be successfully managed with dietary modifications. These include multiple small meals throughout the day to avoid large volume carbohydrate feeding. Meals should be high in fiber and protein, and low in simple, rapidly absorbable carbohydrates [20,25,50].

Pharmacotherapy

Use of pharmacotherapy has been reported in case reports and in small series of patients with postprandial hyperinsulinemic hypoglycemia that is refractory to dietary modifications. Nifedipine, a calcium channel blocker that reduces insulin secretion, has been used at a dose of 30 mg/d to treat severe postprandial hypoglycemia presenting decades after RYGB, based on its successful use in pediatric cases of nesidioblastosis [51]. A small series found the efficacy of α-glucosidase inhibitors, such as acarbose, that reduce the postprandial blood glucose increment and insulin response in patients refractory to dietary modifications. Doses ranging from 100 mg to 300 mg have been effective in treating symptoms [33,52,53]. Diazoxide, an adenosine-triphosphate-dependent potassium channel agonist of β cells that reduces insulin release, has also been used in infants and children, and found moderate success in avoiding pancreatectomy in adults with postprandial hyperinsulinemic hypoglycemia after bariatric surgery [54].

Although glucagon has failed to report any significant effect in treating hyperinsulinemic hypoglycemia [55], GLP-1 receptor antagonists have shown efficacy and promise for long-term treatment. Taking into consideration the presumed pathophysiology of RYGB procedures and their effect on GLP-1 expression with subsequent elevated insulin levels, blocking the action of GLP-1 can suppress postprandial insulin secretion. Infusions of GLP-1 receptor blockers—currently available only as investigative drugs in the research setting—corrected hypoglycemia and increased glucagon levels in individuals with recurrent hypoglycemia after RYGB [26,42,43]. Long-acting somatostatin analogues such as octreotide may also have a role in the treatment of hypoglycemia [23,56]. Used in the treatment of dumping syndrome and nesidioblastosis in pediatrics, octreotide may have some benefit in the treatment of postprandial hyperinsulinemic hypoglycemia.

Gastrostomy tube placement

A gastrostomy tube placed in the remnant stomach can provide a method for nutrient delivery directly into the bypassed stomach and proximal duodenum. Small case series suggest that this can serve both as an efficient therapy for postprandial hypoglycemia and per oral calorie intolerance, and, if necessary, as a potential predictor of positive outcome after reversal of the RYGB [49,57].

Gastric outlet restriction

Gastrojejunostomy restriction to slow the passage of food into the small intestine has been suggested as a surgical modality to treat postbariatric postprandial hyperinsulinemic hypoglycemia. Z'graggen et al. used a silastic ring or an adjustable gastric band in 12 consecutive patients who presented with loss of restriction and disabling hypoglycemia. Symptoms presented 1.5–8.5 years after RYGB [58]. Insulin levels were not measured at the time of hypoglycemia and one patient was found to have adult nesidioblastosis; however, 11 patients reported improvement or resolution of postprandial hypoglycemia symptoms within 3–12 months. One patient underwent a distal pancreatectomy in attempts to treat the condition. Endoscopic transoral plication of the gastric pouch or outlet has been described for treatment of intractable post-RYGB dumping but not specifically for treatment or improvement of post-RYGB postprandial hyperinsulinemic hypoglycemia [59,60].

RYGB reversal

RYGB reversal has been described in a few small series for cases of postprandial hyperinsulinemic hypoglycemia after RYBG resistant to all other treatment modalities. Reversal of RYGB can be technically challenging, and carries potential for significant morbidity and weight regain; however, it may represent a therapy of last resort [49,61]. In a small series of patients, Campos et al. found no neuroglycopenic symptoms and a significant decrease in the number of hypoglycemic episodes per week, 3–22 months after RYGB reversal [49]. Similarly, Vilallonga et al. found symptomatic resolution in 9 patients with postgastric bypass hypoglycemia, with a mean follow up of 11.5 months [61]. Long-term data are lacking, and it is unclear whether the promising results are durable. In fact, there are a few cases reported of recurrent hyperinsulinemic hypoglycemia after RYGB reversal [62,63].

Conversion of RYGB to SG

Conversion of RYGB to SG (primary or staged) has also been described in a few small series/case reports for complications related to RYGB [48,49,61]. Reversal of RYGB with the addition of primary or staged SG specifically for treatment of refractory hyperinsulinemic hypoglycemia has been described in <10 patients with resolution of hypoglycemia symptoms in the majority without findings of short-term weight gain. As with RYGB reversal, these are technically challenging procedures with increased risk of complications, including a greater incidence of gastroesophageal reflux related to the addition of the SG [48,49,61]. Currently, there is insufficient evidence to recommend this as treatment for hyperinsulinemic hypoglycemia.

Distal pancreatectomy

Partial pancreatectomy has been described in over 50 published cases of refractory hypoglycemia [7,8,58,62,64–66]. The operation targets the presumed endocrine end-organ of the clinical disease; however, it remains difficult to determine the efficacy of this procedure, since there remains a lack of consensus on the causality of islet cell hyperplasia or β-cell turnover in postprandial hypoglycemia after gastric bypass [10,67,68]. In addition, reports describe either failure or recurrence of the disease after distal pancreatectomy [62], further suggesting that β-cell volume alone is insufficient to explain the clinical disease. Whereas short-term symptom resolution may be observed in a majority of patients [46], in a survey of patients after partial pancreatectomy for diffuse islet cell disease, 25% reported no long-term benefit after surgery, and 50% of the operations were deemed to be unsuccessful or minimally successful overall [69]. In a small series of 9 patients with postgastric bypass postprandial hyperinsulinemia hypoglycemia who underwent sub-total (80%) pancreatectomy, Mathavan et al. found that 22% of patients had persistent frequent symptoms requiring pharmacotherapy and 22% had severe symptoms of hypoglycemia refractory to medical management [47]. In addition to its variable clinical efficacy, partial pancreatectomy is associated with significant potential

morbidity, including new onset diabetes. Thus, this treatment should not be recommended for treatment of postprandial hyperinsulinemic hypoglycemia after bariatric surgery.

Summary and recommendations

Based on the available evidence to date, the following recommendations are made in the patient with postprandial hyperinsulinemic hypoglycemia after bariatric surgery.

- Postprandial hyperinsulinemic hypoglycemia after bariatric surgery is rare and most commonly associated with RYGB. Nonetheless, patients should be screened for, educated, and counseled to recognize the signs and symptoms of hypoglycemia.
- Extreme, progressive, unrecognized neuroglycopenic symptoms of postprandial hyperinsulinemic hypoglycemia can result in cognitive and neurologic impairment with risk of seizures and loss of consciousness posing risk to both patient and others.
- Insulinoma must be ruled out in patients with confirmed fasting hypoglycemia.
- Diagnosis of postprandial hyperinsulinemic hypoglycemia requires a dietary journal, along with confirmatory laboratory and provocative testing, in the setting of symptoms presenting more than 1 year after surgery. Treatment with dietary modification in mild cases is often implemented successfully without a definitive diagnosis.
- Postprandial hyperinsulinemic hypoglycemia can be effectively treated in the majority of cases with dietary modification alone. A dietitian should be an integral part of the treatment team, and an endocrinologist consulted in cases not responding to initial treatment.
- Pharmacotherapy produces variable results, but should be attempted before surgical intervention. A gastrostomy tube with feeding into the remnant stomach provides nutritional support and in some cases symptomatic relief and should be considered in patients not responding to nonoperative treatment. Partial pancreatectomy is not recommended.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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