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Recognition and management of hyperinsulinemic hypoglycemia after bariatric surgery

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Summary

Hyperinsulinemic hypoglycemia with neuroglycopenia is an increasingly recognized complication of Roux-en-Y gastric bypass (RYGB) due to the changes in gut hormonal milieu. Physicians should be aware of this complication to ensure timely and effective treatment of post-RYGB patients, who present to them with hypoglycemic symptoms. Possible causes of hypoglycemia in these patients include late dumping syndrome, nesidioblastosis and rarely insulinoma. Systematic evaluation including history, biochemical analysis, and diagnostic testing might help in distinguishing among these diagnoses. Continuous glucose monitoring is also a valuable tool, revealing the episodes in the natural environment and can also be used to monitor treatment success. Treatment should begin with strict low carbohydrate diet, followed by medication therapy. Therapy with diazoxide, acarbose, calcium channel blockers and octreotide have been proven to be beneficial, but the response apparently is highly variable. When other treatment options fail, surgical options can be considered.

Keywords

Hypoglycemia; Bariatric surgery; Nesidioblastosis; Dumping syndrome; Glucagon like peptide-1 (GLP-1)

Introduction

Obesity is a global epidemic and is one of the major health concerns in the United States. Bariatric surgery is currently the most effective therapy for severe obesity which results in substantial weight loss, averaging 30–40 kg (about 60% excess weight) utilizing the most effective approaches [1]. It is reported to be one of the fastest growing hospital procedures

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performed in the United States and worldwide. In the most recent global overview of bariatric surgery worldwide, the total number of bariatric procedures performed worldwide in 2013 was reported to be 468,609 [2]. The highest number ($n = 154,276$) was from the USA/Canada region. The most commonly performed procedure in the world was Roux-en-Y gastric bypass (RYGB), 45%; followed by sleeve gastrectomy (SG), 37%; and adjustable gastric banding (AGB), 10%. This survey indicated that there has been a constant increase in the total number of bariatric procedures performed worldwide over the past 10 years.

In 2010, Livingston et al. [3] estimated the procedure incidence of bariatric surgery in the United States by utilizing the data from the National Hospital Discharge Survey (NHDS) databases from 1993 to 2006. The procedures increased in incidence from 8597 procedures in 1993 to a high of 115,194 in 2004, with RYGB constituting 22,436 of these 115,194 procedures. Another interesting study analyzed the data submitted by >800 surgeons and >450 facilities using the Bariatric Outcomes Longitudinal Database (BOLD) [4]. BOLD is a registry of self-reported bariatric surgery patient information from the American Society for Metabolic and Bariatric Surgery-Bariatric Surgery Center of Excellence participants. A total of 57,918 research-consented patients with surgical procedure data between June 2007 and May 2009 were included in this study. According to this data, the most common bariatric surgical procedure performed in the U.S. was the Roux-en-Y gastric bypass (RYGB) (31,668 [54.68%]), followed by gastric banding (22,947 [39.62%]), sleeve gastrectomy (1328 [2.29%]), and biliopancreatic diversion (517 [0.89%]). Thus RYGB continues to be the gold standard procedure [5]. Females were shown to constitute a significant majority of the BOLD study population (45,619 [78.76%]) [4].

Any major surgery, including bariatric surgery, involves the potential for complications, and physicians need to be prepared to recognize such complications in the aftermath of surgery. One complication that has become increasingly recognized in post-bariatric surgery patients is the development of post-prandial hyperinsulinemic hypoglycemia. With the number of bariatric surgeries increasing annually, better defining and diagnosing this condition is important, both for the people who develop it and for the clinicians who attempt to treat such patients. In this review, we describe the current understanding and management of hyperinsulinemic hypoglycemia after RYGB.

Definitions and terminologies

Hypoglycemia is considered to be a glucose level of < 70 mg/dL (< 3.9 mmol/L), as defined by the American Diabetes Association Workgroup on Hypoglycemia [6,7].

Documented symptomatic hypoglycemia

Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration < 70 mg/dL (< 3.9 mmol/L) [7].

Asymptomatic hypoglycemia

Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration < 70 mg/dL (< 3.9 mmol/L) [7].

Neuroglycopenia

Hyperinsulinemic hypoglycemia after RYGB may lead to a potentially life-threatening deficiency of glucose in the central nervous system. This is referred to as neuroglycopenia and usually does not appear until 1 year or more after surgery [8].

Several causes of post-prandial hypoglycemia have been described in the post-RYGB patients, including late dumping syndrome, nesidioblastosis and insulinoma [9]. It is essential to define and differentiate these diagnoses, particularly because of the complexity and possible co-occurrence of these conditions.

Dumping syndrome

Dumping syndrome, a well-recognized complication of post-RYGB, can be separated into early and late forms depending on the occurrence of symptoms in relation to the time elapsed after a meal. Early dumping, which occurs 30–60 min post-prandially and in the early post-operative period, is attributed to rapid emptying of hyperosmolar gastric contents into small bowel which leads to fluid shift from the intravascular compartment into the bowel lumen. The resulting gastrointestinal (GI) and vasomotor symptoms result from bowel distension and intravascular volume depletion (hypovolemia) respectively, and not due to hypoglycemia [10]. Vasomotor symptoms include palpitations, an intense desire to lie down, diaphoresis, flushing, fatigue, dizziness, faintness, syncope and headache. GI symptoms include epigastric fullness, bloating, nausea, diarrhea, abdominal cramps and borborygmi [11]. Various vasomotor and GI symptoms are also detailed in Table 1.

What is termed “late dumping” occurs 1–4 h after a meal. The symptoms are thought to be related to the development of reactive hypoglycemia, which results at least partially from an exaggerated insulin and glucagon-like peptide-1 release post-prandially [12]. It is still not clear why late dumping occurs years after bariatric surgery and why it usually is symptomatic several hours after eating whereas early dumping usually develops within an hour and usually starts to happen shortly after bariatric surgery.

Research suggests that there are several controversies related to the nomenclature, pathophysiology and etiology of late dumping syndrome. According to few studies, late dumping syndrome is considered to have same pathophysiology as noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) and nesidioblastosis; conditions in which involvement of hyperfunctioning beta cells results in hyperinsulinemic hypoglycemia [10]. Whereas, others have reported it to be a separate phenomenon with different mechanisms involving GLP-1, or post-prandial insulin surge [9,11,13,14]. Although dumping syndrome has been described to have early and late phases by many authors [9,11,13–15], others have avoided the use of these terms considering dumping syndrome to manifest only in an early post-operative phase with no late dumping phase [8,16].

Nesidioblastosis

Nesidioblastosis is endogenous hyperinsulinemic hypoglycemia attributable to pancreatic β -cell hypertrophy and hyperfunction. The term “nesidioblastosis” was originally offered by Laidlaw in 1938 [17], who described the neof ormation of islets of Langerhans from pancreatic duct epithelium. The abnormal histologic aspects of the aberrant tissue include pancreatic β -cell hypertrophy, islet hyperplasia, islet cell dysplasia, β cells budding from ductal epithelium, and islets in apposition to ducts [18–21]. Initially it was thought to be a congenital disorder occurring in neonates and infants. However, now the term has been broadened and applied to the adult [11,16]. There is emerging recognition that post-prandial hypoglycemia in adults after RYGB may be due to hyperinsulinemia from hypertrophied islets as a result of nesidioblastosis [13,22,23].

Service and colleagues [24] described six post-RYGB patients with post-prandial neuroglycopenia and reported that nesidioblastosis was the basis for this hyperinsulinemic hypoglycemia in five of these six patients (insulinoma was identified in one of them). Nesidioblastosis in these patients was confirmed by selective arterial calcium stimulation testing, assuagement of symptoms after partial pancreatectomy, and demonstration of histopathological changes in resected pancreatic tissue. Similar tissue changes were observed by Patti and colleagues [25] in three patients with severe post-prandial hypoglycemia following bariatric surgery. Whether the increased β -cell mass develops prior to surgery due to extreme obesity and/or whether it is triggered as a consequence of surgical procedure is still a topic of debate.

Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)

Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is a rare syndrome characterized by endogenous hyperinsulinemic hypoglycemia in adults that is not caused by an insulinoma. Pancreatic specimens from such patients show similar pathological features which are characteristic of nesidioblastosis [26]. NIPHS was first described by Service et al. [27] in 1999 in five adults with symptoms of post-prandial neuroglycopenia secondary to hyperinsulinemic hypoglycemia due to excessive β -cell growth. All of these patients had negative imaging studies, negative 72 h fasts, and positive selective arterial calcium stimulation tests indicative of pancreatic beta-cell hyperfunction.

Insulinoma

Another possible but rare cause of hypoglycemia in post-RYGB patients is insulinoma. Zagury and colleagues [28] described the case of a patient with hypoglycemic symptoms after gastric bypass that were caused by insulinoma. The persistence of hypoglycemic episodes after dietary adjustments led to consideration of an autonomous source of hyperinsulinemia, and MRI and CT identified an insulinoma. Insulinoma can present with hypoglycemia in both fasting and post-prandial states (rarely) whereas in hyperinsulinemic hypoglycemia associated with increased GLP-1 levels, hypoglycemia appears only post-prandially. Thus, fasting hypoglycemia is classically associated with insulinomas [29].

Table 2 further emphasizes on differentiating diagnostic measures and various treatment modalities of causes of post-gastric hypoglycemia.

Prevalence of hyperinsulinemic hypoglycemia

Post-prandial hypoglycemia appears to be observed after procedures that divert nutrients into the mid-small bowel, such as RYGB, and not purely restrictive procedures such as adjustable gastric banding [31].

A few estimates of prevalence have been offered. At the University of Minnesota, 3082 RYGB procedures were performed from July 1964 to April 2006. Through clinic follow-up, Kellogg and colleagues in 2008 [14] identified 11 of these patients who had reported episodes consistent with post-prandial hyperinsulinemic hypoglycemia and suggested a prevalence of 0.36%. Marsk and colleagues in 2010 [32] conducted a nationwide cohort study in Sweden based on national medical registries including 5040 RYGB patients, and found the incidence rate of 0.2% with rate of hospitalization for hypoglycemia being less than 1%. Although the low incidence of hypoglycemia reported in these studies is reassuring, there were some methodological limitations in both studies, including small population group, single center study and no ethnical diversity.

Recently a large cohort study was undertaken to characterize the incidence of hypoglycemia in post RYGB patients, analyzing data on large cohort of 275,618 patients within BOLD who had undergone RYGB ($n = 145,582$), laparoscopic adjustable gastric banding (LAGB) ($n = 100,106$), or SG ($n = 29,930$) [33]. They reported a 0.1% incidence ($n = 82$) of post-RYGB hypoglycemia 0.01% ($n = 15$) for LAGB, and 0.02% ($n = 7$) for SG, respectively. Incidence of hypoglycemia was calculated as the total number of self-reported cases of hypoglycemia post-operatively after each particular bariatric procedure (i.e. RYGB, LAGB, and SG) divided by the total number of the specific bariatric procedure performed.

These estimates likely underreport the true prevalence of post-prandial hypoglycemia given that many patients with this condition are not being identified and most are apparently not hospitalized for this problem [34]. Among the causes of hyperinsulinemic hypoglycemia, dumping syndrome is the one most commonly reported and is encountered in approximately 10–15% of patients after gastric bypass [12,22]. NIPHS is the cause of endogenous hyperinsulinemia in less than 5% of the cases [16,35]. These prevalence rates provide the rough estimates and the true incidence and prevalence of this complication are yet to be determined.

Clinical presentation

Hyperinsulinemic hypoglycemia in RYGB patients is characterized by neuroglycopenia that occurs in the post-prandial state. The symptoms manifested range from mild to severe hypoglycemic symptoms such as lightheadedness, diaphoresis, flushing, fatigue/weakness, dizziness, confusion, palpitations, anxiety, numbness of the lips, slurred speech, blurred vision and rarely more serious neurological manifestations, including tremors/shaking, loss of consciousness, focal neurological deficits, seizures or death [14,22]. Untoward and sometimes even fatal consequences such as motor vehicle accidents have resulted from these symptoms [22,25].

The neuroglycopenic symptoms of hypoglycemia usually develop after ingestion of a high carbohydrate meal and typically occur 1–4 h post-prandially [14]. A time lag of 1–5 years following bariatric surgery is typically observed before the emergence of these symptoms. This time interval suggests that islet dysfunction develops over time after RYGB and is potentially linked to altered incretin secretion [22]. Moreover, insulin sensitivity markedly increases secondary to the surgically induced weight loss after the first year. This confluence of factors seems to result in hypoglycemia [36]. Table 3 summarizes the available case studies and series [9,16,22,24,31,34,37], highlighting the reported time period between bariatric surgery and the development of first neuroglycopenic event.

Pathophysiology

The pathophysiology of post-RYGB hyperinsulinemic hypoglycemia has not been fully elucidated. Several factors have been implicated in its etiology, including the increase in the incretins. Incretins are gut-derived hormones that are released into the blood post-prandially, and stimulate insulin release from the β cells of the islets of Langerhans, among other actions. The two incretins that are most often implicated are: (a) Glucagon-like peptide-1 (GLP-1), and (b) Gastric inhibitory peptide (GIP; also known as glucose-dependent insulinotropic polypeptide).

La Barre [45] originally proposed the name incretin in 1932 for a hormone extracted from the upper gut mucosa that had the ability to augment insulin response to nutrients, thus causing hypoglycemia. In 1971, Brown isolated GIP from intestinal mucosa [46]. It was renamed glucose-dependent insulinotropic peptide in 1973 after Brown and Dupre showed that GIP stimulated insulin secretion [47]. In 1983, Bell and colleagues [48] identified GLP-1 as a cleavage product of the pre-proglucagon gene, and since then it has been shown to function as an even more potent glucose-dependent incretin than GIP [49,50].

The levels of GLP-1 hormone increase after bariatric surgery, probably due to the rapid transit of unabsorbed nutrients to the jejunum and the ileum, the distal portion of which is the site of L cells, the source of GLP-1 [12,51–53]. For example, Rabiee and colleagues [31] studied four post-RYGB patients and reported 3–4 fold increase in GLP-1 levels in all subjects approximately one year after surgery and also a two fold increase in total GIP levels. Goldfine and colleague [22] found incretin levels to be 5–10 fold higher in post-RYGB patients compared to controls. GLP-1 has been implicated in increasing β -cell mass in rodents through proliferation and neogenesis, [54,55] and in decreasing β -cell apoptosis in humans. The GLP-1 induced hypertrophy of pancreatic β cells along with their hyperfunction appear to ultimately culminate in post-prandial hypoglycemia. Besides changes in the secretion of incretins, hypoglycemia in post-RYGB patients has also been attributed to several other possible mechanisms [31]. These include: (a) lack of reduction of β -cell mass which was constitutively increased during the preoperative obese state; (b) increased insulin sensitivity following weight loss; (c) inappropriate β -cell secretion following early entry of ingested nutrients into the small intestine (late dumping syndrome); and (d) abnormal counter-regulatory hormonal (glucagon) responses [56,57]. Alterations in other gastrointestinal hormones, including ghrelin, peptide YY (PYY) and leptin, have also

been implicated in glycemic patterns following RYGB [58,59], but the impact of their altered patterns of secretion in post-RYGB hypoglycemia remains unclear at present.

Meier and colleagues [30] proposed that β cells are hyperfunctioning in pre-surgical obese state and this hyperfunctioning persists post-operatively, a state wherein patients experience improved insulin sensitivity because of reduced fat mass. This increased sensitivity to insulin coupled with the patient's hyperfunctioning β cells precipitate the hypoglycemic episodes. Consistent with this idea are the findings that some patients with post-RYGB who underwent pancreatic resection did not meet the histologic criteria for nesidioblastosis. A single concept has yet not been agreed upon and therefore, all patients with hypoglycemic symptoms need to be carefully evaluated to avoid misdiagnosis.

Protective role of diabetes on post gastric bypass patients

Literature has suggested that most of the post-RYGB patients who develop clinically significant hypoglycemia do not have diabetes pre-operatively [14,22], a possible explanation being that the prerequisite for hyperinsulinemic hypoglycemia is increased β -cell function and decreased insulin resistance. Type 2 diabetes protects against this condition either through a decreased functional β -cell mass or through increased peripheral resistance, or both. Individuals with diabetes are less susceptible to incretin effects and they may require a longer time interval to develop excess islet mass and manifest significant hypoglycemia [22]. The hypoglycemia is "diabetes reversal in people who don't have diabetes," suggested Patti [25].

On the other hand, it is recognized that many RYGB patients with Type 2 diabetes mellitus demonstrate prompt resolution of their diabetes post-operatively [60–65]. In patients with impaired glucose tolerance most studies report high rates of prevention of progression to diabetes, while among those with diabetes, resolution of the disease is reported in 64 to 93% of the cases post-surgery [66]. Remarkably, diabetes typically remits within days to weeks after these operations. In a recent study conducted by Markuszewska and colleagues [67], 73 patients were included with Type 2 diabetes that underwent laparoscopic RYGB. Remission of diabetes was observed in 51 cases (69.8%) during hospitalization, while in 14 additional patients (19.1%), glycemia and glycated hemoglobin (HbA1c) levels were stabilized within 12 weeks postoperatively (total remission rate of 88.9%). This is too early to be explained by weight loss alone, suggesting that the effect of incretins is the most important mechanism behind the rapid improvement in diabetes in post-RYGB patients [68]. Other factors that might contribute include reduced calorie intake and decreased gastric emptying [69].

Diagnosis

Diagnostic criteria

Several diagnostic criteria have been suggested by different authors for post-RYGB hyperinsulinemic hypoglycemia and include: post-prandial hypoglycemia with neuroglycopenia occurring 1 year after surgery [14], a positive Whipple's triad (a. Typical symptoms of hypoglycemia; b. Low plasma glucose measured at the time of symptoms; c. Symptoms relieved by glucose administration) [70], occurrence of symptoms after a high

carbohydrate mixed meal, and lack of such response after a low carbohydrate mixed meal [14].

The diagnosis of dumping syndrome (early and late) is primarily made by obtaining a history of classic symptoms related to food intake [71,72]. Several scoring systems have been developed and used in various studies for diagnosing dumping syndrome including Sigstad's Diagnostic Index, the Visick classification, and the Arts scoring system [73,74].

Biochemical tests

Various specific biochemical tests can assist in confirming the diagnosis of hyperinsulinemic hypoglycemia in post-RYGB patients and also in distinguishing among its causes. Plasma glucose, insulin and C-peptide levels should be measured [14,15,25,38]. Based on laboratory values, Service and colleagues [24] describe hyperinsulinemic hypoglycemia as a serum insulin level of at least 3 uU/mL, a serum C-peptide level of at least 0.6 ng/mL with a concomitant serum glucose level of less than 55 mg/dL and the absence of sulfonylurea in the plasma. Proinsulin levels are usually elevated in patients with endogenous hyperinsulinemic hypoglycemia, with levels being substantially higher in insulinomas compared to nesidioblastosis [13,75]. However, to date, there is not much data on the role of proinsulin levels in the diagnosis of hypoglycemia and very few studies have reported their levels in post-RYGB patients [15,22]. Proinsulin levels might be useful tool in identifying the cause of hypoglycemia and should be employed in future research. GLP-1 levels, when measured, are found to be 3–4 fold higher in post-RYGB patients [31,76–78]. Other glucoregulatory factors, such as, glucagon levels can also be measured [31,78].

The 72-h diagnostic fasting test can be performed, which would be negative in cases of nesidioblastosis and dumping syndrome (normal fasting plasma glucose and insulin levels) [14,79], and positive in insulinoma [28]. Thus, negative 72 h fast is the best test to exclude insulinoma in post-RYGB patients [29].

Radiological investigations

Diagnostic imaging can be performed to rule out exocrine and endocrine pancreatic diseases, in particular insulinoma, in post-RYGB patients presenting with hypoglycemia [38,79]. Imaging techniques are often used to localize insulinoma and the available procedures include spiral CT, MRI, trans-abdominal ultrasonography, 111-In-pentetreotide imaging, and fluorine-18-dihydroxyphenylalanine positron emission tomography [80,81]. In patients with endogenous hyperinsulinemic hypoglycemia and negative non-invasive radiologic localization studies, endoscopic ultrasonography or a selective arterial calcium stimulation test with hepatic venous sampling can be performed to localize the tumor [82,83].

Selective arterial calcium stimulation test

Another specialized test called selective arterial calcium stimulation test (SACS) with hepatic venous sampling can be done to localize the area(s) of the pancreas that over-secrete insulin. It can be used to confirm any suspicion based on imaging modalities [35]. This test uses calcium gluconate injections, an insulin secretagogue, into arteries supplying the pancreas (splenic, superior mesenteric and gastroduodenal) with subsequent sampling of the

hepatic vein to test for insulin levels [37,84]. Localized increase in insulin secretion is observed in patients with insulinoma, whereas the diffuse pattern of insulin secretion favors hyperfunctioning β cells of nesidioblastosis in post-RYGB patients [24,38,79].

Histopathology

Diagnosis of nesidioblastosis is a challenge and can be confirmed only with the histopathological analysis of the pancreatic specimens [35,36]. The currently accepted major histological criteria include: (1) exclusion of an insulinoma by macroscopic, microscopic and immunohistochemical examination; (2) multiple β cells with an enlarged and hyperchromatic nucleus and abundant clear cytoplasm; (3) islets with normal spatial distribution of the various cell types; and (4) no proliferative activity of endocrine cells [38,42].

Glycemic pattern and continuous glucose monitoring (CGM)

Several authors have reported that in post-RYGB patients (with or without previous diabetes), glucose variability is exaggerated and there is a particular glycemic pattern, characterized by early hyperglycemic peaks after a glucose load, followed by a rapid fall in glycemia [14,34,39,85]. Kellogg and colleagues [14] reported that in post-RYGB patients, hyperglycemia associated with hyperinsulinemia occurred at 30 min after a high carbohydrate meal. These patients subsequently became hypoglycemic, with rapidly declining insulin levels, followed by spontaneous correction of their glucose levels. As the post-prandial glycemic swings are large and rapid, they can go undetected if blood glucose is not measured at the right time. Continuous glucose monitoring has been shown to be a useful tool for the diagnosis and the management of such episodes [39,44]. CGM revealed hypoglycemic episodes in free living circumstances that were not present during 72-h fasting and also correlated clinical signs with low interstitial glucose concentrations, eliminating a dumping syndrome [39].

Various CGM devices are available that provide a 3-day evaluation of patient's interstitial glucose levels. Meal size, nutrient composition, and concurrent activity level, which are likely different in real life compared to research settings, could play a role in the magnitude of post-prandial hypo-glycemia. The sensitivity and specificity to detect clinically significant hypoglycemia was reported to be 90% and 50% for CGM compared to 33% and 40% for mixed-meal tolerance test (MMTT) in a cohort of patients with a history of post-gastric bypass neuroglycopenia [44].

CGM is also a valuable diagnostic test not only for symptomatic hypoglycemic patients, but also for identifying those who remain asymptomatic at low glucose values. Many studies have reported a surprisingly high rate of completely asymptomatic hypoglycemia in post-RYGB patients after a mixed meal. In one series by Halperin et al. [34], 3 out of 6 (50%) completely asymptomatic individuals had an interstitial glucose below 70 mg/dL; 2 out of 6 (33%) had a value below 60 mg/dL (and as low as 40 mg/dL). On the other hand, 12.5% of asymptomatic patients were reported to have hypoglycemia (glucose <50 mg/dL) on CGM by Vidal et al. [86]. The differences may be related to different threshold definitions of hypoglycemia, small sample sizes in all studies, and methodology used for evaluation.

Overall, this rate is higher than the 3–4% rate of asymptomatic hyperinsulinemic hypoglycemia after LAGB [87]. Why some patients experience hypoglycemic symptoms at similar glucose concentrations while others do not remains incompletely understood. One possibility is that adaptive mechanisms to hypoglycemia or susceptibility to neuroglycopenia may vary between individuals after RYGB, but these potential differences need further study [34].

Treatment of hyperinsulinemic hypoglycemia after RYGB

Although the treatment of hyperinsulinemic hypoglycemia remains elusive, a number of studies have investigated the following approaches:

- a. Conservative measures (dietary modifications)
- b. Pharmacotherapy
- c. Surgical management

Conservative measures

Most patients with symptomatic hypoglycemia respond well to dietary modifications with a low carbohydrate diet [88]. Kellogg and colleagues [14] reported improvement in most of their post-RYGB patients following a low carbohydrate mixed meal.

Pharmacotherapy

For patients poorly responsive to dietary modifications alone, consideration should be given to a trial of pharmacological agents including diazoxide, octreotide, alpha glucosidase inhibitors (such as acarbose), or calcium channel blockers (such as verapamil, nifedipine and diltiazem) [9,39,40,89–93]. Table 4 summarizes the pharmacological agents used in various studies for the treatment of post-RYGB hyperinsulinemic hypoglycemia. Clinical treatment has been shown to achieve significant reduction of hypoglycemic episodes and their severity, especially in mild/moderate cases.

The goal of medical treatment is to establish a long-term therapy that will maintain blood glucose levels in a safe range. Acarbose is a complex disaccharide that delays the digestion of ingested carbohydrates, thereby resulting in a smaller rise in blood glucose concentrations following meals. This prevents hyperinsulinemia in post-RYGB patients. Diazoxide, on the other hand, works by suppressing insulin secretion by activating opening of the ATP-dependent potassium channel of beta cell. Closure of this channel by the elevation of ATP following binding to somatostatin receptors and is an even more potent inhibitor of insulin than somatostatin. Calcium antagonists work by their direct action on the pancreatic β cells to inhibit glucose-induced insulin secretion.

Surgical management

When medical treatment fails, surgery has been recommended. Partial, sub-total, and total pancreatic resections have been employed to treat refractory hypoglycemia [23,25,42]. However, the most appropriate surgical management is undefined [8]. Clancy and colleagues [23] suggested that the risk of recurrent symptomatic hyperinsulinism after limited

pancreatectomy is significant and relative euglycemia may be achieved with subtotal (85%) or total pancreatectomy. However, the end result of this approach is to cause iatrogenic diabetes, necessitating lifelong treatment with insulin; therefore surgery is being avoided as the treatment option in these patients nowadays [94]. To avoid the morbidity of these aggressive surgical procedures, laparoscopic reversal of RYGB and laparoscopic conversion of RYGB to a sleeve gastrectomy have been advocated [95]. Simple laparoscopic restoration of gastric restriction by placing an adjustable gastric band has also been reported to correct recurrent severe hypoglycemia and maintain weight loss [38]. Following surgical correction, a prolonged period of strict carbohydrate restriction is mandatory for the eventual resolution of excessive incretin secretion [96].

Although various treatment modalities have been proposed so far, the refractory nature of hyperinsulinemic hypoglycemia still makes it difficult to treat. Given the relatively young age of most patients undergoing RYGB, definitive management of this condition is highly desirable.

Hyperinsulinemic hypoglycemia in RYGB vs sleeve gastrectomy and gastric banding

Not much data are available on the prevalence of hyperinsulinemic hypoglycemia after other types of weight loss surgeries, such as laparoscopic adjustable gastric banding (LAGB) and laparoscopic sleeve gastrectomy (LSG). Therefore, it is difficult to understand differences in glucose and insulin regulation after these procedures. However, many studies have shown that the gut hormones that promote satiety (peptide YY, GLP-1) do not show the same magnitude of response following LSG and LAGB, as has been observed with RYGB [57,78,97]. The most obvious reason being the different paths of nutrient flow. As described above, after RYGB, nutrients pass directly from the gastric pouch to the distal small intestine containing L cells. This delivery of concentrated nutrients directly to L cells enhances GLP-1 secretion in RYGB patients [57]. As increased GLP-1 levels are the major factor contributing to hypoglycemia, this complication might not be as significant after LSG and LAGB as compared to RYGB.

Adiponectin is a peptide produced and released to the circulation exclusively by adipose tissue. It regulates insulin by mediating glucose and fatty acid metabolism and can also improve insulin sensitivity [58]. Most of the studies agree that the increase of adiponectin following weight loss surgery varies according to the type of surgery. In a review by Butner et al. [98] including nine studies, there was a greater percentage increase in adiponectin following RYGB (mean 69.9%) compared to restrictive procedures (LAGB and vertical banded gastroplasty; mean 35.8%) which corresponds to the increased insulin sensitivity and higher diabetes resolution rate after RYGB [1].

Conclusions and suggestions for future research

With the rising incidence of bariatric surgeries (8597 procedures in 1993 to a high of 115,194 in 2004) [3], and RYGB constituting majority of these procedures (45–54%) [2,4], it is important to be able to recognize the clinical picture of neuroglycopenia in post-RYGB

patients and to investigate and manage it accordingly. The post-prandial hypoglycemia might be related to the described changes in GLP-1 and other gut hormones. Although prevalence rates for this condition have been reported to be quite low, use of CGM suggests otherwise. Several causes have been described including nesidioblastosis, late dumping syndrome and rarely insulinoma. An understanding of the concepts of these different terms used is necessary for the management of this condition. A thorough and systematic evaluation, including history, serum biochemical analysis, and diagnostic testing might help in distinguishing among these diagnoses.

The dearth of data in this field is a cause of concern and calls for more research to answer some of these questions. Why does neuroglycopenia usually take 1 yr to develop and does not appear in the early post-op period? Is late dumping a separate phenomenon or is it the same as NIPS? Can measurement of proinsulin levels help us in identifying the cause of hypoglycemia? Does it affect patients with the same intensity and frequency after other types of weight loss surgeries? More and larger studies are required to answer the questions on complex hormonal system and other mechanisms underlying this complication of bariatric surgery.

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Table 1

Symptoms of early and late dumping syndrome.

Early dumping		Late dumping
- Desire to lie down	- Epigastric fullness	- Perspiration
- Palpitations	- Nausea	- Shakiness
- Diaphoresis	- Diarrhea	- Weakness
- Flushing	- Bloating	- Dizziness
- Fatigue	- Abdominal cramps	- Difficulty to concentrate
- Dizziness	- Borborygmi	- Hunger
- Faintness		
- Syncope		
- Headache		

Table 2

Differential diagnosis for post gastric bypass hypoglycemia.

	Late Dumping syndrome	NIPHS	Insulinoma
Postprandial hypoglycemia	Present	Present	Present
Fasting hypoglycemia	Absent	Absent	Present
Fasting serum insulin levels [9,16,22]	Normal	Normal	Elevated
Fasting serum C-peptide levels [9,16,22]	Normal	Normal	Elevated
Serum insulin, serum C-peptide, serum proinsulin levels during hypoglycemic episode [9,16,22]	Elevated	Elevated	Elevated
72-h fasting test	Negative	Negative	Positive
Selective arterial calcium stimulation testing	Negative [13,14,30] or diffuse insulin secretion [10]	Diffuse insulin hypersecretion	Localized insulin hypersecretion
Diagnostic imaging of pancreas	Negative	Negative	Positive for pancreatic mass/tumor
Treatment	- Dietary modifications [9,14,26,28] - Pharmacotherapy [11] - Surgical management [11]	- Dietary modifications for mild to moderate symptoms [14,26] - Pharmacotherapy - Surgical management	- Surgical management

Characteristics of bariatric surgery patients and reported time period between surgery and development of neuroglycopenia in various case studies.

Table 3

Authors	No. of subjects	Age range (years)	Gender (M/F)	Procedure	Time from surgery to 1st neuroglycopenic event (years)
Service et al. (2005) [24]	6	39–45	1/5	RYGB	Median: 1 Mean: 2.5
Patti et al. (2005) [25]	3	27–66	1/2	RYGB	Median: 1
Clancy et al. (2006) [23]	2	36–50	0/2	Vertical-banded gastroplasty	Mean: 1.3
Goldfine et al. (2007) [22]	12	Mean: 48 ± 3	2/10	RYGB	Median: 3
Kellogg et al. (2008) [14]	12	27–65	2/10	Vertical-banded gastroplasty	Mean: 3
Moreira et al. (2008) [9]	1	26	F	RYGB	Median: 1.9 Mean: 2.1
Z'graggen et al. (2008) [38]	12	27–64	2/10	RYGB	Median: 1.5 Mean: 1.7
Hanaire et al. (2009) [39]	1	41	F	RYGB	1.3
Spanakis et al. (2009) [40]	1	52	F	RYGB	Median: 2
Rabbee et al. (2010)	4	^a	4F	RYGB	Mean: 2.9
McLaughlin et al. (2010) [41]	1	35	F	RYGB	1
Mathavan et al. (2010) [42]	9	28–62	1/8	RYGB	Median: 1.4 Mean: 1.7
Salehi et al. (2011) [43]	12	30–53	1/11	RYGB	Mean: 3.7 ± 0.4
Hanaire et al. (2011) [44]	10	Mean: 42.3 ± 11.1	0/10	RYGB	Mean: 1.25 ± 0.6
Halperin et al. (2011) [34]	10	Mean: 51 ± 4	^a	RYGB	Mean: 8.9 ± 2.4
Myint et al. (2012) [15]	1	42	F	RYGB	6
Nadelson et al. (2012) [16]	1	51	F	RYGB	2
Qintar et al. (2012) [27]	1	40	F	RYGB	6

^aInformation not presented by author(s).

Table 4

Drugs used in the treatment of hyperinsulinemic hypoglycemia after bariatric surgery.

Author(s)	Drug	Description of drug	Dosage	Route of administration
Moreira et al. (2008) [9] Kellogg et al. (2008) [14] Hanaire et al. (2009) [39] Valderas et al. (2012) [91]	Acarbose	Alpha-glucosidase inhibitor	50 mg TID (100–200 mg daily)	Oral
Spanakis et al. (2009) [40] Rabiee et al. (2010) [31]	Diazoxide	Specific ATP-dependent potassium channel agonist of beta cells	50 mg BID	Oral
Rabiee et al. (2010) [31] Myint et al. (2012) [15]	Octreotide	Somatostatin analog	100 mcg BID	Subcutaneous
Moreira et al. (2008) [9] Hanaire et al. (2009) [39]	- Verapamil - Diltiazem - Nifedipine	Calcium channel blocker	80 mg BID	Oral