Successful management with GLP-1 agonists in postprandial hyperinsulinemic hypoglycemia after roux-en-y gastric bypass: clinical case description and review of the literature

Abstract

Introduction: Obesity is a global pandemic, in Colombia 49% of the adult population is morbidly overweight or obese. Bariatric surgery has proved to be the most effective long-term treatment for the management of morbid obesity and resolution of comorbidities metabolic and mechanical. Laparoscopic Roux-en-Y Gastric Bypass (LRYGB) is related to postprandial hyperinsulinemic hypoglycemia (PPH). This condition can occur up to 70% of patients with gastric resections and generate much morbidity to the patient.

Main: To describe the use of GLP-1 analogs in the management of patients with PPH secondary to bariatric surgery.

Methods: To describe a case of a patient with severe dumping referred for surgical reversion due to refractoriness to the extraintestinal medical management.

Results: Patient with severe hypoglycemia post LRYGB with 17 Sigstad score, 2 years of evolution with impairment of quality of life, is referred for interdisciplinary management in the obesity clinic of our institution. We start with Anatomical and physiological studies of their surgery, nutritional assessment, and endocrinology initiates liraglutide with improvement of 80% of the symptoms.

Conclusion: In LRYGB patients with hypoglycemia, HHP, nesidioblastosis and insulinoma should be ruled out as a diagnosis. The presence of wide anastomoses that allow fast gastric emptying, high carbohydrate foods favor the symptoms. The use of GLP-1 analogs together with dietary measures have shown that they improve symptoms and quality of life in the long term, apparently these results are due to the stabilization of insulin peaks and delayed gastric emptying.

Keywords: obesity, bariatric, surgery, gastric bypass, hypoglycemia

Introduction

Obesity is a public health concern. In 2017, 51% of the Colombian population was reportedly overweight or morbidly obese and suffered the effects of metabolic and mechanical comorbidities associated with these conditions. Medical management, such as dieting, exercise, or drug prescription, has limited success rates, and patients frequently relapse and gain the lost weight. Bariatric surgery is the most effective treatment resulting in significant weight loss and improvement of comorbidities associated with obesity. Bariatric procedures, particularly combined procedures (e.g., gastric bypass), may be related to adverse effects, such as nutritional deficits, dumping syndrome and postprandial hyperinsulinemic hypoglycemia (PPH) caused by anatomical changes, regulatory and kinetic mechanism-related problems in glucose adjustment as well as in the gastrointestinal and pancreatic hormones involved in homeostasis.

Dumping syndrome presents several vasomotor symptoms (e.g., palpitation, hypotension, tachycardia, fatigue, syncope, perspiration, epigastralgia, flushing, diarrhea, nausea, vomiting, colic, and abdominal distension) secondary to the passing of high-calorie foods through the small intestine. This leads to liquid retention, intravascular volume decreases, and hypotension due to the high osmolarity of liquids and their entrance into the intestinal lumen. Early dumping is present in 70%–75% of all gastric bypass patients during the first year after surgery and in 40% of all gastric sleeve patients during the first 30 min after food intake. Two scores are used to accurately diagnose dumping syndrome: Sigstad score [for which >7 points after glucose intake is diagnosed as dumping (Table 1)] and Arts score [based on the severity of the symptoms after glucose intake]. Dumping syndrome can be classified as early or late; it can also be classified according to its severity (0, none; 1, mild; 2, moderate; 3, severe) (Table 2).

Diagnosis is confirmed after the intake of 50 g of glucose dissolved in water. Glycemia, hematocrit, and cardiac frequency are evaluated every 30 min for 3 h. A positive diagnosis is considered when there is initial hyperglycemia with final hypoglycemia <60 mg/dL or 3.33 mmol/L, an increase in hematocrit of >3% or an increase of >10 heartbeats of basal frequency.

Historically, PPH is referred to as “late dumping” a clinical condition wherein symptoms of hypoglycemia present within the first to third hour after each meal. PPH is related to low levels of glycemia and is typically preceded by the peaking of the hyperglycemia and insulin levels. Such a condition could appear between the second and fourth year after surgery. Kellogg et al. reported that the prevalence of such a condition is 0.36%.
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Borborigmus
Headache
Vertigo
Irritability
Perspiration
Tremor
Perspiration, flushing
Loss of consciousness
Hunger
Table 2 Arts score

| Symptoms         | Points | Symptoms         | Points |
|------------------|--------|------------------|--------|
| Pre-Shock Or Shock | +5     | Vertigo         | +2     |
| Loss of consciousness or syncope | +4    | Headache        | +1     |
| Lying down or sitting down | +4    | Perspiration, flushing | +1 |
| Dyspnea          | +3     | Nausea          | +1     |
| Physical fatigue | +3     | Abdominal distension/ tympanites | +1 |
| Blurry vision tingling | +3   | Borborigmus     | +1     |
| Palpitation      | +3     | Eructation       | −1     |
| Restlessness     | +2     | Vomiting        | −4     |

Table 1 Sigstad score

| Symptoms         | Points | Symptoms         | Points |
|------------------|--------|------------------|--------|
| Restlessness     | +2     | Vomiting        | −4     |

Unlike early dumping, which involves symptoms occurring during the first hour after a high-calorie meal (involving refined sugars and fats) causing the release of intestinal hormones and the rapid entrance of liquids into the intestinal lumen, PPH occurs during the first 1–3 h after the intake of refined carbohydrates. The symptoms, however, may not be specific and could include Whipple’s triad: 1) symptomatic hypoglycemia, 2) low blood glucose levels, and 3) symptom disappearance after glucose administration. The symptoms of hypoglycemia can be autonomic (anxiety, perspiration, tremor, or palpitation) or neuroglycopenic (weakness, phosphenes, dizziness, blurry vision, or disorientation).

PPH is more frequent in patients who have undergone laparoscopic roux-en-Y gastric bypass (LRYGB) than in those who have undergone duodenal switch or gastric sleeve surgeries. The rapid transition of food from the gastric pouch to the small intestine causes an acute and excessive increase in the glucose and insulin levels. A peptide similar to glucagon type 1 (GLP-1) is released by the L intestinal cells in response to food; the peptide promotes insulin secretion. This postprandial increase in GLP-1 is the main mechanism underlying improvements in post-bypass diabetes and contributes to reactive hypoglycemia or PPH.

The alteration of glucose, insulin, and GLP-1 metabolism is not elucidated in patients who have undergone bypass surgery because some of them develop PPH while others do not. The risk factors in such patients are as follows: female sex, preoperative hypoglycemic symptoms, duration since surgery, and no diabetic history.

Methods

Description of the clinical case

A 42-year-old female presented with a history of morbid obesity (weight, 105 kg; BMI, 40). She had undergone LRYGB 4 years ago, during the postoperative period she didn’t present symptoms of hypoglycemia except for abdominal pain and occasional distension. A year and half after the surgery, she visited the emergency department with complaints of vomiting and abdominal distension and was diagnosed with intestinal obstruction. Her surgeon performed laparoscopy, which revealed a mesocolic hernia that was repaired. The patient reported symptoms of late dumping as of that time, although they were not disabling and were not related to the intake of simple sugars and carbohydrates. A year after this second surgery, she again presented symptoms of intestinal obstruction. The patient underwent laparotomy in which the professionals performed an intestinal resection procedure; the length of intestine excised is unknown as we didn’t have access to surgery records. Since then, the patient has been presenting symptoms, such as syncope, abdominal pain, the need to sit down, sweating, postprandial diarrhea, and steatorrhea. Hypoglycemia was reported using glucometry and blood glucose levels measurements and values of up to 24 mg/dL of blood sugar, according to the patient information.

The patient was valued for nutrition and endocrinology, however she refers that in her eating habits she consumes carbohydrates and sugars, and that she was not given medical management for the dumping syndrome. The patient was referred to Fundación Valle del Lili in Cali, Colombia for revisional surgery to normal anatomy and symptomatic management. She weighed 64 kg and had a BMI of 24.3 upon admission; she also received medical management and vitamin supplements. During the physical examination, professionals observed that she was sarcopenic and recommended no physical exercise due to hypoglycemia. Her Sigstad score was determined to be 17, which indicates the presence of dumping syndrome.

Several tests, such as endoscopy of the upper gastrointestinal system, were performed; the results revealed a small pouch with signs of reflux and wide Anastomosis (>6 cm). This generates a rapid transit to the intestine and explains the patient’s symptoms. Nutrition assessment was requested by those who made an adjustment of protein intake and use of complex carbohydrates and thickeners of the food.

The patient is hospitalized by the endocrinology service in which a meal test is performed with the presence of hypoglycemia and we could not access the records to these tests. this service was also performed an oral glucose tolerance test, which evidenced postprandial hyperglycemia (200–300 mg/dL), with the subsequent presence of hypoglycemia (44 mg/dL) and central glycemic values in 54 and 70 mg/dL respectively. Thus, treatment with GLP-1 (Victoza) agonist was prescribed to handle her hypoglycemias and with lipase to manage the steatorrhea. The patient’s progress was monitored. She responded well 1 month after the pharmacological and nutritional management, with no presence of hypoglycemies or hyperglycemias. There were no neuroglycopenic or autonomic symptoms. Her progress with the steatorrhea was adequate, which was managed with pancreatic lipase, leading to complete resolution of the symptoms and improvement in stool consistency. A year after the medical intervention, the patient...
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does not present any symptoms; she has also improved her eating habits and is performing physical exercise.

**Discussion**

More than 50% of the patients who undergo gastric bypass surgery present asymptomatic hypoglycemias. The hormonal and biochemical changes caused by PPH include increases in incretin levels, particularly GLP-1, and the insulinotropic polypeptide linked to glucose known as the gastric inhibitor peptide; increases in B-cell sensitivity to GLP-1; failure in the decrease or function of islet cells; increase in sensitivity to insulin due to weight loss; and inadequate hypersecretion of insulin and abnormal regulatory response to hypoglycemia.

In 1940, PPH was defined as a complication of gastric resection in patients with peptic ulcer. The first post-RYGB case was reported in 2005 with the introduction of bariatric surgery. Because an increase in insulin secretion was observed, the cause was suspected to be nesidioblastosis. The prevalence of PPH varies from 10%–75% depending on the diagnostic tool used. Using the Edinburgh hypoglycemia scale, Lee et al. reported that >30% postgastric bypass or sleeve patients presented symptoms of hypoglycemia and that 11.6% of them presented symptoms of severe hypoglycemia. Compared with patients who do not present hypoglycemia, those with symptoms of hypoglycemia reportedly have high postprandial levels of peptide C, insulin, and GLP-1 after LRYGB.

According to the American Diabetes Association, hypoglycemia is defined as a glucose value <70 mg/dL, although the value used in bypass patients is <50 mg/dL. Based on a case report, PPH is defined as hyperinsulinemia related to hypoglycemia and increases in peptide C. Recurrent hypoglycemia is known to cause dementia, lower patients’ quality of life, and increase the risk of mortality. The rise of accidental deaths in LRYGB patients is assumedly related to severe hypoglycemia. At least two peripheric blood samples are needed to diagnose PPH to have a record of the baseline and postprandial glycemia levels. Monitoring the patient for 3 days is more sensitive and allows for determining glucose levels while the patient continues his/her eating routine. The presence of hyperglycemia 30 min after eating followed by hypoglycemia and subsequent spontaneous normalization of glycemia is highly suggestive. In the oral glucose tolerance test measured at intervals of 120–240 min after the administration of 75–100 g of glucose, it was noted that 70% of post-bypass patients presented glycemia <60 mg/dL with and without symptoms. These results are less specific than the ones obtained in the mixed food tolerance test with a standardized percentage of proteins, carbohydrates, and fats. Treatment of PPH is a challenge. Multiple therapies have been described, including diet modifications, medical treatment, gastrostomy, gastric pouch restriction, bypass reversion, transformation to sleeve, and pancreatectomy.

Further, it is important to distribute meals in various intakes (six meals per day), avoiding liquid consumption 30 min before a solid meal as well as simple sugars, and increasing proteins and complex carbohydrates. Sixty grams of protein a day is recommended; avoiding foods with a high percentage of fats and carbohydrates as well as sugary liquids is also recommended. In addition, 64 ounces of non-caloric drinks are advised, although they cannot be ingested with food. Eating slowly, taking at least 30 min per meal, and starting with proteins is also important. When the patient shows symptoms of reactive hypoglycemia, he/she should drink half a glass of orange juice; to avoid the symptoms, the orange juice should be consumed 1 h after eating. The use of food thickeners also helps manage hypoglycemia.

Kellog et al. compared the effects of food tests with a high or a low percentage of carbohydrates (79% vs. 2%) in postprandial glycemia and PPH insulin. The result was that low carbohydrate meals lead to less glycemic fluctuations and lower insulin secretion. Moreover, there are multiple options for pharmacological therapy (Table 3). The efficacy of pharmacological management initially improves the symptoms, although long-term is not sufficient or adverse symptoms appear forcing suspension of the treatment.

Acarbose reduces glycemic peaks and insulin release caused by the inhibition of the alpha glucosidase enzyme present in the border of the intestinal brush responsible for transforming starch into glucose. Adverse effects, such as gas, distension, and diarrhea, limit its acceptance and effectiveness. Diazoxide is a vasodilator that inhibits insulin secretion via ATP-sensitive potassium channels in beta cells. This suppresses insulin secretion. Although tolerance to diazoxide is low due to edema and hyperglycemia, a dose of 100–200 mg eliminates the hypoglycemic symptoms.

The use of calcium channel-blockers decreases insulin release because of the blockage of calcium channels of the beta cells. This has proven to decrease hypoglycemic episodes and their intensity. The agonists of somatostatin block multiple hormones, including those in charge of metabolizing glucose (insulin, glucagon, and GLP-1). The use of somatostatin is limited owing to its adverse effects (including diarrhea and hyperglycemia) and its cost. XOMA 358 is a monoclonal antibody that is currently under investigation; it has been tested for PPH and congenital hyperinsulinism. A type IgG monoclonal antibody confers resistance toward insulin due to the linking to an allosteric location of the insulin receptor and inhibits auto phosphorylation and Akt signaling, which have been proven to increase postprandial glycemia peaks.

GLP-1’s role in PPH was established in the study conducted by Salehi et al. wherein the GLP-1 agonist Exedin 9-39 was administered in post-bypass patients with and without PPH. The result was the disappearance of hypoglycemia and reduction of postprandial hyperinsulinemic, indicating that high levels of GLP-1 contribute to increased postprandial insulin secretion and hypoglycemia.

Liraglutide (Victoza, Novo Nordisk Pharma, Clayton, North Carolina) is a GLP-1 agonist that was approved by the European Commission in 2009 as a treatment for diabetes mellitus 2 in adult patients; it was then approved in 2014 by the FDA as an option for chronic obesity together with physical activity and hypocaloric diet. It increases insulin production and reduces gastric emptying, thereby contributing to satiety through central mechanisms. Our patient was started on a 0.6–1.2 mg dose, which resulted in improvement of the symptoms, together with dietary management. In patients with gastric resection, rapid gastric emptying may lead to an early increase of postprandial glycemia serum levels and GLP-1, thereby leading to reactive hypoglycemia. The key point here is the rapid transit and onset of nutrients in the small intestine, which causes an increase in the glucose, insulin, GIP, and GLP-1 levels, and is the cause for hypoglycemia. GLP-1 agonists (Liraglutide) stabilized the amount of GLP-1 and reduced insulin peaks, thereby resulting in improvement of the symptoms.
If medical management does not improve the symptoms, surgical options, such as gastrostomy tubes, which carry food directly to the bypassed stomach and are a positive predictors of bypass reversion if it works properly, are considered. Restriction of gastrojejunostomy with a silastic ring, which slows down the food reaching the small intestine, may also be considered. Z’graggen et al. reported positive results for this technique in a cohort of 11 patients.

Bypass reversion has been described in small case series and is considered the last option in PPH management owing to its high morbidity and possibility of regaining the lost weight. Campos et al., in a study in which a follow-up of up to 22 months was performed and in which no additional episodes of neuroglucopenia occurred, concludes that a laparoscopic reversal of LRYGB to normal anatomy is feasible and may be a therapeutic option for selected patients with PPH. Although they pose technical challenges, the use of antiperistaltic agents has also been described. Bypass sleeve conversion has only been described in <10 patients with hypoglycemia resolution with little weight gain but a high reflux incidence. Currently, there is little evidence that this procedure is recommended as a PPH therapy. Finally, distal pancreatectomy has been described in >50 cases of PPH, although there have been reports of short-term improvement with recurrence of symptoms in approximately 50% of the cases.

**Conclusion**

After a bariatric procedure, PPH calls for a multidisciplinary approach because a great percentage of bypass patients present these symptoms. It is crucial to assess the patient and evaluate him/her, both anatomically and biochemically to establish adequate treatment. It is also quite important to modify the patient’s eating habits and make them avoid sugars and foods high in carbohydrates. An anatomical evaluation of the size of the anastomosis should be performed because it greatly influences the appearance of symptoms. Considering the pharmacological management, until this moment, GLP-1 agonists have been shown to improve long-term the symptoms with only few adverse effects. If medical management does not improve the symptoms, surgical options, such as bypass reversion, antiperistaltic agent use, or distal pancreatectomy, must be considered.

Our patient has been followed-up for 18 months and is now free of 80% of the symptoms; her quality of life, too, has improved.

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None.

**Conflicts of interest**

The authors declare no conflicts of interest.

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