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SCIENTIFIC LETTERS

Hypoglycemia after Roux-en-Y gastric bypass surgery

Hipoglucemia tras derivación gástrica en Y de Roux

To the Editor:

Morbid obesity is a medical condition associated with multiple comorbidities and increased mortality[1]. Because of its poor response to conservative treatment (dietary, behavioral, and pharmacological) and its increasing prevalence, an alternative treatment, bariatric surgery, has been developed. This surgical procedure has been shown to be effective for long-term weight reduction and the amelioration or resolution of associated comorbidities such as diabetes, arterial hypertension, and dyslipidemia.

The mid- and long-term complications of gastric surgery are well defined and include nutritional deficiencies, gastrointestinal complications, and neuropathy. An uncommon but severe complication, recently reported, is postprandial hypoglycemia[2], due to endogenous hyperinsulinemia. Although some authors consider this a late manifestation of dumping syndrome[3], its clinical characteristics, including severe neuroglycopenic symptoms, its late occurrence months or years after a gastric bypass and its lack of response to dietary treatment make it a well differentiated condition whose pathophysiological mechanisms have still to be clearly elucidated.

We report the case of a 41-year-old female patient with morbid obesity and no prior history of diabetes or similar clinical symptoms who experienced recurrent episodes of severe hypoglycemia one year after repeat gastric bypass surgery (conversion to Roux-en-Y). The patient first attended our department at 34 years of age. She reported progressive weight increase from adolescence, compulsive dietary habits with frequent binge eating, regular nibbling and multiple dietary regimens with subsequent weight gains despite receiving occasional pharmacological help. A physical examination found her to be 142 kg in weight, 164 cm in height, and to have a BMI (body mass index) of 52.8 kg/m^2. An oral glucose tolerance test (OGTT) was performed before surgery, and its only significant finding was an abnormally high insulin level at 2 hours (96.1 µU/mL). Blood glucose was within normal limits (132 mg/dL). Elective gastric bypass was performed, consisting of gastrojejunostomy and jejunojejunal anastomosis, leaving a 30 mL gastric reservoir with a feeding loop of 140 cm, a biliopancreatic loop of 80 cm, and a common loop of 340 cm. The patient's course was initially satisfactory, with a significant weight loss (decrease to 104 kg and a BMI of 38.6 kg/m^2). However, a partial weight recovery to 122 kg and a BMI of 45 kg/m^2 occurred after 2 years. A new surgical procedure was finally decided upon. This consisted of a lengthening of the gastric bypass with resection of the dilated cul-de-sac (15 cm) distal to anastomosis, and reconstruction of a new loop base at 80 cm from the ileocecal valve together with eventroplasty. One year after repeat surgery, the patient weighed 103 kg and had a BMI of 38 kg/m^2. The patient started to experience documented episodes of hypoglycemia (capillary blood glucose < 50 mg/dL, and plasma glucose 41 mg/dL) with mainly neuroglycopenic symptoms (weakness, dizziness and blurred vision, with occasional fall and trauma), gradually increasing in frequency to 1 or 2 weekly episodes, during the late postprandial period, unrelated to intake contents and never after prolonged fasting. There was a mild weight gain (109 kg). Thyroid function and pituitary-adrenal axis were normal. A fasting test performed was negative after 72 hours, and an OGTT resulted in a rapid increase in blood glucose at 30 and 60 minutes, elevated insulin response, and hypoglycemia at 180 minutes, with insulin profile and C peptide inappropriately high for that glucose level (Table 1). Reactive hypoglycemia after bariatric surgery was diagnosed, and frequent intakes every 3 hours, low in carbohydrates, and acarbose 50 mg 3 times daily were recommended and well tolerated (mild flatulence). After 3 months, the patient experienced a reduction in the frequency and severity of these hypoglycemic episodes.

The first cases of postprandial hypoglycemia after bariatric surgery were reported in 2005[2]. This complication occurs months or years after surgery and meets the criteria of so-called non-insulinoma pancreatogenous hypoglycemia syndrome[4]. Its incidence is considered to be low, but it has not yet been quantified[5].

As in our case, it usually occurs as hypoglycemic episodes with mainly neuroglycopenic clinical signs within 2 to 4 hours of intake. Diagnosis is based on a prolonged OGTT, which shows a characteristic pattern, with hyperglycemia and hyperinsulinemia at 30 minutes, a decrease in the following 2 to 3 hours to a blood glucose level lower than

Table 1 Results of the oral glucose tolerance test in the reported patient

	Glucose (mg/(dL)	Insulin (mcg/L)	C peptide (ng/mL)
Basal	85	8.9	2.72
30 minutes	218	91.2	10.01
60 minutes	224	133	15.46
90 minutes	112	44.2	10.21
120 minutes	73	16.9	6.52
180 minutes	49	7.2	3.95
240 minutes	72	2.7	2.35
300 minutes	84	5.4	2.17

50 mg/dL with inappropriately high insulin and peptide C levels, and finally, spontaneous normalization. A fasting test and pancreatic imaging techniques yield normal results. This type of response is similar to that reported in our patient.

Some authors consider this condition a late manifestation of dumping syndrome[3]. However, the case reported showed differences in both its clinical and temporal aspects. In agreement with other authors[6], we think that these are 2 clearly differentiated conditions with different pathophysiological mechanisms. In reactive hypoglycemia there is a severely impaired regulation of insulin secretion associated with pathological changes that perpetuate this situation. Other proposed mechanisms (decreased insulin resistance following gastric bypass, together with hypertrophy of pancreatic beta cells in morbid obese patients, detected early after surgery[7]) also cannot explain this time lapse before the occurrence of reactive hypoglycemia.

Thus, there could be a functional problem associated with metabolic changes, occurring as a result of anatomical changes made in the gastric bypass, which would induce a rapid flow of nutrients to the distal ileum and an increased release of GLP-1 (glucagon like peptide-1) by L cells, as shown by Goldfine et al[8]. This peptide has been related to reactive hyperglycemia, to the increased mass of these cells due to their induced proliferation and neogenesis, and to decreased apoptosis in pancreatic islets in rodents. On the other hand, studies in patients who required surgical treatment as partial pancreatectomy[9] have shown diffuse hyperplasia of pancreatic islets from the ductal epithelium, consistent with the concept of nesidioblastosis. Beta cell hyperactivity and an increased expression of protein factors associated with neogenesis of pancreatic islets have also been suggested[10].

The objective of medical treatment is to avoid the postprandial hypoglycemic peak by dietary measures such as fractionation of intake and avoidance of sugar-rich food, and the administration of acarbose, which delays carbohydrate absorption. In patients with a poor response, somatostatin treatment has been attempted, but with poor results, and surgery has been used as a last resource[11].

In conclusion, hypoglycemia following gastric bypass remains a rare complication, but one that is more common than it once was because of the growing use of bariatric surgery. It is a potentially serious condition because of its clinical impact. Its pathophysiological mechanisms need to be established to improve our therapeutic approach, and patients predisposed to experience the condition should be identified. Although the starting point appears to be rapid nutrient passage with excess release of GLP-1 by L cells in the distal ileum, which causes secondary hyperstimulation of pancreatic beta cells, other anatomical, hormonal, and genetic factors could contribute to the occurrence of the condition, and further studies are required.

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Malignant glucagonoma: an uncommon cause of new onset diabetes

Glucagonoma maligno como causa infrecuente de diabetes de inicio

To the Editor:

A 44-year-old female patient was initially seen at the endocrinology department for hyperglycemia (random blood glucose level of 580 mg/dL and glycosylated hemoglobin of 10.3%) associated with weight loss, cardinal clinical signs, and severe asthenia. Basal-bolus insulin therapy was started because of the presence of clinical signs of insulinopenia. Two weeks later, the patient started to experience erythematous-desquamative plaque-like lesions in the skin of the upper and lower limbs. The lesions progressively enlarged, were coalescent, and had a patchy distribution. They gradually regressed and cleared at their centres. Other periorificial erythematous and crusty lesions (perinasal, peribuccal, and perianal), severe glossitis, nail dystrophy, progressive alopecia, and blepharitis were also observed. The patient also showed a significantly impaired general condition and mood with progressive weight loss and severe anorexia. She was therefore admitted for a complete work-up.

Initial laboratory tests showed normocytic and normochromic anemia (hemoglobin 10 g/dL), hypoproteinemia with hypoalbuminemia (total protein 5.6 g/dL [normal range (NR): 6.5-8 g/dL] and albumin 2.9 g/dL [NR: 3.5-5.3 g/dL]), and decreased plasma zinc levels (46.9 µg/dL; NR: 70-120 µg/dL). A vulvar tissue biopsy was reported as a skin fragment with a neutrophilic pustule with focal parakeratosis, acanthosis, and a perivascular mixed inflammatory infiltrate suggesting necrolytic migratory erythema (NME). Based on the presence of these lesions together with diabetes mellitus and the systemic picture, glucagon and chromogranin A levels were measured. High glucagon levels were found in two measurements (510 and 655 pg/mL; NR: 59-177 pg/mL), and a high chromogranin A value was also measured (798.8 ng/mL, NR: 19.4-98.1 ng/mL). Glucagonoma was suspected, based on clinical and biochemical evidence, and imaging tests were performed to locate the lesion. In these tests (including helical computed tomography [CT] of the abdomen, cholangio-MRI, and echoendoscopy in chronological order), no tumor lesions were seen in the pancreas or in other locations. In order to locate the lesion, a scan was performed using ^{111}In-DTPA-D-Phe-octreotide (Octreoscan®). This showed a large hyperuptake site of the tracer in the epigastrium midline corresponding to the pancreatic anatomical area, and an additional, less intense accumulation of the radioactive drug in the hepatic border (Fig. 1).

Treatment was started with octreotide 50 µg daily by the subcutaneous route every 12 hours for two weeks, and every 8 hours thereafter. This treatment was well tolerated and induced a clinical improvement in the patient, with the virtual disappearance of skin lesions and a marked decrease in insulin requirements.

Pancreatic glucagonoma was diagnosed, and surgery was performed. Intraoperative examination confirmed the presence of a large lesion involving the body and tail of the pancreas. Laparoscopic corporocaudal pancreatectomy was performed, and the liver surface was examined by intraoperative ultrasound, which showed no lesions. The surgical specimen weighed 46 g and was 8.5 x 4.5 cm in size. A pathological study revealed a disorganized parenchyma with multiple confluent nodules. Necrosis, multiple vascular invasions, and infiltration of peripancreatic soft tissue and resection margins were seen by light microscopy. Immunohistochemical staining was positive for neuroendocrine differentiation markers such as chromogranin and CD56, and for glucagon as a specific hormone marker. The Ki-67 index was 5%-10%. The pathological diagnosis was a multifocal and histologically malignant endocrine tumor consistent with glucagonoma (Fig. 2).

After surgery, octreotide treatment was discontinued, skin and mucosal lesions disappeared completely, and insulin administration was not required. Supplemental tests performed after surgery revealed the disappearance of the hyperuptake site of the tracer located in the epigastrium midline, and no other pathological uptake was seen (Octreoscan®). Abdominal MRI after surgery showed no lesions suggesting metastases or signs of locoregional recurrence.

Chromogranin A levels decreased after surgery, but remained high (577 ng/mL), and glucagon levels returned to normal (71 pg/mL). A genetic study was requested in order to rule out the possibility that the glucagonoma occurred in the setting of multiple endocrine neoplasia type 1 (MEN 1).