CASE REPORT

Postgastric bypass hypoglycaemia in a patient with end-stage renal disease: a diagnostic and management pitfall

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SUMMARY

Roux-en-Y gastric bypass (RYGB) surgery is currently one of the most popular procedures to aid weight loss. Hypoglycaemia associated with gastric bypass surgery is an underdiagnosed but life-threatening potential consequence of the surgical procedure. We present a case of a 44-year-old woman with end-stage renal disease presenting with refractory hypoglycaemia after 10 years of RYGB. Extensive history and work-up excluded medications, renal disease, insulinoma and dumping syndrome as the cause of hypoglycaemia. Dietary modifications or pharmacological trial of drugs did not ameliorate her symptoms with progressive worsening of hypoglycaemia leading to continuous dextrose infusion. Distal pancreatectomy was performed with subsequent resolution of hypoglycaemia. Surgical pathology results showed diffuse hyperplastic islet cells, confirming the diagnosis of postgastric bypass hypoglycaemia.

BACKGROUND

Roux-en-Y gastric bypass (RYGB) is the most frequently performed bariatric surgery for the effective treatment of morbid obesity.¹ Some of the potential complications resulting from Roux-en-Y surgery include postoperative bleeding, wound infection, anastomotic leak, anastomotic stricture, marginal ulcers, thromboembolism, cholelithiasis, bowel obstruction, nutritional deficiencies and hypoglycaemia which can be severe and recurrent. Hypoglycaemia as a complication of RYGB was first documented by Service *et al* in 2005.² The prevalence of postbariatric surgery hypoglycaemia has been reported to be <1%.³ Inadequate recognition and reporting of hypoglycaemic symptoms can account for this low prevalence reported in older literature. More recently, the prevalence of hypoglycaemia post RYGB has been reported as high as 34%.⁴ In contrast to dumping syndrome, which is noted soon after the surgery and improves with time, post RYGB hypoglycaemia presents several months to years after surgery. Its hallmark feature is severe postprandial neuroglycopenia, which is characteristically absent in dumping syndrome. We report a case of a 44-year-old woman with end-stage renal disease (ESRD), status post RYGB, who presented to the hospital with recurrent episodes of postprandial dizziness and near-syncope to increase

awareness of this challenging diagnosis in this disease group.

CASE PRESENTATION

A 44-year-old woman with a medical history significant for ESRD secondary to focal segmental glomerulonephritis and morbid obesity necessitating RYGB 10 years ago presented to the hospital with recurrent episodes of postprandial dizziness and near-syncope. She denied any flushing or diaphoresis during these spells. The patient was on haemodialysis three times a week. There was no relation of hypoglycaemia episodes with dialysis sessions. Medications were reviewed, none of which had a potential side effect of hypoglycaemia. Family history was positive for diabetes mellitus type 2 in her mother. The patient was a non-smoker and non-alcoholic with no history of illicit drug use. She weighed 154 kg prior to the procedure and experienced a weight loss of 64 kg within the next year, and her weight had remained stable at 88 kg (body mass index 32.6 kg/m²). Physical examination, including neurological examination, was unremarkable.

INVESTIGATIONS

Laboratory data revealed random postprandial serum glucose of 66 mg/dL with intermittent drop down in serum glucose to 37 mg/dL. Blood drawn from the patient at the time of hypoglycaemia revealed that serum insulin level was 8 µIU/mL, serum proinsulin level of 5.2 pmol/L and C peptide level of 6.7 ng/mL. Serum sulfonylurea and repaglinide screen was negative. Morning cortisol and thyroid-stimulating levels were within normal limits (13.5 µg/dL and 1.33 µIU/mL, respectively). Mixed meal tolerance test was not performed. CT of the abdomen did not show any pancreatic mass. Endoscopic ultrasound to assess pancreatic anatomy was not feasible in the setting of prior gastric bypass surgery.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses include dumping syndrome, insulinoma, exogenous insulin intake, postgastric bypass hypoglycaemia (PGBH), non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS), postdialysis hypoglycaemia and spontaneous uremic hypoglycaemia.

Dumping syndrome can be classified as early or late dumping syndrome. Early dumping syndrome, as the name suggests, occurs early in

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the postoperative period and is due to rapid fluid shift from plasma to bowel in response to rapid emptying of hyperosmolar carbohydrates into small intestine.⁴ As a consequence, gastrointestinal and vasomotor symptoms are seen. Symptoms of early dumping syndrome usually occur within 15 min of ingestion of carbohydrate-rich diet and include abdominal pain, tachycardia, nausea, vomiting, diaphoresis, weakness, dizziness and flushing, but not hypoglycaemia or neuroglycopenia.⁴ On the contrary, late dumping syndrome can present months to years after gastric bypass surgery. Symptoms of late dumping syndrome usually occur 1–3 hours after ingestion of carbohydrate-rich meal as a result of excessive insulin secretion in response to meal.⁴ Symptoms of late dumping syndrome include diaphoresis, dizziness and fatigue. Both early and late dumping syndromes respond very well to dietary modifications in majority of the cases. PGBH is differentiated from late dumping syndrome by the presence of severe neuroglycopenic symptoms and unresponsiveness to dietary modifications.⁴ Hallmark of PGBH is neuroglycopenia which occurs as a result of deprivation of glucose in the brain. Neuroglycopenia can present as confusion, drowsiness, difficulty speaking, blurred vision, seizures and coma.⁴ It is more common in females, and the symptoms can start from months to years after the gastric bypass surgery. In our patient, the symptoms of postprandial dizziness and near-syncope after 10 years of gastric bypass suggest PGBH. In contrast to dumping syndrome, PGBH responds minimally to dietary modification and often requires pharmacological and surgical treatment. Although the pathogenesis of NIPHS is similar to PGBH, diagnostic criteria of this syndrome only include patients without gastric bypass surgery.^{4,5} Since our patient had a history of RYGB surgery, she cannot be labelled as having NIPHS. Exogenous insulin and hypoglycaemic drug intake was ruled out by the raised C peptide level and negative blood screen for serum sulfonylurea and rapaglinide, respectively. CT abdomen was done to rule out insulinoma. Insulinoma primarily causes fasting hypoglycaemia rather than postprandial hypoglycaemia which occurs in the patients with PGBH.

In our patient, due to ESRD, postdialysis hypoglycaemia was an important differential diagnosis to be considered. Postdialysis

hypoglycaemia occurs due to glucose-induced hyperinsulinaemia which is caused by the high amount of glucose in the dialysate.⁶ In our patient, no correlation of hypoglycaemic symptoms was found with the dialysis sessions.

TREATMENT

Dietary modification by decreasing the carbohydrate content was done, but it did not ameliorate her symptoms. A trial of acarbose, diazoxide and somatostatin was attempted, but it did not lead to clinical improvement. The patient's symptoms progressively worsened and necessitated readmission and continuous 10% dextrose infusion to prevent hypoglycaemia. Figure 1 shows a graphical representation of blood sugar values over time during this admission; arrow indicates the day of surgery and discontinuation of 10% dextrose infusion. Since all medical options to manage hypoglycaemia were exhausted, the patient was given different surgical options including gastric bypass reversal and pancreatectomy. The patient chose the latter and underwent open distal pancreatectomy. Subsequently, the patient had resolution of hypoglycaemia.

OUTCOME AND FOLLOW-UP

The resected distal pancreas measured 16×4.1×2.8 with a 14.1×10.7×4.9 cm attached spleen. No tumour was identified in the pancreas. Histological examination of the pancreas demonstrated increase of hyperplastic pancreatic islets (figure 2A) that varied in size and shape and focal ductular-insular complexes (figure 2B). Some islet cells displayed enlarged hyperchromatic nucleus (figure 2C). The overall histological findings are consistent with those of nesidioblastosis.

The patient showed consistent improvement in blood glucose levels with no symptoms of hypoglycaemia at 3-month follow-up.

DISCUSSION

Roux-en-Y gastric bypass surgery involves reconstructing the gastrointestinal tract by creating a gastric pouch that bypasses a large portion of stomach and duodenum and empties into

Figure 1 A graphical representation of fingerstick blood glucose values over time. Arrow: Day of surgery and discontinuation of 10% dextrose at an infusion rate of 100 mL/hour.

Figure 2 Histological examination of the pancreas demonstrating increase of hyperplastic pancreatic islets (A) that varied in size and shape and focal ductular-insular complexes (B). Some islet cells displayed enlarged hyperchromatic nucleus (C).

jejunum. This leads to rapid emptying of ingested food directly from the stomach to small intestine. RYGB aids in weight reduction by decreasing the amount of food that can be ingested and the amount of nutrients that can be absorbed in addition to promoting early satiety.

The exact pathophysiology of post Roux-en-Y gastric bypass hyperinsulinemic hypoglycaemia (PGBH) is still under investigation. It is hypothesised that anatomical and physiological changes post RYGB which include changes in glucose regulatory mechanisms, changes in gut and pancreatic hormones and altered gastric emptying and nutrient absorption play a role.⁷ Current research suggests that after RYGB, food intake and rapid gastric emptying trigger an excessive rise in glucose, which stimulates glucagon-like peptide-1 (GLP-1) secretion. GLP-1 binds to pancreatic beta cell receptors and stimulates release of insulin. In the presence of glucose, GLP-1 also inhibits the release of glucagon. It is hypothesised that these patients have increased secretion of GLP-1 and subsequent increase in insulin in response to a mixed meal resulting in postprandial hypoglycaemia.^{4,8} Another potential theory describes pancreatic islet cell hyperplasia (nesidioblastosis) due to increased levels of GLP-1 resulting in dysregulated insulin secretion.² Nesidioblastosis is diffuse islet hypertrophy and/or hyperplasia with enlarged hyperchromatic beta-cell nuclei in the absence of a mass such as insulinoma in the pancreas. On histological examination of the pancreas in our patient, hypertrophic islets associated with scattered islet cells displaying hyperchromatic nuclei and ductular-insular complexes were seen, consistent with nesidioblastosis.

The kidneys are an important organ in glucose metabolism. Renal gluconeogenesis is impaired in patients with renal failure. Gluconeogenesis is an important mechanism that protects against hypoglycaemia. Insulin is freely filtered at the glomerulus and reabsorbed in the proximal tubule. Insulin clearance is impaired in patients with chronic kidney disease (CKD), resulting in increased half-life of insulin. C peptide is also excreted by the kidneys. Therefore, levels of insulin and C peptide are known to be elevated in patients with CKD,⁵ but no normal values for euglycaemic patients with CKD are known.

In order to diagnose hypoglycaemia, it is important to identify Whipple's triad which includes (1) the presence of hypoglycaemia symptoms, (2) a low plasma glucose level (typically less than 55 mg/dL) at the time of symptoms and (3) improvement in symptoms after food intake.⁷ The patients with post RYGB hypoglycaemia rarely report fasting hypoglycaemia. Their hypoglycaemic symptoms usually start 1–2 hours after meals. A detailed history with emphasis on the timing of onset of symptoms in relation to food ingestion is crucial. Similar to PGBH, patients with insulinoma have inappropriately normal or high insulin and C peptide levels at the time of plasma glucose level <55 mg/dL. The difference is in the timing of hypoglycaemic symptoms which occur in fasting state in majority of patients with insulinoma and in postprandial state in majority of patients with PGBH.⁴

It is reasonable to look for alternate causes of hypoglycaemia in RYGB patients. Laboratory testing should include thyroid-stimulating hormone (TSH), morning cortisol and insulin-like growth factor-1 levels to rule out hormonal deficiencies as a cause of hypoglycaemia. Liver and kidney functions should be assessed to rule out liver disease or renal insufficiency as a cause of hypoglycaemia.^{4,7} In spite of having ESRD and being on haemodialysis, our patient's episodes of hypoglycaemia did not correlate with the haemodialysis or posthaemodialysis sessions and were most often postprandial. Also, the pathology report confirmed nesidioblastosis as the most likely cause of hypoglycaemia.

In the presence of hypoglycaemia, if plasma insulin and C peptide levels are high, it is called hyperinsulinemic hypoglycaemia. The Endocrine Society uses plasma insulin level of >3 μ U/mL and C peptide level of >0.6 ng/mL in the presence of hypoglycaemia (blood glucose level of $\leq$ 55 mg/dL) as definition criteria of hyperinsulinism.⁹ In other studies, the criteria to diagnose hyperinsulinemic hypoglycaemia have been described as documented plasma glucose $\leq$ 55 mg/dL (or 3.0 mmol/L), a plasma insulin $\geq$ 3 μ U/mL (inappropriately high due to dysregulation of beta cell function), C peptide $\geq$ 0.2 nmol/L, a plasma proinsulin $\geq$ 5.0 pmol/L and a beta hydroxybutyrate $\leq$ 2.7 mmol/L.⁴ Our patient's TSH and morning cortisol levels were normal. Documented plasma glucose level was <55 mg/dL, plasma insulin level was >3 μ U/mL and C peptide level was >0.6 ng/mL.

Other tests to rule out alternative diagnosis are sulfonylurea and repaglinide screening (to rule out exogenous causes of hypoglycaemia) and imaging studies of the abdomen (to rule out insulinoma and other neuroendocrine tumours).

Management starts with dietary modification. Since it is hypothesised that rapid gastric emptying and rapid and excessive glucose absorption postgastric bypass surgery stimulates GLP-1 secretion resulting in increased pancreatic beta cell insulin release, reducing the amount of carbohydrate in the diet would decrease postprandial hypoglycaemic events. The recommended daily diet is a total of six meals with three main meals and three small meals. Alpha glucosidase inhibitor, acarbose, is added if patients are refractory to dietary modifications alone.^{4,7,10} Somatostatin analogue (octreotide), diazoxide and calcium-channel blockers (verapamil and nifedipine) can be used to decrease the pancreatic beta cell insulin secretion.⁴ Recently, GLP-1 agonists have been suggested as an upcoming treatment option for patients with PGBH.¹¹ They work as glucose stabilisers by downregulating insulin secretion and upregulating glucagon level during hypoglycaemia. It is conceived that long-acting GLP-1 analogues persistently activate GLP-1 receptors leading to effective control of postprandial hypoglycaemia of gastric bypass.¹¹ However, limited data exist regarding efficacy and safety of these drugs in patients with ESRD. Exenatide is renally excreted and is not recommended for use in patients with ESRD. Liraglutide, albiglutide and dulaglutide are not renally eliminated, but caution

Reminder of important clinical lesson

is recommended when initiating or escalating the doses of these drugs in patients with renal impairment. Furthermore, these drugs have not been studied in ESRD patients with PGBH.

PGBH which is refractory to diet and pharmacological therapy necessitates surgical intervention, as what happened in our case. Reversal of gastric bypass is reported to decrease the symptoms of hypoglycaemia and neuroglycopenia significantly.^{4–7} Another surgical treatment option for refractory cases is pancreatectomy. Recurrence of hypoglycaemia is observed in patients with limited pancreatectomy.¹² As a result, Clancy *et al*¹² suggested subtotal (85%) or total pancreatectomy to resolve hypoglycaemic and neuroglycopenic symptom. The complication of this procedure is iatrogenic diabetes which necessitates lifelong treatment with insulin. Our patient opted for pancreatectomy over reversal of bypass.

Patient's perspective

I have done very well since the surgery but I have had to limit my intake of carbohydrates to less than 25 g per day with a protein intake of 75–90 g per day. I still do not have any signs and symptoms of hypoglycemia until my sugar is well controlled. I am finding this very fascinating (even though very scary in my position) and very preventable in today's youth when caught early. Thank you very much for digging into this case and furthering medical as well as community knowledge.

Learning points

- ▶ As the number of patients undergoing bariatric procedures continues to increase, it is imperative that physicians be aware of the potential complications of these procedures including PGBH.
- ▶ Diagnosis of PGBH in patients with concomitant ESRD is quite challenging.
- ▶ A better understanding of the symptom recognition, diagnosis and different management options of this challenging diagnosis is required.

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REFERENCES

- 1 DeMaria EJ, Pate V, Warthen M, *et al*. Baseline data from American Society for Metabolic and Bariatric Surgery-designated Bariatric Surgery Centers of Excellence using the Bariatric Outcomes Longitudinal Database. *Surg Obes Relat Dis* 2010;6:347–55.
- 2 Service FJ, Thompson GB, Service FJ, *et al*. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med* 2005;353:249–54.
- 3 Sarwar H, Chapman WH, Pender JR, *et al*. Hypoglycemia after Roux-en-Y gastric bypass: the BOLD experience. *Obes Surg* 2014;24:1120–4.
- 4 Rariy CM, Rometo D, Korytkowski M, *et al*. Post-gastric bypass hypoglycemia. *Curr Diab Rep* 2016.
- 5 Sechi LA, Catena C, Zingaro L, *et al*. Abnormalities of glucose metabolism in patients with early renal failure. *Diabetes* 2002;51:1226–32.
- 6 Arem R. Hypoglycemia associated with renal failure. *Endocrinol Metab Clin North Am* 1989;18:103–21.
- 7 Fischer LE, Belt-Davis D, Khoraki J, *et al*. Post-gastric bypass hypoglycemia: diagnosis and management.
- 8 Meier JJ, Butler AE, Galasso R, *et al*. Hyperinsulinemic hypoglycemia after gastric bypass surgery is not accompanied by islet hyperplasia or increased beta-cell turnover. *Diabetes Care* 2006;29:1554–9.
- 9 Ritz P, Vauras C, Barigou M, *et al*. Hypoglycaemia after gastric bypass: mechanisms and treatment. *Diabetes Obes Metab* 2016;18:217–23.
- 10 Frankhouser SY, Ahmad AN, Perilli GA, *et al*. Post-gastric-bypass hypoglycemia successfully treated with alpha-glucosidase inhibitor therapy. *Endocr Pract* 2013;19:511–4.
- 11 Abrahamsson N, Engström BE, Sundbom M, *et al*. GLP1 analogs as treatment of postprandial hypoglycemia following gastric bypass surgery: a potential new indication? *Eur J Endocrinol* 2013;169:885–9.
- 12 Clancy TE, Moore FD, Zinner MJ. Post-gastric bypass hyperinsulinism with nesidioblastosis: subtotal or total pancreatectomy may be needed to prevent recurrent hypoglycemia. *J Gastrointest Surg* 2006;10:1116–9.

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