

CASE REPORT

Prolonged successful therapy for hyperinsulinaemic hypoglycaemia after gastric bypass: the pathophysiological role of GLP1 and its response to a somatostatin analogue

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Abstract

Background: Spontaneous hyperinsulinaemic hypoglycaemia following gastric bypass surgery (GBS) is increasingly recognised. However, its pathophysiology remains unclear. Some patients require pancreatectomy. Medical therapy with calcium channel blockers, acarbose and diazoxide has been reported to be beneficial but has variable adherence and response.

Method: We demonstrate the role of GLP1, counter-regulatory hormones and the subsequent response of GLP1 to somatostatin analogue therapy in a 42-year-old woman with persistent neuroglycopenia 6 years after GBS. Plasma GLP1, insulin and glucose were measured for 5 h on three settings: i) a 75 g oral glucose tolerance test (OGTT); ii) a standard liquid test meal (LTM); and iii) an OGTT 30 min after a s.c. injection of 100 µg octreotide.

Results: In comparison with obese non-diabetic controls, the patient had an elevated fasting and a markedly enhanced GLP1 response during the OGTT, followed by an exaggerated insulin response and a subsequent low glucose level. The GLP1 response to a LTM was similar but greater. Octreotide given prior to the OGTT attenuated both the GLP1 and insulin responses and abolished hypoglycaemia. Octreotide therapy significantly improved the patient's neuroglycopenic symptoms. The hormone profile was reassessed after 6 months following the LTM preceded by octreotide injection. Peak GLP1 and insulin responses were less pronounced than pretreatment responses and without hypoglycaemia. The patient was treated with lanreotide and had remained symptom-free and euglycaemic for 4 years.

Conclusion: An exaggerated incretin response following altered gastrointestinal anatomy was the likely cause of hypoglycaemia in our GBS patient. Somatostatin successfully suppressed this response acutely and in the long term, thereby avoiding pancreatectomy and its sequelae.

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Introduction

Bariatric surgery is an effective treatment for severe obesity, often leading to the 'remission' of type 2 diabetes (1, 2) and a reduction in cardiovascular events and mortality. Spontaneous hypoglycaemia is an increasingly recognised complication of gastric bypass surgery (GBS) (3) and also gastric banding surgery (4). Various mechanisms have been suggested as the cause of spontaneous persistent hyperinsulinaemic hypoglycaemia (PHH). We describe a reversal of PHH with octreotide therapy in a patient presenting with this symptom 6 years after GBS.

History

A 36-year-old woman presented with a history of severe obesity since a teenager. She failed to maintain

weight loss after multiple weight interventions, including dietary counselling, low-energy liquid diets, jaw wiring and anti-obesity pharmacotherapy. She developed type 2 diabetes at the age of 36 years and was treated with metformin. Subsequently, she underwent GBS, weighing 165 kg with a body mass index (BMI) of 71 kg/m². Following the surgery, anti-diabetic medication was withdrawn and she remained 'diet controlled' thereafter. At 18 months post-GBS, she required revision surgery for staple disruption and further bypass of a loop of the small intestine was performed. She achieved a steady weight loss over the first 2 years and maintained a 53% weight loss, achieving a BMI of 32.3 kg/m².

At 6 years after the GBS, with a BMI maintained at 37.2 kg/m², she reported symptoms suggestive of hypoglycaemia occurring at night and in response to

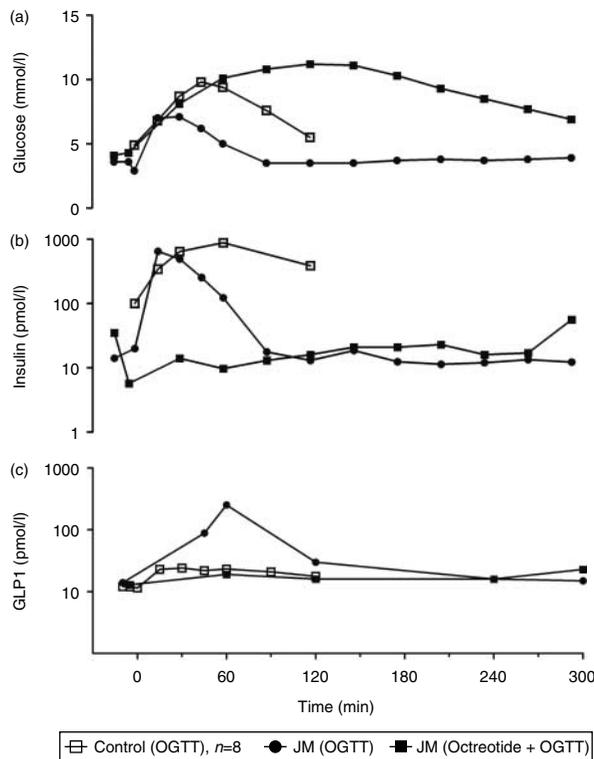


Figure 1 (a) Glucose, (b) insulin and (c) GLP1 response to the OGTT (75 g glucose load) without or with a prior s.c. injection of 100 μ g octreotide.

meals (postprandial hypoglycaemia). HbA1c was 4.9%. After 66 h of supervised fasting, she developed symptomatic hypoglycaemia with a plasma glucose concentration of 1.8 mmol/l and inappropriate levels of insulin (15 pmol/l), proinsulin (2.9 pmol/l) and C-peptide (185 pmol/l). The 32–33 split proinsulin level was undetectable (<2 pmol/l). These findings, together with an appropriate ratio of proinsulin to insulin (19%) below the >25% ratio seen in insulinoma patients (5, 6), are consistent with those observed in non-insulinoma insulin hypersecretion. The sulphonylurea screen was negative. MRI taken at that time and after 18 months showed no pancreatic abnormality.

Further investigations

In order to investigate the cause of hypoglycaemia, the incretin GLP1, insulin and glucose were measured in the plasma for 5 h on three occasions on different days, more than 2 days apart, following: i) a 75 g oral glucose tolerance test (OGTT); ii) a standard liquid test meal (LTM: 50% carbohydrate, 30% fat and 20% protein to provide 20% of the estimated energy requirement); and iii) a 75 g OGTT 30 min after a s.c. injection of 100 μ g octreotide, the somatostatin analogue. The GLP1 responses of eight obese non-diabetic control subjects (mean \pm s.d., age 39 ± 9.8

years; BMI 34.5 ± 4.4 kg/m²) following the 75 g OGTT are also presented as reference data. After 6 months of octreotide treatment, glucose, insulin and GLP1 hormone profiles were analysed throughout the day in relation to meals (estimated total daily energy requirement divided into 20% breakfast, 35% lunch, 10% afternoon snack and 35% dinner).

Analytical methods

To determine plasma glucose concentration, blood was collected in a fluoride oxalate tube and assayed on the same day by the glucose oxidase method (YSI 2300; Yellow Springs Instruments, OH, USA). For the insulin assay, plasma was collected in a lithium heparin-containing tube, frozen and stored at -80 °C until analysis. Then, insulin was quantified using a commercially available immunoassay (AutoDELFIA Insulin Kit; Perkin Elmer, Wellesley, MA, USA), with an intra-assay coefficient of variation (CV) of 3.5–4.5%. For GLP1, blood was collected into chilled EDTA-coated tubes, which were immediately centrifuged for 7 min at 3000 r.p.m. Plasma samples were snap-frozen and stored at -80 °C until analysis. Plasma GLP1 concentrations were measured by RIAs after extraction of plasma with 70% ethanol (vol/vol, final concentration). Carboxy-terminal GLP1 immunoreactivity was determined using antiserum 89390 (7), which has an absolute requirement for the intact amidated carboxy-terminus of GLP1 7–36 amide and cross-reacts <0.01% with carboxy-terminally truncated fragments and 89% with GLP1 9–36 amide, the primary metabolite of dipeptidyl peptidase IV-mediated degradation. The sum of the two components (total GLP1 concentrations) reflects the rate of secretion of the L-cell. Sensitivity was below 1 pmol/l, and the intra-assay CV was below 5% at 20 pmol/l.

Results

In the fasting state, the patient had a high basal level of GLP1 compared with the obese controls (22 vs

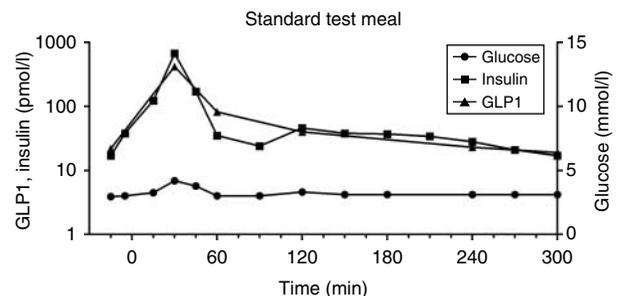


Figure 2 Glucose, insulin and GLP1 response to the standard test meal.

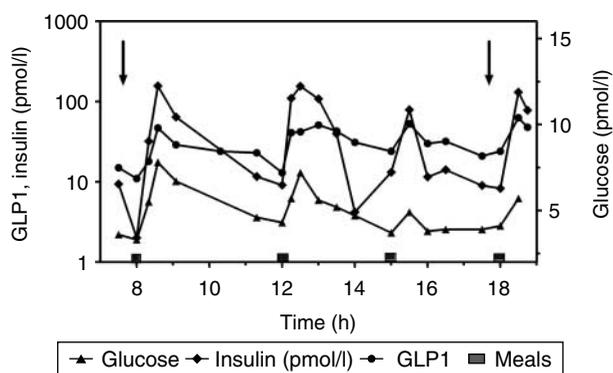


Figure 3 Glucose, insulin and GLP1 levels throughout the day in relation to meals and octreotide injections (arrows).

12.2 pmol/l; Fig. 1). During the OGTT, a markedly exaggerated rise in GLP1 was observed compared with the control group, with peak levels of 254 vs 23.2 pmol/l at 60 min. GLP1 levels returned to baseline by 240 min. Insulin levels also increased to nearly double that in the controls (647 vs 341 pmol/l) by 15 min. Plasma glucose levels showed a rapid peak at 30 min (7 mmol/l) and returned to baseline by 90 min with the lowest recorded level of 3.5 mmol/l. The GLP1, insulin and glucose responses to the standard test meal are shown in Fig. 2 (peak values: GLP1 418 pmol/l, insulin 669 pmol/l and glucose 6.9 mmol/l). The GLP1 response was fourfold higher than that found in previously published data of patients who underwent GBS without hypoglycaemia (96 pmol/l) (8). Octreotide injection prior to the OGTT attenuated both GLP1 and insulin peak responses, and not only reversed the low levels of glucose, but also elevated them into a diabetic range (2 h glucose 11.2 mmol/l; Fig. 1).

The patient was treated with a low-glycaemic index diet, frequent meals and 20 g corn starch three times daily with meals and was commenced on 50 µg octreotide s.c. twice daily before meals. Her symptoms resolved immediately. HbA1c remained normal (5%). Subsequently, the dose of octreotide was increased to

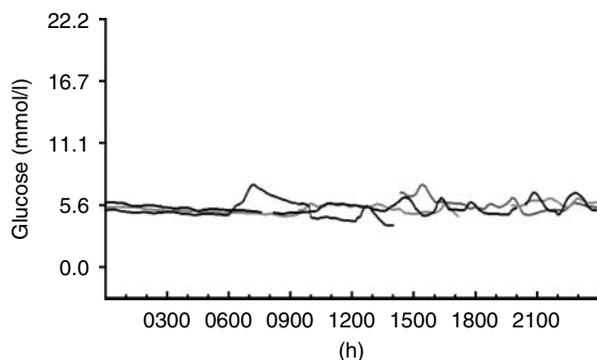


Figure 4 Continuous glucose monitoring indicating tight glycaemic control (each line represents an individual day).

100 µg twice daily. After 6 months of the treatment, the peak GLP1 and insulin responses to the same breakfast meal administered 6 months previously were much less pronounced (47 vs 418 pmol/l for GLP1 and 157 vs 669 pmol/l for insulin). The hormone and glucose responses throughout the day are shown in Fig. 3. No hypoglycaemia was detected during this study day. Octreotide therapy was changed to the long-acting analogue lanreotide. The patient remained asymptomatic for 4 years. The 72 h continuous glucose monitoring showed tight glycaemic control with a mean glucose level of 5.3 (range 3.7–7.4) mmol/l (Fig. 4). HbA1c measured at 3–6 monthly intervals had remained between 4.8 and 5.1%. On two occasions due to problems with accessing lanreotide, the patient was without treatment for 2–3 weeks during which time she reported a recurrence of meal-related hypoglycaemia and reported capillary blood glucose levels below 3.5 mmol/l (lowest 2.9 mmol/l).

Discussion

Sweating, palpitations and fainting episodes, sometimes associated with severe neuroglycopenia and its sequelae, following GBS are traditionally attributed to the dumping syndrome, a well-recognized complication of this procedure (9). 'Early dumping' usually occurs 30–60 min after meals and is thought to be caused by the rapid entry of ingested food into the small bowel causing osmotic shift and hypovolaemia. 'Late dumping' typically occurs 1–3 h after a meal; it is postulated that this is due to hypoglycaemia from rapid absorption of glucose and overactivation of the incretin axis, leading to inappropriate hyperinsulinaemia. Elevated GLP1 levels have been implicated as a cause of this inappropriate insulin response in patients who have undergone partial or total gastrectomy (10, 11).

The improvement in diabetes following GBS is thought to result from decreased insulin resistance associated with caloric restriction and weight loss and enhanced insulin secretion through an altered entero-insular axis (12, 13, 14), and even possibly through the activation of dormant β-cells (15). Reports of PHH following GBS first appeared in 2004 (3, 16). An insulinoma was diagnosed in one patient who underwent pancreatectomy achieving cure. In 2005, Service *et al.* (3) described nesidioblastosis in six cases of PHH following GBS. All patients received distal pancreatectomy with subsequent cure or improvement of hypoglycaemia. A link between GLP1 hypersecretion causing pancreatic β-cell growth, hyperfunction and nesidioblastosis was suggested. Subsequently, more cases of nesidioblastosis following GBS have been reported and all received pancreatectomy to control their symptoms (17, 18, 19).

PHH without evidence of insulinoma is rare in adults. Histologically, these patients have islet enlargement,

hypertrophic β -cells with enlarged hyperchromatic nuclei and abundant clear cytoplasm (17, 20). The detailed histology of the six cases reported by Service *et al.* was reanalysed subsequently using a different control group from autopsy specimens (7, 17). In contrast to the previous report, there was no evidence of increased β -cell formation estimated by the islet cell fractional area (which was not performed in the original study) or decreased β -cell loss in patients post-GBS.

Incretin hormones and the pancreatic insular axis

Incretin are hormones released from the gut in response to nutrient ingestion, enhancing glucose-stimulated insulin secretion (21). The two principal peptides with incretin-like activity are glucose-dependent insulinotropic peptide (GIP) and GLP1. GLP1 is secreted by the L-cells in the distal ileum in response to nutrient delivery. In addition to its glucose-dependent insulinotropic effect, GLP1 decelerates gastric emptying and suppresses glucagon secretion (22). Impaired postprandial GLP1 secretion has been demonstrated in the obese (23) and in patients with type 2 diabetes (24, 25, 26). Patients with impaired glucose tolerance have GLP1 responses intermediate between normal and type 2 diabetic patients (27). Administration of either exogenous GLP1 or a potent GLP1 agonist (exendin 4) has been shown to suppress energy intake in humans (24, 28). Exendin 4 and GLP1 analogues are now available as therapeutic agents for type 2 diabetes.

In morbidly obese patients who have undergone GBS, the GLP1 response to a meal is markedly increased compared with obese control patients without surgery (8, 29). Our patient had an even higher GLP1 peak at 418 pmol/l (12-fold; Fig. 2). An exaggerated GLP1 response (up to 12 times higher than the controls) is also found in non-obese patients who undergo total gastrectomy for indications other than morbid obesity (11), contributing to the late dumping syndrome. Therefore, it appears that the presence of glucose distal to the stomach is necessary to stimulate GLP1 release.

Others have hypothesised that rapid digestion and absorption of carbohydrate is an important contributing feature to PHH after GBS (4). They have demonstrated exaggerated plasma insulin responses and hypoglycaemia following high-carbohydrate mixed meals, compared with little change in plasma insulin and no hypoglycaemia after low-carbohydrate test meals. In the GBS, as part of the proximal jejunum is bypassed, the rise of GIP is less pronounced than GLP1 (30); GIP is less likely to be responsible for excess insulin secretion. McLaughlin *et al.* (31) recently reported a case of PHH following GBS in which delivering food via a gastrostomy tube reduced the incretin response compared with orally and abolished hypoglycaemia. Others (32) have reported that surgical restoration of gastric restriction to slow down the release of glucose into the

intestine improved hypoglycaemia. However, in a recent study, the exaggerated effect of GLP1 on postprandial insulin secretion in surgical subjects was not significantly different from those with and without recurrent hypoglycaemia (14).

In this case, we demonstrated an exaggerated peak GLP1 response during an OGTT and test meal, which was much greater than that observed in matched obese control subjects and post-GBS patients without a history of hypoglycaemia (8). We suggest that this markedly increased incretin effect is the likely cause of postprandial hypoglycaemia. This release of GLP1 after glucose challenge was clearly inhibited by prior octreotide injection, thereby preventing hypoglycaemia. This suggests that the rapid transit of food into the intestine (perhaps exacerbated by the revised surgery) may partly explain the surge of GLP1 that we observed. Octreotide blocks SSR-2, -4 and -5. These receptors are present in the intestine where the L-cells are located. Promisingly, the effect of octreotide and, latterly, lanreotide has been maintained for 4 years, avoiding the need for pancreatectomy and its serious potential complications.

In conclusion, we report a case of successful reversal of PHH with octreotide 6 years following GBS. In this case report, the response of the patient with PHH post-GBS to somatostatin treatment suggests that a trial of octreotide therapy should be considered in patients with this condition, particularly if no lesion is identified on pancreatic imaging. Our case demonstrates that treatment with octreotide may obviate the need for pancreatectomy in selected cases.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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