Case Report

THE USE OF GASTROSTOMY TUBE FOR THE LONG-TERM REMISSION OF HYPERINSULINEMIC HYPOGLYCEMIA AFTER ROUX-EN-Y GASTRIC BYPASS: A CASE REPORT

Colleen M. Craig, MD[1]; Cindy Lamendola, RN[1]; Jens J. Holst, MD, PhD[2]; Carolyn F. Deacon, PhD[2]; Tracey L. McLaughlin, MD[1]

ABSTRACT

Objective: Hyperinsulinemic hypoglycemia is an increasingly reported complication of Roux-en-Y gastric bypass surgery (RYGB), for which there is currently no acceptable treatment. We present a case of the reversal of severe hyperinsulinemic hypoglycemia through gastrostomy tube (GT) feeding to the remnant stomach and uniquely report the durable resolution of neuroglycopenic symptoms 3 years after GT placement.

Methods: The case subject underwent standardized postprandial measurement of plasma glucose, insulin, glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic peptide (GIP), and glucagon concentrations after oral or GT administration of a standardized liquid meal.

Results: Hypersecretion of insulin, GLP-1, and glucagon elicited by oral administration of the liquid meal were reversed with GT feeding. GIP was not secreted in excess of normal after the oral meal.

Conclusion: This case of reversible hyperinsulinemic hypoglycemia through GT feeding illustrates the physiology of this disorder, pointing to an exaggerated GLP-1 response due to rapid nutrient transit to the distal bowel. The sustained resolution of the case subject's neuroglycopenic symptoms supports the use of GT as an effective and durable treatment for severe refractory hyperinsulinemic hypoglycemia after RYGB. **(AACE Clinical Case Rep. 2015;1:e84-e87)**

Abbreviations:
GIP = glucose-dependent insulinotropic peptide; **GLP-1** = glucagon-like peptide-1; **GT** = gastrostomy tube; **RYGB** = Roux-en-Y gastric bypass

INTRODUCTION

Since hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass (RYGB) surgery was first reported, its cause has been a matter of debate. The topic has generated interest not only because symptoms can be severe and refractory to treatment, but also because the physiology underlying the disorder may mediate the early resolution of diabetes after RYGB. Understanding the mechanisms that result in glucose lowering after RYGB could guide the development of targeted therapies, both for diabetes and for hyperinsulinemic hypoglycemia, for which there is currently no acceptable treatment.

Previously, we reported a unique case wherein hyperinsulinemic hypoglycemia after RYGB was reversed through enteral feeding to the remnant stomach via gastrostomy tube (GT) (1). This case pointed to altered nutrient transit and the consequent elicitation of a glucagon-like peptide-1 (GLP-1) surge as the cause of hyperinsulinemic hypoglycemia after RYGB. In the present study, we present a second case of reversible hyperinsulinemic hypoglycemia with the use of GT feeding and uniquely report the sustained resolution of neuroglycopenia 3 years after GT placement. This report confirms our prior interpretation and establishes GT as a safe, effective, and durable treatment for refractory hyperinsulinemic hypoglycemia.

CASE REPORT

A 38-year-old woman (body mass index [BMI], 34.1 kg/m^2) underwent RYGB to relieve pain and paresthesias

Submitted for publication October 16, 2013
Accepted for publication November 27, 2013
From [1]Stanford University School of Medicine, Department of Medicine, Division of Endocrinology, Stanford, California, and [2]University of Copenhagen, Panum Institute, Copenhagen, Denmark.
Address correspondence to Dr. Colleen M. Craig, Stanford University School of Medicine, Department of Medicine, Division of Endocrinology, 300 Pasteur Drive, Room S019, Stanford, CA 94305-5103.
E-mail: cmcraig@stanford.edu.
DOI:10.4158/EP14218.CR

associated with a spinal disk herniation. Within 6 months of surgery, she had lost 30% of her weight, and while her radiculopathies remitted, other more disabling symptoms began to evolve. She began experiencing frequent episodes of diaphoresis, tachycardia, palpitations, and syncope with loss of consciousness. Symptoms occurred postprandially and improved in the fasting state. Her plasma glucose concentration was documented at <50 mg/dL. Symptoms were refractory to dietary modification or treatment with acarbose, diazoxide, verapamil, or nifedipine. Cognitive and psychomotor functioning worsened, and the subject lost the ability to carry on lucid conversations, care for her children, or perform activities of daily living. Her postprandial glucose, insulin, and C-peptide levels were documented as 37 mg/dL, 164 μU/mL, and 14.9 ng/mL, respectively. Imaging ruled out a pancreatic mass, and selective arterial calcium stimulation testing was negative. A GT was inserted into the gastric remnant as a route of nutrient delivery, resulting in a marked resolution of symptoms within 2 weeks of placement. Six weeks following the GT placement, the subject was referred for standardized evaluation. Her cognitive and psychomotor deficits eventually resolved and she was able to resume her work and care for her children.

The study was approved by the Stanford Investigational Review Board, and written informed consent was obtained. The subject was admitted to the Stanford General Clinical Research Center after a 12-hour fast. One 240-mL can of Ensure® liquid formula (250 kcal, 6 g fat, 40 g carbohydrates, 9 g protein) was administered orally over 15 minutes. Plasma glucose, insulin, GLP-1, glucose-dependent insulinotropic peptide (GIP), and glucagon were assayed in 30-minute intervals from 0 to 180 minutes. The next morning, the protocol was repeated but with the liquid meal delivered through the GT, again over 15 minutes.

Glucose concentrations were determined by the glucose oxidase method using a glucose analyzer (Analyzer 2; Beckman, Brea, CA). Insulin was measured using a commercial radioimmunoassay kit according to the manufacturer's specifications (Millipore Corp, Billerica, MA). Total GLP-1 and GIP concentrations were determined by radioimmunoassay using C-terminally-directed antisera (nos. 89390 and 80867) (2,3). Glucagon concentrations were determined by radioimmunoassay employing C-terminally-directed antiserum (no. 4305), which reacts mainly with fully processed glucagon of pancreatic origin (4).

The subject's weight on evaluation was 71.3 kg (BMI, 25.5 kg/m^2). The oral meal resulted in a peak glucose at 30 minutes that was nearly 1.5-times higher than after the GT meal (174 mg/dL vs. 128 mg/dL), followed by a rapid decline in plasma glucose, accompanied by reported symptoms of hypoglycemia, with a plasma glucose nadir at 90 minutes (79 mg/dL). The drop from peak to nadir glucose was over 2-fold greater after the oral versus GT meal (95 mg/dL vs. 44 mg/dL) and occurred more rapidly (60 minutes vs. 150 minutes; Fig. 1 *A*). The oral meal resulted in a peak insulin at 30 minutes that was over 4-fold higher at that time (143 μU/mL vs. 31 μU/mL; Fig. 1 *B*). The insulinogenic index was over 2-fold greater after the oral meal (1.79 [μU/mL insulin]/[mg/dL glucose] vs. 0.79 [μU/mL insulin]/[mg/dL glucose]).

The oral meal resulted in a GLP-1 peak at 30 minutes that was 5.5-times higher than after the GT meal. By 120 minutes, the GLP-1 responses to the 2 test meals were nearly identical. The incremental elevations in GLP-1 were 6-fold higher (85 pmol/L vs. 15 pmol/L) in the first 30 minutes after the oral meal, and area under the curve for GLP-1 was over 3-times greater after the oral meal (Fig. 2 *A*). The GT meal elicited a greater GIP response, with a peak concentration at 60 minutes that was over 2-fold higher than after the oral meal (65 pmol/L vs. 31 pmol/L; Fig. 2 *B*). Despite higher GLP-1 concentrations, glucagon concentrations were higher after the oral meal, including at 30 minutes, when glucose peaked, and at 90 minues, when glucose nadired (Fig. 2 *C*).

DISCUSSION

This case illustrates a safe and effective treatment for severe hyperinsulinemic hypoglycemia after RYGB. GT feeding to the remnant stomach allows nutrients to travel through the original intact gut, in essence reversing the bypass without incurring the risk of another surgery. Current pharmaceutical treatments are limited in their efficacy, and patients may undergo pancreatectomy, which carries a 6% mortality rate and results in insulin-dependent diabetes. Endoscopic advances in GT placement after RYGB have made GT insertion simpler and safer (5). Thus, GT represents a safe and effective alternative and should be considered in the treatment algorithm for severe refractory disease.

This case also illustrates the physiology of hyperinsulinemic hypoglycemia after RYGB. The subject's appropriately low fasting insulin concentrations were consistent with the insulin sensitive state. This, together with hyperinsulinemia only following her oral meal, points to altered nutrient transit and a GLP-1 surge as the cause of hypoglycemia, rather than generalized beta-cell actions, irrespective of nutrient transit route. This may be the same process that underlies the early resolution of diabetes after RYGB. A study of sequentially recruited post-RYGB subjects found that 33% had a glucose nadir of <50 mg/dL after an oral glucose tolerance test, with plasma glucose, insulin, and GLP-1 responses nearly identical between patients who experienced symptomatic hypoglycemia and those who remained asymptomatic (6). What determines whether a patient will develop symptoms of hypoglycemia at a given plasma glucose concentration remains unclear. Of consideration is the role that the extent and rapidity of the descent in plasma glucose from peak to nadir may play in eliciting hypoglycemic symptoms. Within the span of

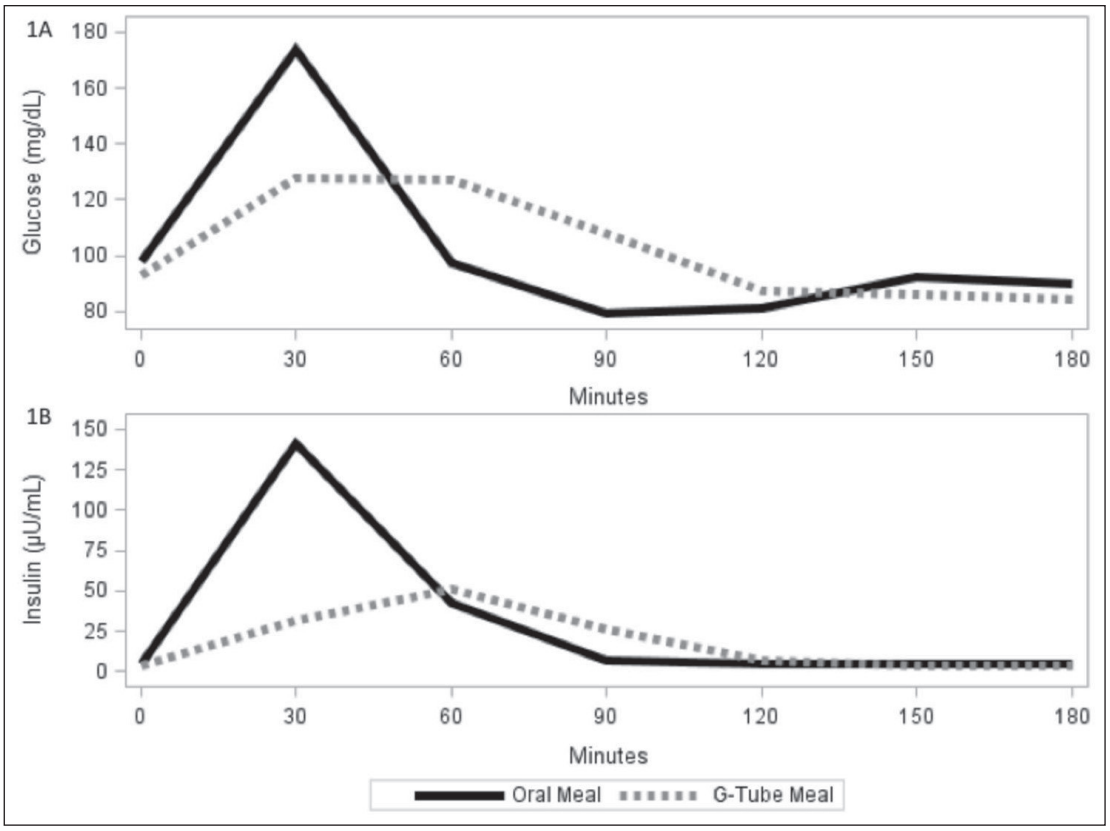

Fig. 1. (*A*) Glucose and (*B*) insulin concentrations after orally or gastrostomy tube–administered liquid meal in a case subject with hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass surgery.

60 minutes, the present case subject experienced a nearly 100 mg/dL drop in plasma glucose after the oral meal, compared to the 20 mg/dL change after the GT meal. It is possible that anatomic variations, such as differences in the length of the jejunal limb of the Roux, the distribution of entero-endocrine cells, or whether a vagotomy was performed could cause a left-shifting and steepening of the glucose curve. Alternatively, differences in the rates of gastric emptying or the strengths of innate biologic defenses, such as through the secretion of glucagon or catecholamines, could contribute.

This study also has implications on the effects of RYGB on GLP-1, GIP, glucagon, and GLP-2. After the oral meal, the subject had an increase in GLP-1 secretion and a lack of GIP stimulation, implicating GLP-1 over GIP as the primary stimulus to insulin secretion. Postprandial GIP results have been inconsistent in other studies (7). Interestingly, glucagon was 3.5-times higher after the oral meal versus the GT meal, including at 30 and 60 minutes, when glucose and GLP-1—both of which are known to suppress glucagon—were elevated. Increases in postprandial plasma glucagon after RYGB have been reported, and it has been proposed that these elevations may, in fact, represent inadequate processing of proglucagon as a consequence of overstimulation of L cells after RYGB, resulting in release of intestinally derived, inactive proglucagon 1-61, which would cross-react with the glucagon assay (8). It has also been proposed that the glucagonostatic effects of GLP-1 may be opposed by the concomitant glucagonotropic actions of GLP-2, which is cosecreted with GLP-1 (9).

CONCLUSION

In conclusion, this case of reversal of hyperinsulinemic hypoglycemia through GT feeding confirms our view that hyperinsulinemic hypoglycemia after RYGB is largely mediated through an exaggerated GLP-1 response due to rapid nutrient transit to the distal bowel. A less exaggerated GLP-1 response may underlie the early resolution of diabetes after RYGB. What determines which patients will develop hyperinsulinemic hypoglycemia after RYGB or whether it also occurs following other surgeries such as vertical sleeve gastrectomy remains to be clarified. At the moment, a safe and effective treatment, such as GT, is needed. Now 3 years post-GT placement, this case subject continues to optimize her nutritional and metabolic health through a combination of GT and oral meals. The prolonged resolution of this subject's symptoms, her recovery of cognitive and psychomotor functioning, and the confirmation of prior results support the use of GT in the treatment algorithm for severe hyperinsulinemic hypoglycemia after RYGB.

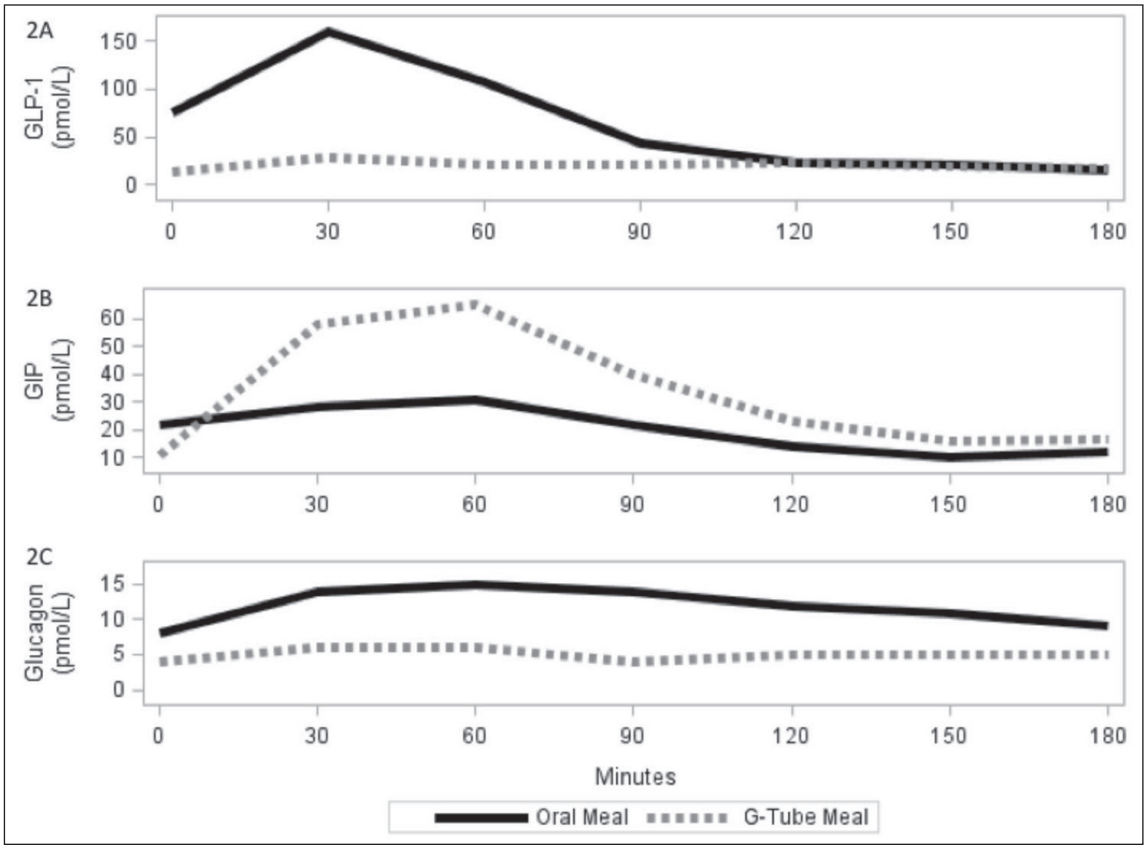

Fig. 2. (*A*) GLP-1, (*B*) GIP, and (*C*) glucagon concentrations after orally or gastrostomy tube–administered liquid meal in a case subject with hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass surgery. *GLP-1* = glucagon-like peptide-1; *GIP* = glucose-dependent insulinotropic peptide.

ACKNOWLEDGMENT

We thank Raymond R. Balise for his statistical assistance. This work was conducted with support from a KL2 Mentored Career Development Award of the Stanford Clinical and Translational Science Award to Spectrum (NIH KL2 TR 001083), and an NIH/NCRR CTSA award, number UL1 RR025744.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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