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Abnormal glucose tolerance testing following gastric bypass demonstrates reactive hypoglycemia

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Abstract
Background Symptoms of reactive hypoglycemia have been reported by patients after Roux-en-Y gastric bypass (RYGB) surgery who experience maladaptive eating behavior and weight regain. A 4-h glucose tolerance test (GTT) was used to assess the incidence and extent of hypoglycemia.
Methods Thirty-six patients who were at least 6 months postoperative from RYGB were administered a 4-h GTT with measurement of insulin levels. Mean age was 49.4 ± 11.4 years, mean preoperative body mass index (BMI) was 48.8 ± 6.6 kg/m^2, percent excess BMI lost (%EBL) was 62.6 ± 21.6%, mean weight change from nadir weight was 8.2 ± 8.6 kg, and mean follow-up time was 40.5 ± 26.7 months. Twelve patients had diabetes preoperatively.
Results Thirty-two of 36 patients (89%) had abnormal GTT. Six patients (17%) were identified as diabetic based on GTT. All six of these patients were diabetic preoperatively. Twenty-six patients (72%) had evidence of reactive hypoglycemia at 2 h post glucose load. Within this cohort of 26 patients, 14 had maximum to minimum glucose ratio (MMGR) > 3:1, 5 with a ratio > 4:1. Eleven patients had weight regain greater than 10% of initial weight loss (range 4.9–25.6 kg). Ten of these 11 patients (91%) with weight recidivism showed reactive hypoglycemia.
Conclusions Abnormal GTT is a common finding post RYGB. Persistence of diabetes was noted in 50% of patients with diabetes preoperatively. Amongst the nondiabetic patients, reactive hypoglycemia was found to be more common and pronounced than expected. Absence of abnormally high insulin levels does not support nesidioblastosis as an etiology of this hypoglycemia. More than 50% of patients with reactive hypoglycemia had significantly exaggerated MMGR. We believe this may be due to the nonphysiologic transit of food to the small intestine due to lack of a pyloric valve after RYGB. This reactive hypoglycemia may contribute to maladaptive eating behaviors leading to weight regain long term. Our data suggest that GTT is an important part of post-RYGB follow-up and should be incorporated into the routine postoperative screening protocol. Further studies on the impact of pylorus preservation are necessary.

Keywords Reactive hypoglycemia · Roux-en-Y gastric bypass · Gastric bypass · Morbid obesity

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Obesity has become an epidemic in the USA [1]. With incidence of morbid obesity on the rise, gastric bypass surgery has become more common, not just for weight loss but also for treatment of associated comorbidities, especially type 2 diabetes mellitus. To date, there have been numerous studies looking at amelioration and remission of diabetes after gastric bypass, with remission rates in excess of 80% reported [2–5]. Several explanations for the improvement in glucose regulation and insulin resistance after gastric bypass surgery have been proposed. Some of

these include decreased caloric intake leading to decreased stimulation of incretins and insulin release, weight loss through changes in fat mass and release of adipocytokines, and bypass of the distal stomach and proximal small intestine leading to decreased production of foregut hormones, such as glucagon-like peptide 1 (GLP-1), gastric inhibitory peptide (GIP), and ghrelin [6].

Recently there has been some interest in hyperinsulinemic hypoglycemia following gastric bypass surgery. Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) was first described in 1999 [7], characterized by postprandial hypoglycemia, hyperinsulinemia, and negative 72-h fasting test. This was subsequently reported in some patients who had undergone gastric bypass surgery, presenting with symptoms of hypoglycemia 1–3 years after the bypass surgery, which were not ameliorated by dietary modifications [8–10]. There is ongoing controversy about the etiology of this hyperinsulinemic hypoglycemia reported in patients after gastric bypass surgery. One theory is that of increased beta cell mass and consequent hyperfunction of islets (nesidioblastosis) [8, 11–13]. This is believed to be secondary to increased levels of GLP-1, from the L cells of the distal ileum, due to rapid presentation of nutrients to the distal small bowel. GLP-1 has been shown to be a beta-cell trophic factor in rodents [14–16] and to decrease apoptosis of islets in humans [17]. However, this theory has been challenged by some, who suggest inappropriately increased insulin secretion due to failure to adapt after gastric bypass surgery, in combination with dumping syndrome, as being responsible for hyperinsulinemic hypoglycemia after gastric bypass surgery [18].

Despite the controversy about the etiology, there is definitely agreement on the presence of hyperinsulinemic hypoglycemia in several patients 1–3 years after gastric bypass surgery. The clinical severity of this syndrome varies, with some authors reporting profound symptoms of hypoglycemia, leading them to propose partial pancreatectomy for treatment [8]. Certainly, symptoms this severe are seen in very few patients after gastric bypass. However, the development of more subtle forms of reactive hypoglycemia can certainly have an impact on appetite control.

The cyclical regulation of glucose has been shown to be a primary chemical mediator of appetite. Following a meal, there is a transient rise in glucose level, which in turn causes insulin release. Certain simple sugars such as glucose, or substances rapidly converted to simple sugars, cause the greatest rise in insulin. A ranking of foods based on their overall effect on blood sugar levels, called the glycemic index factor, has been developed [19]. Low-glycemic-index foods provide a slower, more consistent source of glucose to the bloodstream, minimizing fluctuations in blood glucose levels, which leads to increased insulin sensitivity and reduced secretion of insulin over the day [20]. Low-glycemic-index foods have been shown to be more likely to result in satiety. A recent Cochrane analysis concluded that obese people on low-glycemic-index diets, regardless of the actual quantity of food intake, lost more weight than if they were on conventional restricted low-fat diets [21].

Over time, gastric bypass has emerged as the superior procedure for weight loss. Studies evaluating gastric bypass and gastroplasty procedures have proposed three explanations for the superiority of gastric bypass: (1) technical challenges in maintaining a small gastroplasty stoma [22, 23], (2) decreased carbohydrate absorption by bypassing the duodenum [24], and (3) avoidance of sweets, due to the negative association caused by dumping syndrome symptoms [25–27]. In 1987, Sugerman published an influential paper in the field of bariatric surgery [25]. He randomized patients classified as "sweet-eaters" based on self-reported diaries to undergo either Roux-en-Y gastric bypass or vertical banded gastroplasty. The study was stopped early because the data strongly indicated the superiority of gastric bypass for weight loss. Dr. Sugerman attributed his results primarily to the unpleasant symptoms of dumping syndrome, with most gastric bypass patients reporting flushing, nausea, diarrhea, and lightheadedness with ingestion of sweets. These studies, amongst others, have led to the widespread belief that morbidly obese patients who consumed frequent simple carbohydrates (sweet-eaters), were best served by gastric bypass surgery, leading to greater weight loss.

Interestingly, when the gastric bypass patients in Sugerman's study were followed at 2 and 3 years, the sweet-eaters had increased incidence of weight recidivism as compared with non-sweet-eaters. Over time, the sweet-eaters reported no associated negative symptoms of dumping with ingestion of sweets. This is an interesting finding and suggests that the instant negative reinforcement that was counted on to deter simple carbohydrate ingestion in sweet-eaters may be attenuated over time.

As gastric bypass surgery is becoming more common, and more of these patients are being followed long term, we have noted increased complaints of severe hunger, especially 2–3 h following a meal, with increased rates of weight recidivism in this population. Our hypothesis is that the dumping caused by the gastric bypass anatomy, where distal stomach is bypassed and pyloric valve is not utilized, causes an early and significant insulin surge which results in reactive hypoglycemia shortly thereafter. This glucose fluctuation may be responsible for return of hunger a few hours after a meal, leading to frequent snacking or meals, and subsequent weight recidivism in this patient population. To evaluate our hypothesis, we decided to study glucose regulation in patients who had gastric bypass

surgery, by adding a 4-h glucose tolerance test to serum glucose and insulin levels.

Methods

Thirty-six patients who were at least 6 months post laparoscopic Roux-en-Y gastric bypass (LRYGB) were included. This was an unselected group of patients who presented for postoperative follow-up at some time greater than 6 months from their initial operation. A 4-h GTT with concomitant measurement of serum insulin was performed in this group. Tests were done at a commercial laboratory using standard methodology. All patients were given 100 g oral liquid glucose load. This was done in a monitored setting where medical attention was available should patients develop severe symptomatic hypoglycemia. The parameters collected from the GTT were serum glucose and concomitant serum insulin levels at the following time intervals: fasting, 1, 2, 3, and 4 h post glucose load. From these serum glucose values, the ratio of maximum to minimum serum glucose level was calculated. All analyses were performed using MS Excel.

Baseline characteristics of age, preoperative weight, preoperative BMI, presence of preoperative diabetes, date of surgery, postoperative nadir weight, and weight at time of latest follow-up were collected in a deidentified database. As a result, postoperative weight loss and percent excess BMI lost (%EBL) were calculated. Table 1 lists the baseline characteristics of the study cohort.

All operations were performed at the same institution, by two surgeons. The gastric pouches created during LRYGB were all fashioned based on the lesser curvature of the stomach. All gastrojejunostomies were performed by either using the CEEA25 (Autosuture, Norwalk, CT) with subsequent circumferential oversewing with 2-0 polydioxanone (PDS) or using a 45-mm Endocutter (Ethicon, Cincinnati, OH) linear stapler with suturing over a 34-French bougie to standardize the anastomotic outlet.

Table 1 Baseline characteristics of study cohort

Characteristic	
Age (years)	49.4 ± 11.4
Female:male	6.2:1
Preoperative diabetes (%)	33.3% (12/36)
Follow-up (months)	40.5 ± 26.7
Preoperative weight (kg)	135.9 ± 26.3
Preoperative BMI (kg/m^2)	48.8 ± 6.6
Weight change from nadir (kg)	8.2 ± 8.6
%EBL	62.6 ± 21.6

Results

Thirty-six patients underwent a 4-h GTT, with 31 of these 36 patients (86%) having concomitant measurements of serum insulin levels. Mean follow-up was 35 months.

Thirty-two of 36 patients (89%) had abnormal GTT. Six of these patients were diagnosed as having diabetes based on GTT parameters. All six of these patients had type II diabetes preoperatively and underwent remission of their diabetes in the immediate postoperative period. None of them were on hypoglycemic medications at time of testing. Only one of these six patients had an elevated fasting serum glucose level (202 mg/dL, normal 65–100 mg/dL) at the time of their GTT. The remaining five patients had normal to mildly elevated fasting glucose levels. The GTT curves for these six patients are graphed in Fig. 1. This represents a 50% (6/12) persistence of diabetes at follow-up. Figure 2 shows the mean plasma glucose and insulin levels for the 30 patients in the diabetic cohort.

Twenty-six patients (72%) showed evidence of reactive hypoglycemia by GTT. Our criterion for classifying a patient as having reactive hypoglycemia was an absolute serum glucose level ≤60 mg/dL, or a drop of 100 mg/dL in serum glucose level in 1 h.

The majority of these 26 patients with reactive hypoglycemia were found to have a rapid rise in plasma glucose level at 1 h post glucose load followed by a rapid decline to hypoglycemic levels at 2 h post glucose load. We quantified this relationship by calculating a maximum to minimum plasma glucose ratio (MMGR). A ratio of approximately 1.5–2:1 is found in normal glucose tolerance curves. Of these 26 patients, 14 had MMGR greater than 3:1, including 5 with MMGR greater than 4:1.

A subset analysis of 11 patients who had undergone LRYGB and regained more than 10% of their total weight

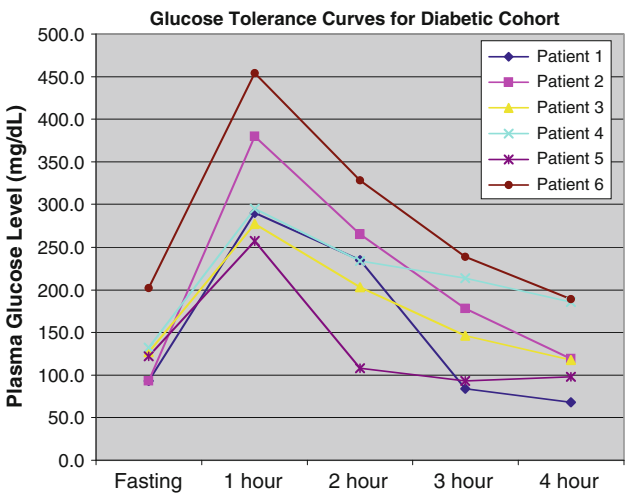

Fig. 1 Glucose tolerance curves for diabetic cohort

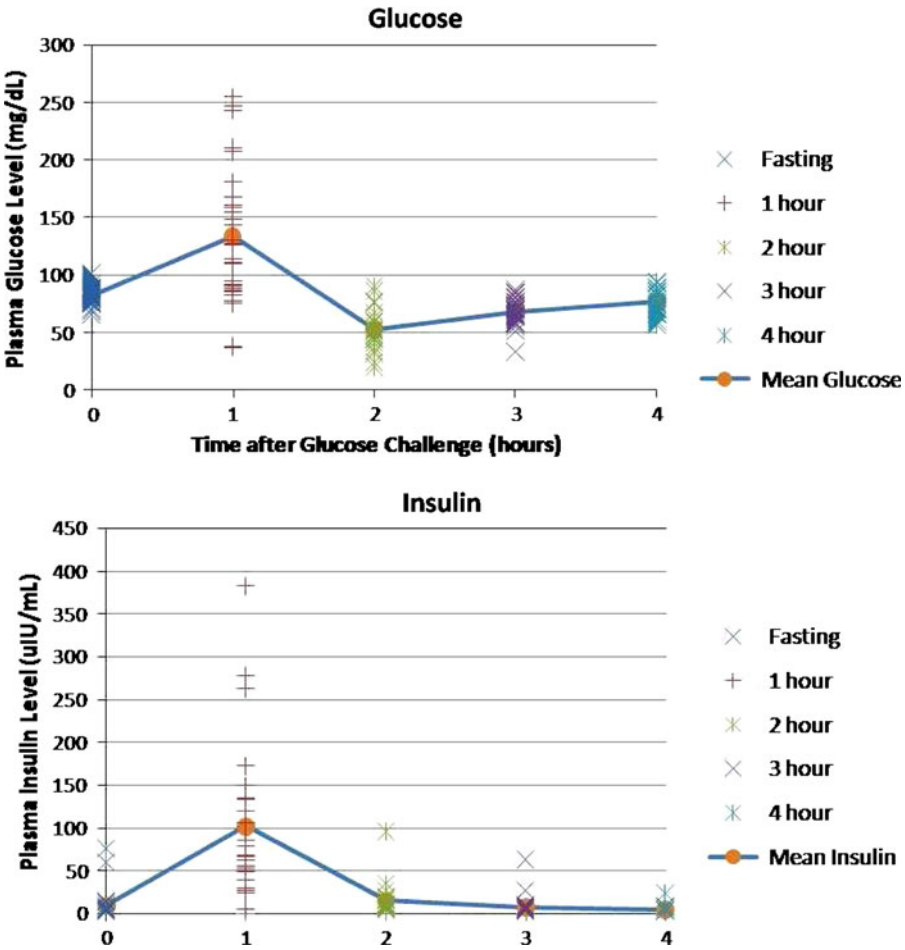

Fig. 2 Mean plasma glucose and insulin in nondiabetic cohort

loss (Table 2) showed that 10 of the 11 (91%) patients had abnormal GTT. All of the patients had a fasting plasma glucose level within normal limits (range 65–92 mg/dL). At the 1-h interval, six patients had normal glucose levels, three patients had elevated glucose level (>200 mg/dL), and one patient had a severely hypoglycemic level. At the 2-h interval, seven patients had hypoglycemia, one of which was severe (32 mg/dL) (Fig. 3).

Discussion

This study was prompted by our observation of many gastric bypass patients reporting high levels of postprandial hunger, driving snacking or grazing eating behavior, and a realization that recidivism after gastric bypass was more common than literature suggests. In this unselected group, the recidivism rate was almost 30%. The traditional understanding of mechanisms of recidivism has focused primarily on anatomical or patient behavior issues. If the pouch and stoma anatomy are not dilated, there is little that we can offer beyond additional nutritional guidance and encouraging exercise. Some patients have presented with a consistent pattern of symptoms which suggested hypoglycemia as a driver for their eating behavior. Glucose tolerance tests have not traditionally been a part of long-term postoperative monitoring of these patients.

Our data show that abnormal glucose tolerance is far more common following gastric bypass than expected. In our study, six patients were found to have diabetic

Table 2 Subset of patients with > 10% weight gain

Age (years)	49.5
Mean preoperative weight (kg)	137.3 ± 28.7 (99.8–169)
Mean preoperative BMI (kg/m^2)	50.1 ± 6.8 (39.7–60.0)
Mean postoperative nadir weight (kg)	86.8 ± 21.4 (54.4–128)
Mean weight increase from nadir weight (kg)	13.6 ± 6.35 (4.90–25.6)
Mean follow-up duration (months)	60.5 ± 21.2

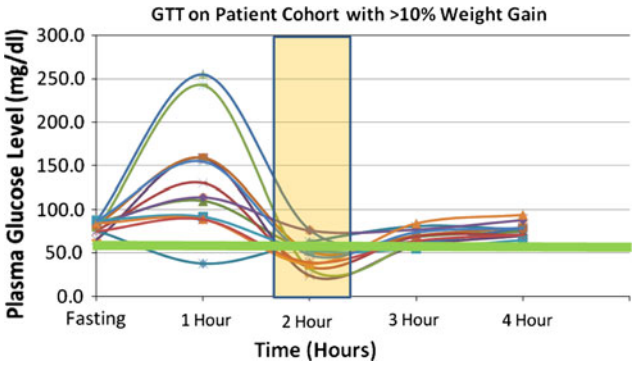

Fig. 3 Glucose tolerance tests on cohort with > 10% weight gain

parameters based on GTT. Of the six patients with abnormal GTT, two had normal fasting blood glucose levels. Importantly, all six were on medication for diabetes preoperatively and were believed to have had resolution of diabetes postoperatively.

Twenty-six of 36 patients (72%) met the parameters for reactive hypoglycemia. More notable is the presence of reactive hypoglycemia seen in patients who were not diabetic based on GTT (26/30 patients, 86%). Of these 26 patients, 14 (54%) had ratios of maximum to minimum glucose that exceeded 3:1. More notably, 10 of 11 patients (91%) with significant weight regain after LRYGB had abnormal GTT, with 6 of the 11 patients (54%) having blood glucose levels consistent with hypoglycemia at 2 h. In our study, blood glucose levels were measured on an hourly basis. The actual insulin peak and thus the nadir glucose level may well be at less than 2 h, which would mean that we potentially could have underestimated the severity of the reactive hypoglycemia. While rapid shifts in insulin and glucose levels are predictable in a gastric bypass anatomy, the magnitude of these shifts and the drop of serum glucose to pathologic levels were seen more commonly than otherwise expected in this population.

Following gastric bypass, we believe many patients develop the ability to rapidly empty their gastric pouch since there is no pyloric valve to regulate passage of food. The passage of food is based on the type of food ingested (e.g., liquid or solid), the size of the gastric pouch, as well as the size of the anastomotic outlet. With no valve to control coordinated release of food substances, rapid transport of glycemic load to the small intestine causes a rapid rise in insulin levels due to transient stimulation of beta cells, with a subsequent drop in plasma glucose. Since there is no sustained gradual release of insulin, there are rapid fluctuations in blood glucose, ranging from an initial surge after a meal to a precipitous decline 90–120 min after a meal. These rapid fluctuations in plasma glucose are likely to lead to a return of hunger. These effects may be more pronounced in patients consuming high-glycemic-index foods.

The implications of this data may be fairly significant. Since glucose regulation is an important chemical mediator of appetite, these vast fluctuations in glucose levels would certainly have an impact on physiological drivers of hunger. The sharp drop in glucose levels and subsequent hunger may be a cause of the maladaptive eating behavior and weight recidivism that is being encountered nationally. In fact, long-term follow-up at 5–10 years in gastric bypass patients has shown weight regain in up to 50% of patients [28, 29]. In our practice, we continue to see increased complaints of weight regain and hunger, and many patients have been requesting enrollment in clinical trials for endoscopic-based revisions of their gastric pouch. Similar endoscopic procedures have been reported by others for treating weight regain after gastric bypass [30, 31].

Based on these observations, we have carefully redesigned our postoperative dietary recommendations. We emphasize that patients should eat a low-glycemic-index diet and encourage them not to go long periods without eating. We recommend adding bulk to their food, incorporating whey gelatinous protein in their diet, and a healthy snack in the afternoon. The goal of these dietary recommendations is to minimize these glucose level fluctuations, and subsequent hunger.

Interestingly, the majority of patients in our series who experienced the greatest glucose fluctuations had no history of diabetes, suggesting no intrinsic abnormality in insulin/glucose homeostasis. In our patients, even though we did see increased insulin levels, we did not see the abnormally high levels consistent with nesidioblastosis. This supports our hypothesis that reactive hypoglycemia is based on anatomical considerations of gastric bypass surgery with loss of a pyloric valve, and not beta cell hypertrophy.

There are substantial limitations to our study. It is primarily observational in nature, and based on patients seen at follow-up at varying postoperative intervals. As a result, besides a standard demographic profile, and medical history, we have no baseline glucose tolerance testing, insulin level, C-peptide level or measurement of β cell function or response. The use of a liquid-based GTT also accentuates the vulnerability of the fixed gastric outlet created by the gastric bypass procedure. It is not yet clear whether the severe fluctuations we have recorded are also seen with a more varied density of food. Currently, we are beginning a prospective trial comparing operations that preserve the pyloric valve (duodenal switch and sleeve gastrectomy) versus gastric bypass. In that trial we plan to use both liquid glucose tolerance tests and a solid simple carbohydrate challenge. In the preoperative period we will obtain measurements of fasting glucose, insulin, C-peptide, 2-h GTT, insulin sensitivity, and beta cell response, with repeat measurements at 6, 9, and 12 months postoperatively.

Thus, while physiologic factors in the gastric bypass, such as markedly suppressed circulating ghrelin levels, are given credit for early results and weight loss [32], relapse has been attributed to poor choices and a return of maladaptive eating behavior. While we recognize that behavioral and psychological factors may contribute to weight regain [33], our study suggests that physiological factors may play a more significant role than previously thought in weight recidivism being encountered after gastric bypass. Nonphysiologic transit of food to the small intestine due to lack of a pyloric valve after RYGB, causing glucose fluctuations and reactive hypoglycemia, may contribute to return of hunger and maladaptive eating behaviors leading to weight regain long term. It is our speculation that morbidly obese patients who want stapling procedures may be better served with sustained weight loss by pylorus-preserving surgery, such as sleeve gastrectomy or duodenal switch without severe malabsorption. Further investigation will be needed before any definitive conclusions can be drawn. Our data also suggest that GTT is an important part of post-RYGB follow-up and should be incorporated into the routine postoperative screening protocol.

Disclosures Dr. Mitchell Roslin is a consultant for Johnson & Johnson, Bard, and Covidien. He is on the surgical advisory board for ValenTx Scientific Intake. He has equity interests in Ventralfix, gets royalties from Allergan, and has a research grant from Covidien. Dr. Paresh Shah has an equity interest in SuturTek and Ventralfix, and is a consultant for Stryker, Covidien, Ethicon, and Davol. Drs. Tanuja Damani, Jonathan Oren, Robert Andrews, and Edward Yatco have no conflicts of interest or financial ties to disclose.

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