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# Hypoglycemia After Gastric Bypass Successfully Treated With Calcium Channel Blockers: Two Case Reports

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Postprandial hyperinsulinemic hypoglycemia is an uncommon yet well-established complication of Roux-en-Y gastric bypass (RYGB) that can result in serious morbidity and adversely affect quality of life. It is often unrecognized and may be difficult to diagnose. Management is challenging. As the number of bariatric procedures increases in parallel with the obesity epidemic, clinicians will be tasked to offer effective medical therapies for this complication. Two patients presented several years after RYGB with severe postprandial hypoglycemia. In one of the patients, we were able to document simultaneous postprandial hypoglycemia and hyperinsulinemia. Conventional treatment approaches, including medical nutrition therapy, acarbose, diazoxide, and octreotide, were either ineffective or limited by poor tolerance. Nifedipine and verapamil were used adjunctively with dietary modification, resulting in resolution of symptomatic hypoglycemic episodes. These agents are therapeutic options that can be used for some patients refractory to more traditional treatments. They should be tried before surgical procedures are considered for affected patients. These two cases demonstrate that calcium channel blockers may be efficacious and appropriate for select patients refractory to dietary interventions alone.



**Freeform/Key Words:** hypoglycemia, bariatric surgery, gastric bypass, calcium channel blockers, nifedipine, verapamil

Bariatric surgery is the most effective therapy for obesity with serious comorbidities. Despite well-documented benefits for long-term morbidity and mortality [1, 2], bariatric procedures are not without risks even years after the initial intervention. Postbariatric hypoglycemia (PBH) is one potential complication that can occur many years after surgery. Patients with PBH can experience serious morbidity, including hypoglycemic seizures, and report adverse effects on quality of life [3]. Hypoglycemia in general has been associated with premature death [4]. Interestingly, early reports documented an increased incidence of accidental deaths of patients after bariatric surgery, and some investigators have postulated that one plausible explanation may be undiagnosed hypoglycemia [5]. Neuroglycopenic and autonomic symptoms are often dismissed as expected phenomena after bariatric surgery, and patients can

Abbreviations: BMI, body mass index; CCB, calcium channel blocker; CR, controlled release; GLP-1, glucagon-like peptide 1; PBH, postbariatric hypoglycemia; RYGB, Roux-en-Y gastric bypass.

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suffer for years before a diagnosis is established. Successful management is often elusive, because of the difficulties in adherence and effectiveness of medical nutrition therapy.

The purpose of this report is to describe successful use of calcium channel blockers (CCBs) for the treatment of PBH in two patients. Dietary modification alone, as well as treatment with acarbose, diazoxide, and octreotide, had failed. We describe the diagnostic approach and response to two different CCBs.

## 1. Case Presentation 1

A 51-year-old woman with a history of hypertension and obesity presented to our comprehensive obesity and bariatric surgery clinic with severe postprandial hypoglycemia. She had undergone Roux-en-Y gastric bypass (RYGB) 17 years before, with a preoperative body mass index (BMI) of 47.7 kg/m$^2$. Eight years postoperatively she began experiencing episodes of clamminess, weakness, diaphoresis, and visual symptoms, occurring 60 to 90 minutes after high-carbohydrate meals. Episodes seemed to be more pronounced with stress, physical activity, and warm ambient temperature. She did not report any episodes of fasting hypoglycemia. The episodes became unpredictable and more severe, with capillary blood glucose values commonly dropping to 40 mg/dL. A contrast-enhanced CT scan at that time revealed a normal pancreas. An inpatient 72-hour fast performed 9 years before presentation to our clinic did not reveal hypoglycemia, and therefore fasting insulin levels were not checked. Strict high-protein, low–glycemic index carbohydrate dietary adjustments, and acarbose were unsuccessful. Partial pancreatectomy and gastric bypass reversal were considered at various times.

At presentation, her symptoms limited her daily activities and caused distress. Physical examination was unremarkable except for a BMI of 37.3 kg/m$^2$. Blood pressure was 118/76 mm Hg. Medications included lisinopril, hydrochlorothiazide, omeprazole, and various vitamins and supplements. Attempts to document laboratory values after a meal provocation test were unsuccessful for logistical reasons. Fasting laboratory results are summarized in Table 1. Because of the severity of her symptoms and hypoglycemic episodes, we decided to initiate therapy for PBH.

Fearing potential side effects, the patient declined acarbose therapy. Lisinopril was proactively discontinued, and verapamil was initiated at 40 mg three times daily. One month later, she noted resolution of hypoglycemic events, with capillary blood glucose never falling below 70 mg/dL. Five months later, she reported a few low values ranging from 30 to 40 mg/dL. Further questioning revealed that these episodes were associated only with missing her regularly scheduled meals and occasionally missing doses of verapamil in the context of competing work commitments. After the patient resumed a regular meal and medication

**Table 1. Values for Fasting Laboratory Analyses**

| | Patient 1 | Patient 2 |
|---|---|---|
| Glucose, mg/dL | 95 | 84 |
| Insulin, μIU/mL | 5.0 | 5.0 |
| C-peptide, ng/mL | 1.80 | 1.78 |
| Proinsulin, pmol/L | <1.6 | 2.2 |
| β-hydroxybutyrate, mg/dL | <2.1 | <2.1 |
| HbA1c, % | 4.8 | 5.4 |
| HOMA for insulin resistance | 0.66 | 0.64 |
| HOMA for β-cell function | 64 | 82 |
| HOMA for insulin sensitivity | 151 | 156 |

Phlebotomy was performed in the early morning after a 12-hr fast. Reference ranges: Fasting insulin 3 to 19 μIU/mL, C-peptide 0.8 to 3.5 ng/mL, proinsulin ≤8.0 pmol/L, β-hydroxybutyrate <2.8 mg/dL.
Abbreviation: HOMA, homeostatic model assessment.

schedule, hypoglycemic episodes resolved. Two years after starting the CCB, the patient was free of symptomatic hypoglycemia.

To further support the diagnosis and assess the continued therapeutic efficacy of nifedipine, the patient held the CCB for 72 hours, and laboratory tests were checked during postprandial hypoglycemia after a provocation meal (food known to commonly induce hypoglycemic episodes) in a supervised outpatient setting (Table 2). Two and a half hours after the meal, insulin and C-peptide levels were elevated during hypoglycemia.

## 2. Case Presentation 2

A 45-year-old woman with a history of hypertension, chronic kidney disease, and deep venous thrombosis presented with chronic postprandial hypoglycemia. She had undergone RYGB 14 years before, with a preoperative BMI of 52.7 kg/m$^2$, and lost 90 kg (nadir BMI 24.3 kg/m$^2$). Shortly after her surgery she developed dumping syndrome, characterized by diarrhea, abdominal cramps, nausea, diaphoresis, and lightheadedness, always occurring 15 minutes after she consumed concentrated sweets and subsequently controlled with dietary restriction. Medications included lisinopril, gabapentin, metoprolol, ranitidine, and coumadin.

One year before our evaluation, the patient presented to the emergency department with neuroglycopenic symptoms, described as very different from her dumping syndrome, and a glucose level of 32 mg/dL. Her symptoms resolved with a dextrose infusion. Home capillary glucose measurements 2 to 3 hours after meals were in the 30s, occurring up to three times daily and associated with visual symptoms, lightheadedness, tremors, paresthesias, and diaphoresis. Sweets and glucose tabs relieved her symptoms. She did not report fasting hypoglycemia, and a 72-hour fast was not performed.

Her physical examination was unremarkable except for a BMI of 40.6 kg/m$^2$ and borderline bradycardia. Blood pressure was 142/96 mm Hg. Fasting laboratory studies are shown in Table 1. CT scan did not reveal evidence of a pancreatic mass. Before her presentation, dietary modifications and acarbose therapy had been attempted unsuccessfully. Octreotide caused gastrointestinal symptoms. Also, because of the severity of her symptoms and hypoglycemia, we initiated nifedipine 30 mg controlled release (CR) daily. Metoprolol was continued at a lower dosage because of a history of palpitations. Two weeks later, the patient reported a dramatic improvement in the frequency and severity of hypoglycemia, occurring once or twice daily and falling below 50 mg/dL on only three occasions. Nifedipine was increased to 60 mg CR daily. On follow-up 4 months later, symptomatic hypoglycemia had resolved, with lowest reported blood glucose levels in the 70 to 80 mg/dL range. At 1 year after starting nifedipine, she continued to be free of symptomatic postprandial hypoglycemia, other than a few episodes when she had short lapses of medication adherence.

Similar to the first case, to further support the diagnosis and assess the continued therapeutic efficacy of verapamil, the patient held the CCB for 72 hours, and laboratory tests were checked during postprandial hypoglycemia after a provocation meal in a supervised outpatient setting (Table 2). At 2.5 hours after the meal, the patient became anxious and

**Table 2. Values for Provocative Tests**

| | Patient 1 | Patient 2 |
|---|---|---|
| Time after meal, h | 2.5 | 2.5 |
| Glucose, mg/dL | 44 | 74 |
| Insulin, μIU/mL | 8.0 | 4.0 |
| C-peptide, ng/mL | 4.0 | 1.9 |
| Proinsulin, pmol/L | 4.6 | 3.2 |
| $\beta$-hydroxybutyrate, mg/dL | <2.1 | <2.1 |

Reference ranges: Fasting insulin 3 to 19 μIU/mL, C-peptide 0.8 to 3.5 ng/mL, proinsulin ≤8.0 pmol/L, $\beta$-hydroxybutyrate <2.8 mg/dL.

requested termination of the test when her capillary glucose level reached 68 mg/dL. Results did not demonstrate hyperinsulinemic hypoglycemia.

Neither patient reported diarrhea during the hypoglycemic episodes. Both had normal values for TSH, cortisol, liver function tests, and insulin antibodies. Neither patient tested positive for serum sulfonylurea or meglitinides during hypoglycemia (data not shown). The patients did not report any adverse effects of the CCBs, including constipation.

## 3. Discussion

Metabolic bariatric procedures, including RYGB, are thought to exert their effect through pleiotropic mechanisms that modify both weight and glucose regulation, partly through changes in gut hormone responses [6]. The breadth of benefits has been well documented, but procedure-specific adverse effects must always be considered. Although uncommon, symptomatic PBH is a potentially serious long-term complication after RYGB and, less often, sleeve gastrectomy.

The pathophysiology driving PBH is not fully understood, but several plausible explanations have been investigated and reported. Details of these processes have been published recently [7] and may involve accelerated delivery of nutrients into the roux limb, stimulating a hypersecretory incretin effect, and thus very elevated postprandial levels of glucagon-like peptide 1 (GLP-1) and supraphysiologic insulin secretion from $\beta$-cells. Other mechanisms induced by RYGB may include relative suppression of counterregulatory hormones, improved insulin sensitivity and glucose disposal, and reduced clearance of circulating insulin levels.

Various diagnostic algorithms for PBH after RYGB have been published recently [8, 9]. Based on retrospective reviews from several institutions, salient clinical characteristics include the appearance of neuroglycopenic symptoms, usually several years after the procedure, occurring 1 to 4 hours after eating (as opposed to the earlier postprandial onset of dumping syndrome), and a higher incidence in women [10]. The generally accepted level for hypoglycemia is a documented glucose measurement of $\leq$55 mg/dL with the presence of Whipple's triad. It is recommended to check levels of glucose, insulin, C-peptide, and proinsulin with a mixed meal test [8] or meal provocation test [9]. Based on data from continuous glucose monitors, a provocation meal test using foods that typically trigger hypoglycemia for a given patient may better reflect real-life situations and may be more sensitive than a mixed meal test, for which there is no standardized protocol [11]. Atypical features, such as fasting hypoglycemia or early onset postprandial symptoms, should prompt investigation for alternative diagnoses. Provocation meal tests are often challenging and impractical, however, and others have suggested performing these studies only if patients do not respond to the usual therapeutic measures or if the diagnosis is in question.

Although a provocation meal test resulted in documented hyperinsulinemic hypoglycemia for patient 1, we were not able to demonstrate the same for patient 2. Therefore, it should be pointed out that the latter case represents a provisional diagnosis. One possibility for the failure to show hyperinsulinemic hypoglycemia in this case is that the phlebotomy was performed too early, because the patient requested to terminate the test. Moreover, although nifedipine was held for 72 hours beforehand, she was on a CR formulation, and hypoglycemia may have been suppressed by residual drug effect. We also cannot rule out remission of PBH at the time of provocative testing. Because of her underlying hypertension, however, the CCB was continued.

The foundation of treatment for PBH is medical nutrition therapy, which includes frequent, small meals high in protein and fiber and low in fat and high–glycemic index carbohydrates [9]. Unfortunately, adherence to dietary modification is inconsistent and sometimes ineffective [12]. If hypoglycemia continues, pharmacologic treatment should be added. Most of these therapies are based on case series or reports and extrapolated from their use in other conditions that cause hypoglycemia. Acarbose has been used as first-line treatment [13], although adverse gastrointestinal symptoms limit this option. Diazoxide

[14] and octreotide [15] have been used with mixed results, but side effects and patient nonadherence limit their utility. Interestingly, exogenous GLP-1 receptor agonists have also demonstrated improvement in PBH, possibly through downregulation of insulin secretion from $\beta$-cells and increased secretion of glucagon from $\alpha$-cells during conditions of hypoglycemia [16].

Historically, surgical treatments were recommended more commonly and included gastrostomy tube placement, reversal of gastric bypass anatomy, and distal pancreatectomy [17]. To bridge the treatment gap between nutrition and surgical therapy, it is worth considering the use of CCBs, specifically nifedipine or verapamil. Our first patient declined acarbose because of possible gastrointestinal symptoms and responded well to verapamil. Our second patient had not responded to dietary modification, acarbose, and octreotide, then demonstrated a complete response to nifedipine. Of note, both patients experienced mild relapses when they relaxed their adherence to nutrition modification, underlining the importance of continuous dietary vigilance.

CCBs have been shown to block insulin secretion through inhibition of voltage-gated calcium channels on $\beta$-cells [18] and have been used successfully for the treatment of hypoglycemia in other conditions. Nifedipine was used successfully by three patients with persistent hyperinsulinemic hypoglycemia of infancy after failure to achieve euglycemia with diazoxide or a somatostatin analog [19]. A report of hypoglycemia in a patient with metastatic insulinoma revealed a partial response to verapamil [20]. Recent case reports have shown CCBs to be effective in treating PBH when combined with strict dietary restrictions, acarbose, or both [21–23]. Although some investigators, using self-reported symptoms of hypoglycemia, have shown that the incidence of PBH may be as high as 30% [24], clinical detection in practice is much lower, and there currently exist no large, prospective, controlled trials to definitively guide pharmacological management. In addition, there are only two published reports demonstrating a complete response to CCB monotherapy [21, 22], and more documented cases on this topic will help guide efficacious and safe treatment options.

In conclusion, as the prevalence of severe obesity continues to grow at an unprecedented rate, clinicians will care for an increasing number of patients who have undergone bariatric surgery, and they will need to recognize long-term complications. PBH is a potentially serious adverse outcome presenting years after RYGB. In addition to medical nutrition therapy, several pharmacologic options should be attempted before surgical interventions are considered. Our cases offer additional evidence that therapy with inexpensive and well-tolerated CCBs represents a viable alternative for symptomatic PBH. Moreover, they illustrate how monotherapy with either nifedipine or verapamil may be sufficient.

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***Data Availability:*** All data generated or analyzed during this study are included in this published article or in the data repositories listed in References and Notes.

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