REVIEW

CME MOC

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# Hypoglycemia after bariatric surgery: Management updates

## ABSTRACT

Bariatric procedures have been shown to decrease mortality in patients with obesity and even induce remission of type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea. One common complication of bariatric surgery is hypoglycemia, which can be observed months to years later and can significantly impact patient lifestyle. No medications are currently approved for this indication. In this article, we discuss the treatment options available and being studied for post–bariatric surgery hypoglycemia (PBH).

## KEY POINTS

PBH typically occurs more than 12 months after bariatric surgery, with symptoms presenting 1 to 3 hours after eating. Symptoms that occur in a fasting state, nocturnal hypoglycemia, or exercise-induced hypoglycemia are less likely to be PBH.

Use of continuous glucose monitors and a food diary while tracking symptoms may assist in diagnosis, although the limitations of false lows and variable sensitivity should be considered when evaluating data from continuous glucose monitors.

Off-label medications to treat PBH are currently widely available (acarbose, diazoxide, nifedipine, verapamil), with other agents on the horizon, including glucagon pumps, avexitide, and insulin receptor antibodies.

Surgical intervention by reversal of gastric bypass or with gastric pouch restriction is considered a last resort.

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Bariatric procedures decrease long-term mortality in patients with obesity and even induce remission of type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea.[1–3] Given these benefits, more patients are choosing to undergo bariatric procedures to lose weight, and clinicians now encounter an increasing number of patients, both inpatient and outpatient, with a history of bariatric surgery. Hypoglycemia is a common complication of bariatric surgery that can be observed months to years after surgery.[4–10] Up to one-third of patients who underwent bariatric surgery reported symptoms of hypoglycemia during mixed meal challenges, while oral glucose tolerance testing has detected a variable incidence of 9.1% to 32.8%.[4–6]

A recently published meta-analysis of data from studies that assessed post–bariatric surgery hypoglycemia (PBH) by continuous glucose monitoring showed that more than 50% of individuals who had undergone bariatric surgery exhibited hypoglycemia.[7] Although these data may overestimate the rate of PBH, given the frequent false lows documented with use of continuous glucose monitors (CGMs), they underscore the high burden of hypoglycemia in this population. Hypoglycemia can be debilitating when symptomatic and has unknown consequences when asymptomatic. With the increased frequency of patients presenting with reported hypoglycemia, especially as continuous glucose monitoring becomes more common, diagnosing hypoglycemia, determining its cause, and knowing the available treatment options are imperative to tailor therapy and improve patient lifestyle.

The approach to PBH was thoroughly outlined in the review by Millstein and Lawler[8] in 2017. In this article, we discuss advances made since then and briefly summarize treatment options that are currently available as well as those being studied.

## DIAGNOSIS

The diagnosis of hypoglycemia is based on the Whipple triad, which consists of the following[8]:

- Low glucose measured in a blood sample
- Concurrent symptoms of hypoglycemia (palpitations, shakiness, sweating, anxiety, irritability, dizziness, hunger)
- Reversal of symptoms when low blood glucose is corrected.

PBH typically occurs more than 1 year after bariatric surgery and is more severe in patients undergoing Roux-en-Y gastric bypass (RYGB) surgery compared with sleeve gastrectomy, although the incidence remains similar.[4,9,10] Risk factors for PBH other than the RYGB procedure include female sex, lower preoperative body mass index and hemoglobin A1c, lower fasting glucose, lower glucose during the oral glucose tolerance test, and greater weight loss at 6 months.[9] The symptoms of PBH typically occur 1 to 3 hours after eating, and neuroglycopenic symptoms (behavioral changes, confusion, impaired cognitive function, seizure, loss of consciousness) are seen in severe hypoglycemia.

Symptoms that occur less than 6 to 12 months after surgery, in the fasting state, or less than 1 hour or more than 4 hours after eating are less likely to be PBH. In patients who report any of these, other causes for hypoglycemia should be explored through complete history, physical examination, and laboratory testing.[9] Differentials include dumping syndrome, side effects from medications (sulfonylureas, meglitinides, insulin use), hypothyroidism, hypoglycemia due to malnutrition, adrenal insufficiency, liver dysfunction, insulinoma, and insulin antibody syndrome, among others.

Dumping syndrome is quite common after bariatric surgery and typically occurs soon after surgery, while the onset of PBH can take years.[11] The symptoms of the 2 conditions are similar, but dumping syndrome occurs within 1 hour after eating vs 1 to 3 hours after eating with PBH.[11] It has been postulated that dumping syndrome and PBH are part of the same spectrum, known as early and late dumping syndrome, respectively.

Patients should be encouraged to check their fingerstick glucose at home during episodes before self-treating and to keep a food diary to document the timing of hypoglycemia in relation to food intake. An oral glucose tolerance test may provoke symptoms of severe dumping syndrome and should not be used. The mixed meal tolerance test is a more natural and helpful diagnostic tool but is laborious and can precipitate symptoms.[9]

## CONTINUOUS GLUCOSE MONITORING

A healthy person typically spends less than 1.1% of their time in a state of hypoglycemia (glucose < 70 mg/dL).[12] Continuous glucose monitoring for diagnosis of hypoglycemia in patients without diabetes has not been approved and should be used cautiously because CGMs have poor specificity for low interstitial glucose, leading to high false-positive rates, which can promote anxiety. Inaccurate readings can result from calibration errors, error margin (mean absolute relative difference), the position of sensors, interference from certain medications, humidity and extreme temperature, skin changes, and compression of sensors (if the patient lies on the site of the sensor).[13]

CGMs can assess the timing of symptoms in relation to interstitial glucose levels (with a typical lag time of some minutes) and association with food and can unveil asymptomatic or nocturnal hypoglycemia. The newer CGMs (eg, Dexcom G6 or G7, Freestyle Libre 3) are more accurate than those of previous generations. CGMs have greater sensitivity and specificity in diagnosing PBH than the mixed meal tolerance test, but a study comparing CGMs and fingerstick glucose monitoring has not been done.[14,15] Continuous glucose monitoring has been associated with reductions in both hypoglycemia and hyperglycemia in the PBH population, likely because it helps patients detect glycemic variability, allowing dietary modification and self-treatment to avoid hypoglycemia.[16]

Recently, the Dexcom Stelo was approved by the US Food and Drug Administration as the first over-the-counter CGM for patients without diabetes, followed by Abbott's Lingo, although cost and insurance coverage may remain a barrier.[17,18]

## PATHOPHYSIOLOGY

Meal-induced gut factors (glucose-dependent insulinotropic polypeptide, glucagon-like peptide [GLP] 1, direct neural factors, and nutrient factors) regulate glucose homeostasis after food intake. Secretion of gut factors after a meal induces a robust pancreatic beta-cell secretory response.[19] Alterations in the anatomy of patients following bariatric surgery leads to accelerated emptying of nutrients into the intestine, bypassing the stomach and allowing for earlier, more rapid absorption of glucose, which causes an earlier and

**TABLE 1**
**Medications for managing post–bariatric surgery hypoglycemia: Mechanisms of action**

| Medication | Mechanism of action |
|---|---|
| Acarbose[8,23,25,26] | Inhibits intestinal alpha-glucosidase—delays absorption of glucose from the intestine, decreases postprandial glycemic and insulinemic peaks |
| Diazoxide[26–28] | Reduces insulin secretion by inhibition of beta-cell adenosine triphosphate–sensitive potassium channels, induces hepatic gluconeogenesis |
| Octreotide, pasireotide[25,26,29] | Somatostatin analogs delay gastric emptying, reduce insulin and GLP-1 secretion |
| Nifedipine or verapamil[25,30] | Inhibits insulin release by inhibiting calcium channels in pancreatic beta cells |
| GLP-1 analogs[25,26,31] | Decreases variability in GLP release, which causes synchronous insulin and glucose peaks, delays gastric emptying, decreases appetite, stimulates glucagon secretion |
| Dipeptidyl peptidase 4 inhibitors[25,26] | Reduces the degradation of GLP-1 and glucose-dependent insulinotropic polypeptide and raises their levels |
| GLP-1 antagonist[32–34] | Prevents surges in GLP-1 and insulin, increases glucagon secretion |
| SGLT-2 inhibitors[35,36] | Reduces carbohydrate absorption by inhibiting intestinal SGLT-1 and increasing hepatic glucose production |
| Interleukin 1 beta antagonist (anakinra)[37] | Decreases dysregulated proinflammatory signaling, which can cause excessive insulin response |
| Glucagon[38,39] | Glucagon receptor agonist, stimulates glycogenolysis and hepatic gluconeogenesis |
| Insulin receptor antibody (XOMA 358)[40,41] | Reverses insulin-induced hypoglycemia by significantly decreasing insulin sensitivity and increasing hepatic glucose output |

GLP = glucagon-like peptide; SGLT = sodium-glucose cotransporter

greater rise in peak postprandial glucose. This results in increased GLP-1 release from the intestine, which induces increased insulin release from the pancreas and a subsequent drop in blood glucose.[8,9]

Thus, postprandial hypoglycemia after RYGB is typically attributed to the combined effects of more rapid nutrient transit from the gastric pouch to the gut and the enhanced incretin effect. Salehi et al[20] reported that continuous infusion of the GLP-1 receptor antagonist avexitide (exendin 9-39) reduced the meal-induced insulin response in patients without diabetes who had undergone RYGB compared with patients who did not undergo surgery.

Other factors that may impact PBH are a decreased glucagon response to hypoglycemia, postoperative increased insulin sensitivity, and decreased insulin clearance.[19] An increase in beta-cell mass after surgery (nesidioblastosis) was initially thought to contribute, but a subsequent analysis revealed no difference in overall beta-cell mass in patients with PBH compared with autopsy samples from obese and lean individuals.[21] Moreover, pancreatectomy has not been found to always be curative.

Use of alcohol or medications such as beta-blockers, some fluoroquinolones, nonsteroidal anti-inflammatory drugs, and sulfonylureas has been documented to worsen hypoglycemia.[22]

## MEDICAL MANAGEMENT

Dietary modifications are the cornerstone of PBH management. Frequent small, nutrient-dense meals rich in protein and low-glycemic foods and low in carbohydrates (15–30 g per meal) are recommended.[8] Healthy fats should be included to compensate for the lower carbohydrate content. Pure carbohydrates

**TABLE 2**
## Medications for managing post–bariatric surgery hypoglycemia: Dosages and side effects

| Medication | Dosage | Side effects | Notes |
|---|---|---|---|
| Acarbose[8,23,25,26] | 25 mg with 1 meal per day, slowly titrate up to 100 mg at every meal daily | Bloating, abdominal cramping, diarrhea | Used as first line because it's affordable and available<br>Not recommended in significant renal impairment<br>If hypoglycemia occurs, correct with simple carbohydrates (glucose, dextrose, honey)—complex carbohydrates (table sugar, juice, soft drink, candy) will not be effective |
| Diazoxide[26–28] | 50–100 mg twice daily to start | Fluid retention, edema, nausea, hypotension, hirsutism, headache | Consider dose reduction with renal impairment<br>Typically used for hypoglycemia from insulinomas<br>Affordability and insurance coverage are barriers |
| Octreotide, pasireotide[25,26,29] | Octreotide 25–100 µg SC before meals<br>Octreotide long-acting repeatable 20-mg intramuscular injection monthly<br>Pasireotide 50–300 µg SC before meals or 300 µg SC daily | Diarrhea, steatorrhea, cholelithiasis, hyperglycemia (more with pasireotide), QT prolongation | Safe to use in renal impairment<br>Expensive<br>Screening abdominal ultrasonography and electrocardiogram required<br>Pasireotide is longer acting than octreotide and is available for compassionate use in severe PBH<br>Oral octreotide is available but has not been used for this indication |
| Nifedipine or verapamil[25,30] | Verapamil 40 mg 3 times daily<br>Nifedipine 30–60 mg daily | Hypotension, edema | Safe to use in renal impairment |
| GLP-1 analogs[25,26,31] | Liraglutide 0.6 mg titrated to 1.2 mg SC daily, up to 1.8 mg daily | Nausea, constipation | Contraindicated in patients with family or personal history of medullary thyroid carcinoma<br>Use with caution in patients with history of pancreatitis<br>Safe to use in renal impairment but avoid dehydration<br>Expensive |
| Dipeptidyl peptidase 4 inhibitors[25,26] | Sitagliptin 100 mg once daily | Nausea, constipation | Inconclusive results—not recommended |
| GLP-1 antagonist[32–34] | Avexitide 30 mg SC twice daily | Headache, nausea, injection-site reaction | Recently granted breakthrough therapy designation by the US Food and Drug Administration for treating PBH and congenital hyperinsulinism, currently in phase 3 trial |
| SGLT-2 inhibitors[35,36] | Canagliflozin 100 or 300 mg daily<br>Empagliflozin 10–25 mg daily | Dehydration, urinary tract and genital mycotic infections, euglycemic diabetic ketoacidosis | Dosage adjustment required in renal impairment<br>Canagliflozin and empagliflozin shown to improve glycemic response to oral glucose tolerance and mixed meal tolerance tests, respectively, in patients with PBH |
| Interleukin 1 beta antagonist[37] | Anakinra 100 mg SC daily | | Anakinra and SGLT-2 inhibitor empagliflozin reduced the number of hypoglycemic events during a liquid mixed meal test |
| Glucagon[38,39] | Dasiglucagon 80 or 120 µg SC injection as needed for hypoglycemia | Nausea, vomiting, hyperglycemia, reduced appetite | Still under clinical investigation, use of glucagon in an insulin pump has shown satisfactory results<br>May be used for treatment of acute severe hypoglycemia |
| Insulin receptor antibody[40,41] | XOMA 358<br>3–9 mg/kg daily | Headache, hyperhidrosis | Results from phase 2 trial not announced yet |

GLP = glucagon-like peptide; SC = subcutaneous; PBH = post–bariatric surgery hypoglycemia; SGLT = sodium-glucose cotransporter

without protein or fat should be avoided as this can precipitate severe hyperglycemia.[23] Avoiding excessive caffeine and alcohol, which can cause hypoglycemia via inhibition of hepatic glucose release, is also important. Commercial products containing uncooked cornstarch, which degrades slowly in the intestines and is absorbed slowly, are reported to be helpful.[24] However, sustaining strict dietary modifications can be difficult for patients.

Patients with PBH should treat their hypoglycemia with a simple carbohydrate combined with protein or fat, as they will often have recurrent hypoglycemia if a simple carbohydrate is used alone.

No medications are currently approved for management of refractory PBH, but several medications are used off-label (**Table 1** and **Table 2**).[8,23,25-41] In a comparative study on the effect of acarbose, sitagliptin, verapamil, liraglutide, and pasireotide on PBH after RYGB, acarbose and pasireotide reduced postprandial hypoglycemia in persons with PBH.[25] Acarbose appeared to have a glucose-stabilizing effect, reducing peak postprandial hyperglycemia. Glucocorticoids have been used off-label to prevent hypoglycemia, but because of the possibility of causing iatrogenic Cushing syndrome, use for this indication is not recommended.[8]

## SURGICAL OPTIONS

In cases of nutrition- and medication-refractory severe hypoglycemia or complicated malnutrition management, enteral nutrition through a gastrostomy tube placed into the remnant stomach or jejunum should be considered.[42]

Surgical options, considered a last alternative due to risks and complications, include RYGB reversal, RYGB conversion to sleeve gastrectomy, and gastric pouch restriction.[43] If gastric bypass reversal is being considered, a trial of solely remnant stomach tube feeds (with no oral intake) should be pursued first. If this ameliorates hypoglycemia, then gastric bypass reversal may be of benefit.[8] Partial or complete pancreatectomy has been performed for this indication, but owing to a high rate of hypoglycemia recurrence and poor success rate, it is no longer recommended.[44,45]

## CONCLUSION

While bariatric surgery is an excellent treatment for obesity and its complications, the long-term repercussions of recurrent hypoglycemia may lead to impaired quality of life, motor-vehicle accidents, cardiovascular events, and regain of body weight (due to overcompensation by overeating). Thus, it is important to treat PBH with currently available agents concomitantly with dietary changes. CGM use should be considered in these patients as a mode of intervention, when possible, although it is important to consider the limitations of false measured lows.

Medications currently widely available to use off-label include acarbose, diazoxide, nifedipine, and verapamil. Other medications such as GLP-1 agonists, sodium-glucose cotransporter 2 inhibitors, dasiglucagon, octreotide, and pasireotide can be used off-label when available. Agents on the horizon include glucagon pumps, avexitide, and insulin-receptor antibodies. Surgical intervention by reversal of gastric bypass or with gastric pouch restriction is considered a last alternative.

## DISCLOSURES

Dr. Makin has disclosed teaching and speaking for Bayer. Dr. Iqbal reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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