

# Hypoglycemia After Upper Gastrointestinal Surgery: Clinical Approach to Assessment, Diagnosis, and Treatment

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**Context:** Post-bariatric hypoglycemia (PBH) is an increasingly encountered complication of upper gastrointestinal surgery; the prevalence of this condition is anticipated to rise given yearly increases in bariatric surgical procedures. While PBH is incompletely understood, there is a growing body of research describing the associated factors, mechanisms, and treatment approaches for this condition.

**Evidence Acquisition:** Data are integrated and summarized from studies of individuals affected by PBH and hypoglycemia following upper gastrointestinal surgery obtained from PubMed searches (1990–2020).

**Evidence Synthesis:** Information addressing etiology, incidence/prevalence, clinical characteristics, assessment, and treatment were reviewed and synthesized for the practicing physician. Literature reports were supplemented by clinical experience as indicated, when published data were not available.

**Conclusion:** PBH can be life-altering and severe for a subset of individuals. Given the chronic nature of this condition, and sequelae of both acute and recurrent episodes, increasing provider awareness of both the condition and associated risk factors is critical for assessment, prompt diagnosis, treatment, and preoperative identification of individuals at risk.

**Keywords:** hypoglycemia, post-bariatric hypoglycemia, upper gastrointestinal surgery, bariatric surgery

## Introduction

Increasing evidence indicates the importance of the gastrointestinal tract as a regulator of systemic metabolism. For example, metabolic surgery, such as Roux-en-Y gastric bypass (RYGB), produces profound improvements in glucose metabolism within days postoperatively, is more effective than medical therapies at improving control of type 2 diabetes (T2D), and reduces the need for medications.<sup>1–3</sup> However, with this metabolic benefit comes an increased incidence of hypoglycemia, or post-bariatric hypoglycemia (PBH). While hypoglycemia most commonly occurs following Roux-en-Y gastric bypass (RYGB), it can also occur with other bariatric or upper gastrointestinal surgeries including sleeve gastrectomy (SG),<sup>4</sup> duodenal switch (DS),<sup>5</sup> Nissen fundoplication (NF),<sup>6</sup> esophagectomy, gastrectomy,<sup>7</sup> and others.

While hypoglycemia can be mild in some individuals, PBH can be life-altering and severe for a subset, with hypoglycemia-associated injuries, disability, job and

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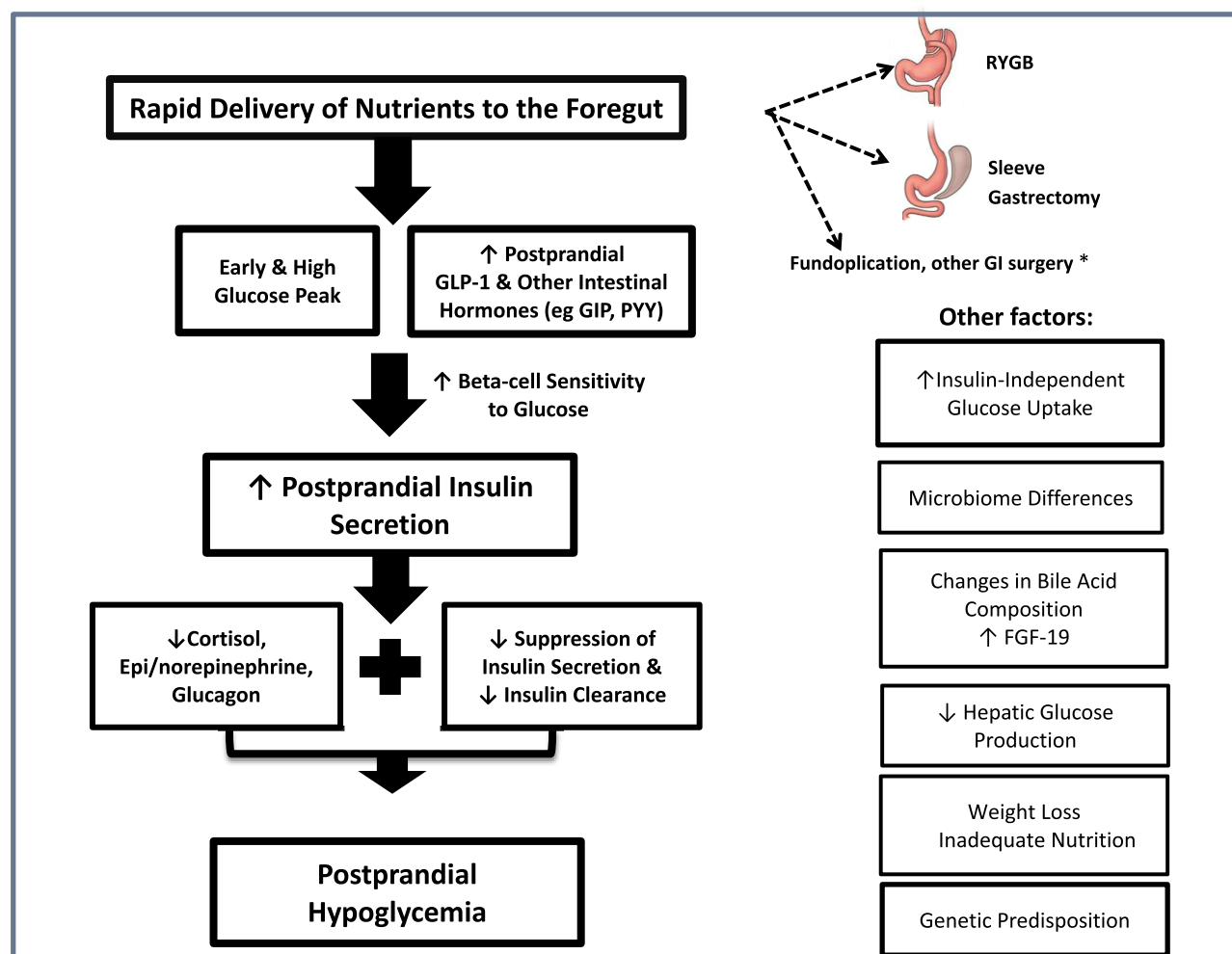
income loss, as well as impairment in broader activities of daily living and social functioning. With ever-increasing rates of bariatric and other gastrointestinal surgical procedures, raising provider awareness to aid in assessment (including pre-operative assessment), diagnosis, treatment, and timely referral is important and a goal of this review.

## Etiology

Following bariatric or upper gastrointestinal surgery there are profound alterations in postprandial glucose metabolism which are likely to contribute to the pathophysiology of PBH (summarized in Figure 1).<sup>8</sup> Surgical alterations in gastrointestinal anatomy result in the rapid emptying of nutrients out of the pouch or sleeve and into the foregut.<sup>9</sup> The ensuing rapid absorption of glucose leads to an early and high plasma glucose peak.<sup>9–11</sup> In parallel, secretion of the hormone glucagon-like peptide-1 (GLP-1) from the small intestine is

increased by as much as 10-fold.<sup>12</sup> These high levels of GLP-1, together with high postprandial glucose levels, markedly stimulates insulin release.<sup>10,13,14</sup> Surging postprandial insulin levels stimulate increased tissue glucose uptake, resulting in a rapid drop in plasma glucose levels 1–3 hours after meals.<sup>9,15–18</sup> Decreased insulin clearance and reduced beta cell suppression with hypoglycemia may further contribute.<sup>13</sup> Additionally, insulin-independent glucose uptake is increased in patients with PBH,<sup>17</sup> potentially linked to a >3-fold increase in plasma levels of the intestinally-derived hormone fibroblast growth factor-19 (FGF-19).<sup>19</sup>

Increases in intestinally-derived GLP-1 and FGF-19 in PBH suggest that intestine-specific mechanisms may contribute to changes in glucose metabolism after bariatric surgery. These include changes in bile acid composition and metabolism, which can modulate both GLP-1 and FGF-19,<sup>20</sup> and microbiome diversity and composition.<sup>21,22</sup> Interestingly,



**Figure 1** Mechanisms of hypoglycemia after upper gastrointestinal surgery. \*indicates that information about hypoglycemia after fundoplication and other upper GI surgeries is limited, and largely from published case reports and clinical experience.

a recent study reports that individuals post-bariatric surgery who have undergone cholecystectomy (vs those without cholecystectomy) have significantly increased risk for both PBH and dumping syndrome, further supporting the potential role of changes in the kinetics or composition of circulating or enteral bile acids in the pathogenesis of PBH.<sup>21,23</sup> Likewise, differences in the microbiome may contribute to inter-individual differences in glycemic and hormonal response to meals. Fermentation products of the microbiome, such as short chain fatty acids (SCFA), which are increased after RYGB,<sup>24</sup> can stimulate GLP1 release,<sup>25</sup> and may modulate insulin secretion,<sup>6,27</sup> potentially contributing to altered glucose metabolism.

Genetic factors may also be contributory.<sup>8</sup> For example, mutations in voltage-gated potassium channels KCNQ1 and KCNH1, identified as pathogenic in some individuals with long QT syndrome, may also increase secretion of GLP-1, GIP, and insulin, and impair glucagon secretion.<sup>26</sup> This would be predicted to increase the risk for an affected patient who chooses bariatric surgery, as in the case report by Mateo et al.<sup>27</sup> Research is ongoing to elucidate additional possible genetic factors related to PBH.

Individuals who have had upper GI surgery also have blunting of counterregulatory mechanisms, such as cortisol, catecholamines, and sympathetic nerve responses,<sup>13,28</sup> and these may be further impaired in patients with hypoglycemia.<sup>29</sup> Additional mechanisms implicated in hypoglycemia are decreased alpha cell responsiveness, insufficient glucagon secretion, inadequate glycogen stores, or reductions in substrates for gluconeogenesis.<sup>12,30</sup> Such impaired counterregulatory responses to hypoglycemia could result from recurrent hypoglycemia (sometimes unrecognized), but may also contribute to more prolonged duration of hypoglycemic episodes and reduced awareness of hypoglycemia. These patterns are similar to the impaired counterregulation and reduced awareness observed in patients with diabetes who experience frequent hypoglycemia.<sup>31</sup>

Recent studies have demonstrated elevated postprandial glucose levels induce macrophages to secrete interleukin-1 $\beta$  (IL-1 $\beta$ ), which stimulates insulin secretion and also increases glucose uptake into macrophages.<sup>32</sup> IL-1 $\beta$  also decreases the threshold for noradrenergic response in the hypothalamus (where IL-1B is expressed).<sup>33,34</sup> Treatment of individuals with PBH with an IL-1B antagonist increased nadir glucose during meal testing.<sup>35</sup>

Whether aberrant inflammatory responses contribute more broadly to PBH will require additional study.

## Incidence/Prevalence

The precise incidence and prevalence of PBH is unknown, due to differences in diagnostic criteria, the challenges of self-reporting of symptoms which are often non-specific, and the high rates of asymptomatic low glucose values. Severe hypoglycemia requiring hospitalization occurs in less than 1% of individuals;<sup>36</sup> however, estimates suggest that symptomatic hypoglycemia occurs in 10–30% of individuals,<sup>37,38</sup> and occurs after both RYGB and vertical sleeve gastrectomy (SG), with similar presentation and spectrum of severity.<sup>39</sup> There are no published data on the prevalence of hypoglycemia occurring after other upper gastrointestinal surgeries such as Nissen fundoplication or esophageal or gastric procedures, beyond case reports.<sup>6,7,40,41</sup>

## Risk Factors for Hypoglycemia

Risk factors for PBH identified during retrospective epidemiologic studies include female sex, younger age, no diagnosis of diabetes pre-surgery, history of hypoglycemia pre-surgery (not associated with diabetes or diabetes medications), lower pre-surgery hemoglobin A1C, and greater excess weight loss postoperatively.<sup>42,43</sup>

Given that risk for PBH may be increased in those with pre-operative hypoglycemia, the preoperative history should include questions about symptoms suggestive of hypoglycemia (eg, sweating, palpitations, tremors, and lightheadedness). If these are present, additional evaluations should be considered, such as laboratory testing, meal testing, and/or blinded CGM, to identify patterns of glucose excursions.

Interestingly, prospective studies have demonstrated that individuals who have hypoglycemia postoperatively had lower glucose levels on preoperative oral glucose tolerance testing (OGTT)<sup>44,45</sup>

However, differences between those who develop hypoglycemia and those who do not are of relatively small magnitude, and there are no defined diagnostic thresholds at present. It will be important in future studies to identify diagnostic thresholds which could be used clinically to identify high-risk individuals during the pre-operative evaluation and inform decision-making about the type of surgical procedure planned (or not).

EKG should be considered during the preoperative evaluation to rule out a long QT interval, given the

association between long QT caused by mutations in genes *KCNQ1*<sup>46</sup> and *KCNH1*<sup>47</sup> and postprandial incretin and insulin hypersecretion. One would predict that this would potentially pose increased risk to an affected individual who chooses bariatric surgery as in the case report by Mateo et al.<sup>27</sup> Moreover, as hypoglycemia can further prolong the QT interval, risk for arrhythmia may be increased.<sup>48</sup> Thus, each clinician should use clinical judgment and carefully consider patient-specific factors before recommending surgery for an individual with long QT syndrome.

## Assessment and Clinical Characteristics

Meticulous history-taking remains a critical first step in assessment of the patient with possible hypoglycemia. Information about episodes should include the severity (frequency, presence of neuroglycopenia, whether assistance required) and timing (relationship to fasting, meals, specific provocative foods, activity, and presence of nocturnal symptoms). Detailed records of symptoms, intake (both solid food and liquids), and activity can be helpful in identification of patterns linked to symptoms.

Symptoms of hypoglycemia can include sweating, tremor, profound hunger, palpitations, rapid heartbeat, changes in thinking, dizziness, difficulty concentrating, confusion, and alteration or loss of consciousness. Individuals may also report bizarre dreams or morning headaches, suggesting nocturnal hypoglycemia. Family or friends may report mood swings or changes in behavior during episodes of hypoglycemia, and that the patient has a distant stare or does not “look like themselves”. With severe hypoglycemia, brain function can be impaired (neuroglycopenia), potentially causing altered cognition, seizures, falls, motor vehicle accidents, and loss of consciousness. Reduced memory, both acutely during a hypoglycemic event, as well as a more generalized change in memory, may be reported.

Standardized questionnaires can be useful tools for measuring and tracking hypoglycemia symptoms clinically as well as in research settings. The Edinburgh Hypoglycemia Symptom Scale (EHSS) assesses adrenergic, cholinergic, and neuroglycopenic symptoms, while Gold and Clarke scales measure the awareness of hypoglycemia.<sup>49,50</sup>

The key clinical characteristics suggesting that PBH may be the cause of hypoglycemia are detailed in [Table 1](#).

Symptoms typically begin at least 1 year after surgery, although diagnosis may be delayed even longer given the non-specific nature of symptoms. Symptoms typically do not occur in the fasting state, but occur most commonly 1–3 hours (or even longer) after eating, especially after ingestion of rapidly absorbed, high glycemic index carbohydrates.<sup>51</sup> Other triggers for some patients may include activity, stress, prior alcohol ingestion, and caffeine. Ethanol inhibits hepatic gluconeogenesis, thereby increasing the risk of hypoglycemia,<sup>52,53</sup> and potentially attenuating the counterregulatory effect of glucagon.<sup>54</sup> Caffeine intake is associated with significant increases in cortisol, epinephrine, and norepinephrine, increased perception of symptoms of postprandial hypoglycemia at low-normal glucose levels, and greater symptoms at frankly hypoglycemic levels.<sup>55</sup> By contrast, a meta-analysis reported caffeine acutely decreases insulin sensitivity in individuals without diabetes.<sup>56</sup> Conflicting reports may explain the individual effects reported clinically to ingestion of caffeine. More studies will be required to fully assess relationships between caffeine intake and PBH. Consumption of liquids with meals can accelerate delivery of nutrients and stimulation of the intestine, further increasing the risk of hypoglycemia. Some patients with PBH have middle-of-the-night hypoglycemia; however, fasting hypoglycemia (upon arising) is not typical of PBH, and should prompt evaluation for other causes.

There is substantial overlap between symptoms of hypoglycemia and the so-called dumping syndrome. Typically, early dumping symptoms occur 10–30 minutes after a meal, and may include diarrhea, palpitations, lightheadedness, severe fatigue, nausea, and vomiting. At the time of these symptoms, glucose values are typically not low. However, hypoglycemia can develop later after the meal, sometimes as a component of “late dumping”.<sup>57</sup>

Individuals can have multiple episodes of hypoglycemia per day in response to foods and drinks that cause a spike and then drop – a so-called “roller coaster” pattern.<sup>58</sup> A vicious cycle can occur after self-treating severe symptoms of hypoglycemia with high glycemic index carbohydrates, sometimes in excess. While these raise glucose levels and improve symptoms in the short-term, they may cause another “spike” in glucose and subsequent recurrent hypoglycemia. This pattern may contribute to the observation that PBH is independently associated with significantly less weight loss at 2 years follow-up,<sup>43</sup> and that symptoms of hypoglycemia are

**Table I** Clinical Characteristics of Hypoglycemia

<b>Risk Factors:</b>	<b>Female sex, younger age, no diagnosis of diabetes pre-surgery, lower hemoglobin A1c pre-surgery, history of hypoglycemia pre-surgery, and greater excess weight loss postoperatively.</b> <sup>27,28</sup> <b>Clinically observed (not formally tested): associations with nutritional deficiencies and dysregulation of autonomic control.</b>
<b>Onset:</b> <b>Signs and symptoms of hypoglycemia:</b>	Typically 1–3 years or more after surgery. Sweating, tremor, profound hunger, palpitations, rapid heartbeat, dizziness. Bizarre dreams or morning headaches may suggest nocturnal hypoglycemia. Mood swings or changes in behavior. Individuals may be told that they have a distant stare or do not “look like themselves.” Severe hypoglycemia may cause neuroglycopenia, manifested as difficulty concentrating, confusion, alteration or loss of consciousness, hypoglycemic seizure.
<b>Timing of hypoglycemic events:</b>	<b>Characteristically:</b> 1 to 3 (or more) hours postprandial or with increased activity (so-called reactive pattern). For some can also occur in the middle of the night (not fasting), or with activity.
<b>Triggers:</b>	<b>Characteristically:</b> ingestion of rapidly absorbed, high glycemic index carbohydrates. <b>Others observed clinically may include:</b> activity, stress, alcohol ingestion, caffeine, and consumption of liquids with meals.
<b>Acute “Roller Coaster” Pattern:</b>	Multiple episodes of hypoglycemia per day in response to foods and drinks that cause a spike and then drop. <sup>33</sup> This may result in a vicious cycle whereby individuals are treating symptoms of hypoglycemia with high glycemic index carbohydrates, sometimes in excess. While these raise glucose levels and improve symptoms in the short-term, they may cause another “spike” in glucose and subsequent recurrent hypoglycemia.
<b>Chronic Patterns:</b>	Usually a chronic condition. Severity can fluctuate over time. Hypoglycemia may still be unpredictable even with strict adherence to recommendations and pharmacotherapies.
<b>Dumping Syndrome (DS) versus PBH:</b>	<b>Similarities:</b> <ul style="list-style-type: none"> <li>• Symptoms of palpitations, lightheadedness, weakness, dizziness, clammy, diaphoresis, and severe fatigue in both DS and PBH.</li> </ul> <b>Differences:</b> <ul style="list-style-type: none"> <li>• 10 to 30 minutes postprandial (early DS) vs 1 to 3+ hours postprandial (PBH).<sup>39</sup></li> <li>• At the time of symptoms, glucose values are typically not low in DS.</li> </ul> Note that hypoglycemia which develops later after the meal is sometimes considered a component of “late dumping.”

associated with increased risk of weight regain, and less self-reported adherence to nutritional recommendations.<sup>59</sup>

## Diagnosis

If the history is typical for PBH (postprandial neuroglycopenia occurring >1 hour after meals in patients with a history of GI surgery at least 6–12 months before symptom onset, no hypoglycemia with fasting), laboratory testing is performed to confirm hypoglycemia, rule out other causes of hypoglycemia, and assess hormonal responses to hypoglycemia. The diagnosis can be established by documented hypoglycemia at the time of neuroglycopenic symptoms, with resolution of symptoms with treatment to raise glucose (Whipple’s triad).<sup>60</sup> Glucose levels defining hypoglycemia vary widely. Recently published

American Diabetes Association guidelines define glucose levels <70 mg/dL as level 1 hypoglycemia and <54 mg/dL as level 2 hypoglycemia,<sup>61</sup> while Endocrine Society Guidelines define hypoglycemia as glucose <55 mg/dL in individuals without diabetes.<sup>62</sup> Venous glucose levels are required to establish the diagnosis, as capillary glucose measurements can be falsely low in the setting of relative hypotension or Raynaud’s disease.<sup>63–65</sup> This is an essential element of diagnosis of PBH, and is needed to help distinguish from symptoms of dumping syndrome.

Once hypoglycemia is established, differential diagnoses include malnutrition, side effects of medications or supplements, critical illness, hormone deficiencies (eg, adrenal), autoimmune hypoglycemia, insulinoma/proinsulinoma,<sup>66</sup> or nonislet cell tumors.<sup>62,67</sup> Laboratory



analysis to assess these possibilities can include plasma glucose, insulin, proinsulin, C-peptide, beta-hydroxybutyrate, and cortisol. While it is preferable to analyze these hormonal responses at the time of spontaneous hypoglycemia, this is often challenging to accomplish. Alternative strategies include provocation of hypoglycemia using the triggers reported by the patient, with the same hormonal testing noted above. If this is not possible or cannot be accomplished safely, and suspicion is low for fasting hypoglycemia based on history, we often perform laboratory evaluation in the morning after an overnight fast to permit analysis of the adrenal axis and to assess the impact of fasting on blood glucose levels and beta cell peptides. If morning cortisol levels are low ( $<10$  mcg/dL), an ACTH stimulation test should be considered to more fully define the adrenal axis.<sup>68</sup>

Other laboratory testing may be indicated depending upon individual or family history. A history of autoimmune or hematologic disease, postprandial hypoglycemia, or recent viral illness may raise suspicion for autoimmune hypoglycemia and prompt measurement of insulin autoantibodies. Measurement of IGF-1 and IGF-2 should be considered in those with fasting hypoglycemia, suspicion for MEN syndromes, neuroendocrine tumors, or non-islet cell tumors.<sup>69,70</sup> Additional symptoms such as flushing, hypotension, malnutrition, diarrhea, and weakness can be signs of carcinoid syndrome and should prompt measurement of urinary 5-HIAA.<sup>71</sup>

If history or laboratory testing suggest fasting hypoglycemia, a prolonged fast should be performed to determine whether beta-cell peptides are appropriately suppressed with hypoglycemia. This is typically performed in the hospital (traditional 72 hour fast); a shorter-term fast may be adequate for some patients and may be performed in the outpatient setting if appropriate monitoring to ensure safety is available.

Administering a provocative meal and then obtaining lab testing at the time of an episode is rarely required if history is typical. Most studies report the use of liquid meals (eg, commercial nutritional liquids) as these are less influenced by interindividual differences in gastric emptying rates, but these are not physiologic and there is no consensus for a standardized test meal. An alternative is to use a test meal identified by the patient as a provocative meal in daily life. Both of these possibilities are highlighted in the Endocrine Society guidelines on the evaluation of hypoglycemia.<sup>62</sup> Some have advocated glucose tolerance testing, but this can yield false positive results,

as 10% of the healthy asymptomatic population can have asymptomatic low glucose levels (nadirs of 47 mg/dL or below) during oral glucose tolerance testing.<sup>72</sup> Moreover, this test can provoke severe “early” dumping syndrome in this population, with symptoms including abdominal pain, cramping, diarrhea, diaphoresis, dizziness, palpitations, nausea, and vomiting.<sup>62,73,74</sup> Testing may also provoke severe hypoglycemia, and should only be done in the appropriate setting where rescue treatment is available to ensure safety. Moreover, there are no established diagnostic thresholds for testing, making interpretation of results challenging.

Continuous glucose monitoring (CGM) in the blinded (masked) mode is valuable – not for diagnosis, but for elucidating glycemic patterns and linking these patterns to symptoms. Individuals are asked to wear a CGM sensor for 7–10 days, while keeping a diary of food, activity, and symptoms. While CGM is less accurate in the hypoglycemic ranges, and should not be used for diagnostic purposes, this method allows pattern analysis and links to diary events can also help the patient identify their triggers for hypoglycemia.

## Acute Treatment of Hypoglycemia

While there are some similarities in treatment of hypoglycemia between individuals with diabetes and PBH there are key differences as well. When symptomatic hypoglycemia develops, 10–15 g of oral carbohydrates (eg 3–4 glucose tabs or gel, 4 ounces of juice) are recommended to relieve symptoms and rapidly increase glucose to safe levels. However, if the individual is being treated with acarbose, treatment with glucose exclusively is recommended, as absorption of other forms of carbohydrate (eg, sucrose, juice) will be delayed. If severe neuroglycopenia develops, glucagon can be administered by family members via either injection or nasal delivery.

Since oral carbohydrates can produce a glucose “yo-yo” effect, initial treatment should be followed by a snack containing low glycemic index (LGI) carbohydrate mixed with fat/protein, such as one tablespoon of natural (unsweetened) peanut butter on a half-slice of whole-wheat bread, to reduce rebound hypoglycemia.<sup>8,75</sup> While nut butters have high caloric density, they are convenient and generally effective for preventing rebound hypoglycemia. In the short-term, achieving safety is paramount. However, long-term nutritional guidance should incorporate the need to optimize overall caloric balance to reduce weight gain. Since some individuals are very sensitive to

oral carbohydrate, the dose of treatment needed to increase glucose should be individualized after review of glycemic responses in order to balance efficacy of treatment vs avoidance of rebound hyperglycemia.

## Chronic Treatment of PBH

Goals of treatment should include decreasing the frequency and severity of hypoglycemia, thereby helping to avoid injury, disability, and improving quality-of-life. Treatment approaches include medical nutrition therapy and medications (summarized below).

## Patterns of Intake at Presentation

While there is a great degree of variability in how individuals attempt to manage hypoglycemia symptoms, two patterns are often observed clinically. Many individuals severely reduce overall food intake (or carbohydrates specifically) in an attempt to feel better and/or prevent hypoglycemia during critical periods of the day (eg, work hours). Modified ketogenic plans are often adopted. Unfortunately, we have observed clinically that this pattern can sometimes result in weight loss, malnutrition, fatigue, activity, or exercise-induced hypoglycemia, and in some cases emergence of more nocturnal hypoglycemia. Fear of eating, food intolerance, or aversion can be additional challenges to address.

A second pattern can be the near-continuous intake of either solid or liquid carbohydrates, in an effort to avoid or treat the symptoms. Consequences of this pattern can include weight gain, and repeated cycles of rebound hypoglycemia (initial treatment provoking hyperglycemia and then another episode of hypoglycemia) multiple times per day. Overnight hypoglycemia may follow bedtime or nocturnal eating. Individuals presenting with this pattern may be reluctant to decrease intake of foods or liquids which are perceived to help treat their hypoglycemia; however, in many cases, avoidance of high glycemic index carbohydrates will actually be effective in breaking this cycle and reducing hypoglycemia.

## Medical Nutrition Therapy

Medical nutrition therapy (MNT) is foundational to the treatment of PBH, and ongoing follow-up with a registered dietitian nutritionist who is experienced in this condition is essential. The key components of MNT are summarized in Table 2.<sup>75</sup> It is recommended that individuals with PBH eat meals and snacks containing 20–30 grams and 10–15 grams of LGI carbohydrate, respectively, every 3–4 hours;

**Table 2** Key Components of MNT for Post-Bariatric Hypoglycemia

Choose low glycemic index (LGI) carbohydrate, and avoid high glycemic index carbohydrates.
Controlled portions of LGI carbs: 20–30 grams for meals and 10–15 grams for snacks.
Include heart-healthy fats: 15 grams per meal and 5 grams per snack.
Emphasize optimal protein intake at each meal and snack.
Space meals and snacks 3–4 hours apart.
Avoid liquids with meals and for 30 minutes after meals.
Avoid caffeine and alcohol always.
Optimize vitamins and minerals.

**Note:** Data from Suhl et al.<sup>75</sup>

these should be paired with proteins and healthy fats, while avoiding liquids for at least 30 minutes following intake of food. While this is an initial recommendation, it is important to review glycemic patterns and revise the meal plan (including carbohydrate content) as needed for the individual patient.

Cornstarch (CS), in uncooked form, is another helpful adjunctive tool which has been used for years by individuals with glycogen storage disorders and in children with type 1 diabetes.<sup>76</sup> CS can be combined with MNT in PBH.<sup>77</sup> CS is not readily absorbed by the small intestine, but is slowly hydrolyzed by pancreatic amylase and intestinal glucoamylase to provide a steady supply of exogenous glucose. It can be purchased easily at the grocery store, mixed in unsweetened beverages, plain yogurt, or cottage cheese, and can be consumed during the day and/or before bed, depending upon the timing of hypoglycemia. Commercial products that contain uncooked CS (eg, nutritional bars, drinks) are also available.

The patient should be aware that MNT is unlikely to completely eliminate hypoglycemia, that MNT needs to be individualized based on initial response, and that even optimal MNT often requires the addition of one or more medications.

## Micronutrient Status

Ensuring a lifetime intake of prescribed vitamins and monitoring of levels of vitamins D, A, B1, B12, and other B-complex vitamins, as well as iron, calcium, zinc, copper, and folic acid is recommended.<sup>78</sup> Assessment of prior or current micronutrient deficiencies is important, as bariatric surgery may reduce both intake and absorption. While a direct link with PBH has not yet been formally established, the association of micronutrient deficiencies

(eg, B1, B12, magnesium, D)<sup>79</sup> and autonomic neuropathy has been reported in the literature.<sup>80,81</sup> Compromised autonomic nervous system functioning could impair counter-regulatory responses to hypoglycemia. For example, one case report of an individual with type 1 diabetes demonstrated that correction of B12 deficiency resulted in increased counter-regulatory hormone response and improved hypoglycemia awareness.<sup>82</sup>

## CGM

Use of a personal CGM (not blinded) can be helpful in detection and treatment of dropping glucose levels before impairment in cognition (neuroglycopenia) develops, especially for those with unawareness or reduced awareness of hypoglycemia. Unfortunately obtaining insurance coverage for CGM devices can be difficult, as they are not uniformly approved for this indication at present, and the out-of-pocket cost is prohibitive for most.

## Pharmacotherapy

Pharmacotherapy is utilized as an adjunctive therapy when MNT is insufficient (summarized in Table 3). Acarbose is a first step due to its effect of slowing carbohydrate absorption, thus attenuating the postprandial glucose and insulin spike.<sup>74,83–86</sup> Additional strategies aimed at reducing incretin (eg, GLP1) and insulin responses to meals include diazoxide (oral medication which reduces insulin secretion), and somatostatin receptor analogs (inhibit secretion of insulin and GLP1, but also glucagon and other gastrointestinal peptides).<sup>74,87–90</sup> Octreotide can be self-administered via subcutaneous injection 3–4 times per day depending upon individual patterns. While there is some evidence that this short-acting octreotide is more effective in terms of symptom control,<sup>74,91</sup> long-acting somatostatin analogs (LAR)<sup>92</sup> may be an easier option for some. These are administered once every 3–4 weeks, but require a nurse skilled in depot injections. Both short- and long-acting somatostatin analogs have been shown to also improve early dumping.<sup>74</sup>

The use of these medications is often limited by tolerability and side effects, and patients should be closely monitored. Cost and insurance approval can be an added barrier to care, and appeals may be needed to obtain coverage.

Additional therapies which have been reported to have efficacy in PBH include calcium channel blockers<sup>93</sup> and liraglutide<sup>94</sup> (Table 3), but caution must be used due to the potential for hypotension and worsening of hypoglycemia, respectively.

## Additional Therapies

When MNT, CGM, and pharmacotherapy are not successful and quality-of-life is severely compromised, additional more invasive treatments may be considered. Placement of a feeding gastrostomy (G)-tube into the remnant stomach (bypassed portion) can be successful, as this delivery route does not stimulate incretin or insulin secretion.<sup>95–97</sup> However, individuals will still develop hypoglycemia if they take carbohydrates by mouth, so oral carbohydrates should be avoided. Involvement of a RDN experienced in PBH is needed to help optimize the choice of formula and delivery rates.

Rare individuals with PBH continue to have episodic hypoglycemia despite continuous G-tube feeding. In this setting, reversal of the surgical procedure toward normal anatomy may be considered, when feasible; while this typically improves hypoglycemia, it does not always fully resolve hypoglycemia,<sup>97–100</sup> and may result in additional (but typically modest) weight regain.<sup>101,102</sup>

While initial reports describing PBH utilized pancreatectomy to reduce hypoglycemia, pancreatectomy is no longer considered as an appropriate therapy for the majority of patients with severe PBH for several reasons. First, the pancreas is typically an innocent bystander, with altered nutrient flow and excessive incretin stimulation, rather than increased islet mass, driving insulin production. Consistent with this concept, pancreatectomy is associated with high rates of recurrent hypoglycemia.<sup>103</sup>

## Investigational Treatments (Not FDA Approved)

Given that current therapeutic options are limited, clinicians often have questions regarding the status of investigational approaches described in the literature, and ongoing research aimed at identifying new therapeutic options for PBH. It is important to note that these are not FDA-approved.

To target the excessive secretion of GLP-1 in PBH, clinical trials of a GLP-1 receptor antagonist are underway. Twice-daily administration of SC avexitide increases the glucose nadir and prevents severe hypoglycemia.<sup>104</sup> At the time of this publication, a Phase II clinical trial has been completed.

Another approach under investigation is the use of a closed-loop glucose-responsive automated glucagon delivery (AGD) system.<sup>105</sup> Automation was achieved by development of a hypoglycemia algorithm,<sup>106</sup> which was embedded in an artificial pancreas system, guided by CGM. The AGD system delivered a mini-dose of stable liquid glucagon via a patch pump when glucose levels were dropping rapidly, or



**Table 3** Pharmacotherapy for Hypoglycemia After Upper GI Surgery

	Route	Dosing Schedule*	Mechanism of Action	Possible Side-Effects/Adverse Events
Acarbose	PO	20 minutes before each main meal up to 300 mg/day	Delays digestion of carbohydrate via enzymatic inhibition.	Flatulence, diarrhea, abdominal pain. May decrease over time. Less with prescribed MTN.
Diazoxide (suspension)	PO	Q 8–12 hours (including hs)	Inhibits insulin release.	Fluid and sodium retention, anorexia, nausea, vomiting, abdominal pain, ileus, diarrhea, hirsutism.
Octreotide	SQ	Q 6–8 hours, pre-meal (timing individualized based on response)	Short-acting somatostatin analog which inhibits secretion of insulin and other GI peptides, slows gastric emptying.	Cholelithiasis, sinus bradycardia, conduction abnormalities, arrhythmia, diarrhea, loose stools, nausea and abdominal discomfort, pain on injection, headache, dizziness, hypothyroidism, worsening hypoglycemia.**
Sandostatin LAR Depot	IM	Q 3–4 weeks	Long-acting somatostatin analog, inhibits insulin secretion, as well as other GI peptides, slows gastric emptying.	Nausea, headache, abdominal pain, dizziness, myalgia, generalized pain, back pain, fatigue, flatulence, upper respiratory tract infection (URI), pruritis, rash, sinusitis, vomiting.*** Typically cannot be self-injected.
Pasireotide <sup>57</sup>	IM	Q 4 weeks	Somatostatin analog which inhibits secretion of insulin and other GI peptides, slows gastric emptying.	Diarrhea, abdominal pain, nausea, fatigue, abdominal distention, vomiting, upper abdominal pain, hyperglycemia, hypertension, QT prolongation, sinus bradycardia, cholelithiasis, liver enzyme abnormalities, headache, alopecia, arthralgia, back pain, extremity pain, anemia.
<b>If the above are contraindicated, not tolerated, or cannot be used for other reasons consider options below, though reports of efficacy in the literature are inconsistent.</b>				
Calcium channel blockers (eg, verapamil, nifedipine) <sup>70,71</sup>	PO	Daily	Block calcium channels, including in the pancreatic beta cell, decreasing insulin release.	Hypotension, constipation, fatigue, dizziness, dyspnea, nausea, bradycardia, AV block total, headache, edema, 2nd/3rd degree block, rash, congestive heart failure, pulmonary edema, flushing, elevated liver enzymes.
Liraglutide <sup>71</sup>	SQ	Daily	Slows gastric transport. Case reports indicate may reduce hyperglycemia and glucose variability.	Nausea, diarrhea, headache, nasopharyngitis, vomiting, decreased appetite, dyspepsia, URI, constipation, back pain, worsening hypoglycemia. Warning in place regarding pancreatitis, renal impairment, thyroid C-cell tumors.

**Notes:** \*Dosing schedule, amount, and titration requires individualization based upon patterns of hypoglycemia, presence of side-effects/tolerability. \*\*Hypoglycemia may occur due to concurrent inhibition of glucagon. \*\*\*Frequency and presence vary by dose and indication for Sandostatin LAR depot.

when hypoglycemia developed. Compared with vehicle (placebo), the AGD closed-loop system resulted in significantly less hypoglycemia, with no rebound hypoglycemia.

Investigation of the same ready-to-use (stable) glucagon as a SQ injectable medication for use as rescue for hypoglycemia is also ongoing.

## Challenges

Challenges in the treatment of PBH are many and multifactorial (summarized in Table 4). There is a spectrum of severity of

PBH, and this can fluctuate over time. Even with strict adherence to recommendations and pharmacotherapies, individuals may still experience hypoglycemia that is unpredictable.

Some individuals respond to a combination of MNT and behavioral modifications (eg, avoiding meal-related triggers), and may not require pharmacologic therapy. However, many individuals will require medications, particularly in those with severe PBH. Individuals with severe PBH may experience frequent hypoglycemia requiring assistance, neuroglycopenia (seizures, loss of consciousness),

**Table 4** Potential Treatment and Self-Care Challenges Observed Clinically in Individuals with Hypoglycemia After Upper GI Surgery

<b>Trust</b>	<ul style="list-style-type: none"> <li>• History of multiple diets, and possibly conflicting recommendations</li> <li>• Fear of increasing hypoglycemia with treatment</li> <li>• Fear of weight gain with treatment</li> <li>• Frustration with new/unanticipated diagnosis of hypoglycemia after surgery</li> </ul>
<b>Physiologic Factors</b>	<ul style="list-style-type: none"> <li>• Stomach capacity</li> <li>• Food intolerance</li> <li>• GI symptoms: nausea, vomiting, reflux, abdominal pain, and bloating</li> <li>• Dumping syndrome</li> <li>• Possible malnutrition</li> </ul>
<b>Treatment Factors</b>	<ul style="list-style-type: none"> <li>• Changing long-established patterns</li> <li>• Frequent glucose monitoring by fingerstick or CGM</li> <li>• Frequent attention to glucose levels in relation to food, drinks, activity, and other triggers</li> <li>• Preparation &amp; planning needed to help avoid and treat potential hypoglycemia</li> <li>• CGM alarms requiring attention and action (potential alarm fatigue)</li> <li>• Some medications with multiple daily dosing (possibly injectable)</li> <li>• Side-effects from medications limiting tolerability</li> </ul>
<b>Social Factors</b>	<ul style="list-style-type: none"> <li>• Cultural practices/norms which vary from MNT recommendations</li> <li>• Family/social group food and drink choices differing from MNT</li> <li>• Holidays &amp; celebrations</li> <li>• Educational needs of the family/friends</li> </ul>
<b>Occupational Factors</b>	<ul style="list-style-type: none"> <li>• Need for accommodation to eat every 3 hours, monitor glucose, and treat hypoglycemia</li> <li>• Fatigue after acute hypoglycemia impacting ability to function at work</li> <li>• Cognitive changes impacting occupational functioning</li> <li>• Concern about drawing attention to hypoglycemia and impact on job security</li> <li>• Potential to affect safety of self or others at work</li> <li>• Disability resulting from severe PBH</li> <li>• Loss of driving privileges if severe disease has threatened safety</li> </ul>
<b>Economic Factors</b>	<ul style="list-style-type: none"> <li>• Reduction in income related to need to change jobs, decrease hours, or disability status</li> <li>• Cost of foods recommended in MNT</li> <li>• Potential for food insecurity and less control over options if accessing community services</li> <li>• Other costs of care: appointment copays and charges, chronic medications, acute treatment (glucose and glucagon), glucose monitoring supplies (CGM, strips, meter)</li> </ul>
<b>Emotional Factors</b>	<ul style="list-style-type: none"> <li>• Stress and fatigue related to treatment, CGM alarms which interrupt sleep</li> <li>• Possibly symptomatic for years without diagnosis</li> <li>• Stigma of hypoglycemia (formerly attributed to psychiatric conditions or stress)</li> <li>• Concerns about safety when leaving home</li> <li>• Feelings of isolation</li> <li>• Expectations of quality-of-life after bariatric surgery</li> <li>• Demoralization/frustration when even if strictly adherent to treatment, hypoglycemia can still recur and at times be unpredictable</li> </ul>

falls, motor vehicle accidents, job, and income loss. Individuals may express feelings of social isolation and loneliness. Memory impairment or changes in cognition have been reported both acutely and chronically. The relationship between PBH, psychosocial impact, and cognitive functioning has not yet been reported in the literature.

Further, while clinical experience has demonstrated that PBH is usually a chronic condition, data are lacking on the long-term impact of PBH on health; thus providing guidance about the prognosis of PBH is challenging, and the uncertainty can be difficult for clinicians, patients, and their families alike.

## Conclusion

Hypoglycemia is an increasingly encountered complication of upper gastrointestinal surgery and its prevalence is anticipated to rise in the setting of yearly increases in bariatric surgical procedures. Given the spectrum of severity, sequelae from both acute and recurrent episodes, and potential for life-altering disability, prompt diagnosis and treatment is essential for safety. Additionally, individuals with hypoglycemia who are considering bariatric surgery should be carefully evaluated for the presence of any signs and symptoms of hypoglycemia; if these are present, referral to an endocrinologist should be considered to help make informed decisions about the possible risk of PBH.

Future research should continue to investigate the mechanisms of PBH to increase understanding, identify risk factors, develop treatments, and possibly identify modifications to upper-gastrointestinal surgical procedures to reduce the risk of hypoglycemia while retaining the efficacy of surgery.

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