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Medical Nutrition Therapy for Management of Post-Bariatric Hypoglycemia: A Team-Based Approach

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Abstract

As the number of bariatric surgeries performed increases yearly, Post-Bariatric Hypoglycemia (PBH) is an increasingly encountered late complication. Increasing awareness and identification of individuals at risk for or with PBH is critical given the potential impact on an individual's safety, nutrition, and quality of life. This mini-review provides a background of PBH, with a special focus on the role of the RDN and recommendations for medical nutrition therapy as the foundation for management of PBH. A team-based approach involving the individual, the RD, and other clinicians is critical in providing on-going assessment and individualization of MNT in the long-term management of PBH.

Keywords: Mal nutrition; Quality of life; Detitian; Metabolism; Carbohydrates

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Introduction

The number of bariatric surgical procedures performed in the US continues to rise each year, with 256,000 procedures in 2019 [1]. Bariatric surgery achieves not only weight loss, but also improved systemic metabolism; in those with type 2 diabetes, bariatric surgery can improve glycaemic control and induce remission [2-4]. Unfortunately, with these metabolic benefits also comes an increased risk for hypoglycaemia, termed Post-Bariatric Hypoglycaemia (PBH).PBH may emerge as a late complication of bariatric surgery one to three years or more after the initial procedure, and can be severe for a subset of individuals. Severe low glucose events can significantly impact quality of life, threaten safety, and are disabling for some individuals.

PBH most commonly occurs following Roux-en-Y gastric bypass (RYGB) but can also occur with other bariatric or upper gastrointestinal surgeries including sleeve gastrostomy [5,6]. Laparoscopic adjustable gastric band, [7], duodenal switch [8], gastrostomy or esophagectomy [9], and Nissan fundoplication [10],

The purpose of this review is to increase dietitian awareness of PBH and to present current treatment approaches with a special focus on Medical Nutrition Therapy (MNT).

Etiology

The physical changes and hormonal shifts after upper gastrointestinal surgery that impact glucose metabolism and contribute to the pathophysiology of PBH are summarized in **Figure 1** [11]. Rapid emptying of undigested nutrients out of the stomach or pouch into the small intestine leads to rapid absorption of glucose and an early and high glucose peak after meals [12-14]. This influx of nutrients also signals intestinal secretion of the hormone Glucagon-Like Peptide 1 (GLP1) - at levels up to 10-fold higher after surgery. In turn, these high levels of glucose and GLP1 synergize to stimulate excessive insulin release; [13,15,16] additional contributors to hypoglycaemia are also listed in **Figure 1** [11,17-19].

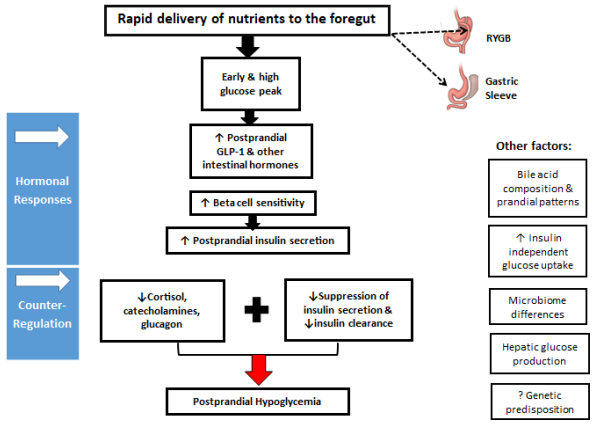

Figure 1 Potential mechanisms contributing to post-bariatric hypoglycemia.

Once hypoglycemia develops, a protective counter regulatory hormonal and neural response should occur; however, in post-surgical patients, these counter regulatory responses are impaired [20,21], potentially contributing to more severe and prolonged hypoglycaemia. These patterns are similar to those observed in individuals with diabetes who experience recurrent hypoglycaemia [22].

Literature Review

Clinical presentation

It is important to recognize that symptoms of hypoglycaemia are nonspecific and can be due to many underlying conditions. In the post-surgical population, these symptoms overlap substantially with those of dumping syndrome, including feeling hot, sweating, fatigue, weakness, palpitations, nausea, and the need to lie down. Often the timing of symptoms can help to distinguish, as dumping often occurs 10-30 minutes postprandial, while PBH typically occurs 1-3 hours after eating [23]. To add further complexity, patients may experience both symptoms of early dumping as well as subsequent hypoglycaemia (formerly referred to as "late dumping").Additional conditions which may produce similar symptoms include hypotension, tachycardia's, anxiety, or other conditions accompanied by adrenergic activation.

Individuals who experience PBH may not initially recognize that symptoms they are experiencing are related to their history of bariatric surgery, as the onset of symptoms typically occurs 1-3 (or more) years after surgery. Onset of symptoms before 1 year postoperatively is atypical and should prompt further investigation to rule out other etiologies.

Prevalence: Prevalence estimates for PBH are uncertain, varying based on the methods used to define it. Estimates for severe PBH based on analysis of hospitalization records, clinic visits, and surgical databases suggest prevalence below 1% [24-26]. However, survey-based studies have found that 34% of patients reported symptoms suggestive of at least mild postprandial hypoglycaemia post-RYGB or VSG [27] and 11.6% reported severe and/or medically confirmed hypoglycaemia [24]. Without documentation of low blood glucose, it is difficult to determine with certainty whether symptoms are indeed related to hypoglycaemia, dumping syndrome, or other disorders with overlapping symptoms. While Continuous Glucose Monitor (CGM) monitoring may overestimate the frequency of low glucose, one study using CGM showed that 75% of asymptomatic post-RYGB patients (average 7 years post-surgery) had sensor glucose values below 55 mg/dL, while nonsurgical controls entirely remained above that threshold [28].

Diagnosis: A detailed medical history, including prior surgical procedures, meal patterns and composition, weight, and severity and timing of potential hypoglycaemic events, both before and after surgery, are essential elements in the assessment of PBH. This initial information helps the clinical team determine the severity and guide further evaluation and treatment.

A thorough assessment of hypoglycaemic events includes an understanding of both severity and timing. To gauge severity, the history should focus on the presence and frequency of neuroglycopenia (changes in thinking, difficulty speaking and concentrating, confusion, seizures, falls, loss of consciousness), hypoglycaemia unawareness, and need for assistance to treat a low glucose. Timing of events can be determined by an interview, complemented by an event and symptom log completed by the patient, both including relation to fasting, meals (specific provocative foods), liquids, activity, and presence of overnight symptoms. Coupling a detailed event log with professional CGM, while not diagnostic, can help identify patterns and triggers. Detailed review of additional medical conditions, medications and supplements, and intake of alcohol and other recreational drugs is also essential.

If the history and data are suggestive of PBH, additional steps are required to establish the diagnosis. First, it is important to determine whether symptoms of hypoglycaemia are associated with low glucose levels (<54 mg/dL deemed as severe hypoglycaemia), and whether symptoms are relieved by the intake of carbohydrate (Whipple's triad) [29,30]. An Oral Glucose Tolerance Test (OGTT) is not recommended as this testing is not physiologic, can yield false positive results even in healthy individuals [31], and can provoke severe dumping syndrome in this population [11,32,33].

Once the diagnosis is established, analysis of fasting glucose and hormones (e.g. adrenal, beta-cell peptides) and general health indices (liver, kidney function, blood count, vitamin levels) are recommended to help exclude additional potential contributors to hypoglycaemia [30].

When individuals present with features atypical for PBH (either initially or during on-going follow-up), such as hypoglycaemia occurring in the fasting state, more than four hours after caloric intake, or with an onset early in the postoperative period (less than 6-12 months), prompt referral is needed to rule out other potential contributing conditions. Malnutrition, side effects of medications or supplements, critical illness, hormone deficiencies (e.g. adrenal), autoimmune hypoglycaemia [34], insulinoma [35], proinsulinoma [36], and nonislet cell tumors [37], all may result in hypoglycaemia. Further medical assessment is indicated, typically by an experienced endocrinologist; some individuals may require extended inpatient fasting evaluation (72 hours).

Risk Factors: Risk factors for PBH include female sex, no history of diabetes pre-bariatric surgery, greater magnitude of weight loss after surgery, use of SSRI/SNRI antidepressants, gastric bypass (vs. sleeve gastrectomy) and a history of symptoms potentially related to hypoglycaemia prior to surgery [27,38-41].We do not fully understand the mechanisms responsible for these relationships.

MNT goals and assessment: Patients with PBH should be counselled that hypoglycaemia is not their fault, and not caused by food; however, MNT is the primary focus to manage the alterations in glucose metabolism. The goal of MNT is both decreased frequency and severity of hypoglycaemia. The individual should

be counselled that MNT is unlikely to completely eliminate hypoglycaemia. Even an optimal food regimen often requires the addition of one or more medications. Individualization of MNT is important and recommendations may evolve over time based on glucose data, hypoglycemia event log, food preferences, and nutritional needs. Given the chronic nature of the condition, a strong relationship between the patient and the care team is essential. This can promote PBH-related behaviour change for patients who may struggle to balance what they may perceive as conflicting medical and nutritional recommendations to treat coexisting conditions. Motivational interviewing is a useful tool to explore benefits of and barriers to MNT recommendations.

Suggested physical and psychological factors to discuss during nutrition appointments **(Table 1)** states the overall meal plan, macronutrient content and portion size, and meal timing recommendations.

Table 1: Key components of the PBH nutrition assessment that inform the evolving relationship to food and body and approach to MNT.

Psychological	Physical
Meal planning and food preparation engagement and skills, potential barriers to food access	Meal and snack timing related to physical activity and hypoglycemia symptom onset
Nutritional guidance provided by bariatric clinic or other dietitian to address current symptoms	Caffeine and alcohol use
History of disordered eating behaviors both before and after surgery, food aversion	Food allergies and intolerances
Fear of hypoglycemia	Timing of fluid intake with meals, and overall fluid intake status
Weight gain or weight loss, supplemental nutrition history and formulations used	Gastrointestinal diagnoses and symptoms, including nausea, vomiting
Beliefs about what are triggers and what helps to avoid hypoglycemia	Presence or absence of hunger cues
Level of support present from family and friends	Supplements and herbal use, including oral meal replacement products

Macronutrient content and portions: Table 2 summarizes general meal plan guidelines based on practical clinical experience and limited data available from research studies. MNT is aimed at reducing high glycaemic index carbohydrates in an attempt to minimize post-meal glucose "spikes" [42] while maintaining optimal nutrition. This includes several key components: (1) measured portions of low glycaemic index carbohydrates, (2) intake of healthy fats, (3) eating protein first [43]. With total intake up to 1.5 g/kg ideal body weight, [44] and (4) dividing food intake into 6 small meals and snacks, spaced every 3-4 hours.

Table 2: MNT recommendations.

Choose only low-glycemic carbohydrates
Consume a meal or snack every 3-4 hours
Meals: Include 20-30g low-glycemic carbohydrates paired with fat and 15g protein
Snacks: Include 15g low-glycemic carbohydrates paired with fat and 5-10g protein
During a meal, eat protein and fat-based foods before the carbohydrate (Trico, Trifiro reference)
Avoid liquids during meals and both 1 hour before and after
Avoid alcohol
Limit caffeine only if caffeine provokes hypoglycemia

Recommendations for the quantity and types of carbohydrates often vary from person to person based on tolerability and individual response to specific foods. We find that many patients, believing that carbohydrates are the culprit, try to reduce or eliminate carbohydrates entirely. However, inadequate carbohydrate intake may actually worsen the frequency and severity of hypoglycaemia, potentially due to reduced glycogen stores. [45] Liquid calories should be minimized unless they are low carbohydrate, nutrient-dense, and consumed over a long period of time (e.g. protein drink sipped over the course of 1-2 hours).

Meal timing: A meal or snack every 3-4 hours that contains low-glycaemic carbohydrate promotes on going glycogen storage. Frequent meals also promote adequate nutrient intake given the small pouch capacity and thus early satiety experienced with larger meals. Beverages should be consumed before meals, or at least 1 hour after meals to reduce distension of the pouch and more rapid delivery of nutrients to the intestine which can increase risk for hypoglycaemia.

Activity: Hypoglycemia can follow activity, particularly in individuals who are consuming less than the recommended amount of carbohydrate, in those with on going weight loss or under nutrition, or in those with inadequate counter regulatory hormone levels. Assess the activity type (aerobic vs. anaerobic), duration, and timing. The treatment plan should include fueling strategies to help avoid hypoglycaemia during and after physical activity, including use of low-glycaemic carbohydrates in combination with fat, protein, and resistant starch.

Resistant starch: Corn-Starch (CS) in the uncooked form is a well-established tool for hypoglycaemia prevention inindividuals with glycogen storage disorders or type 1 diabetes [46]. CS is not readily absorbed by the small intestine, but is slowly hydrolysed by pancreatic and intestinal amylase to provide a steady supply of exogenous glucose. corn starch can be purchased at the grocery store and mixed into unsweetened beverages, plain yogurt or cottage cheese, and can be consumed during the day, prior to exercise, and/or before bed, depending upon the timing of hypoglycaemia. While a starting dose is typically 1 tbsp., higher doses may be required based on patient response. Commercial products that contain uncooked CS (e.g. nutritional bars, drinks) are also available.

Analysis of glucose patterns: When available, a review of capillary glucose values (finger stick) or CGM data can inform treatment and model use of glucose data to self-monitor and identify hypoglycaemia triggers. Professional, or masked CGM, when available, can also help with identifying the relationships between symptoms, food/liquid intake, activity, and changes in glucose, and help to identify the degree of unawareness. If CGM data are not available, journal entries detailing hypoglycaemic

episodes and the food and drink consumed 1-3 hours prior can also help identify provocative foods.

Acute treatment of hypoglycaemia: The goal of acute hypoglycaemia treatment is to rapidly increase glucose levels to reduce symptoms, and improve neuroglycopenia if present. Typically, 10-15 grams of oral carbohydrate are recommended. Glucose tablets, gel, liquid or powder is recommended over the use of food or beverages for several reasons. Firstly, food and beverage intake may be difficult to limit when symptoms are severe, and over-treatment can contribute to rebound hyperglycaemia and vicious cycles of recurrent hypoglycaemia. Secondly, if a patient is taking acarbose (a commonly used medication for PBH), glucose is absolutely required for treatment. Acarbose slows the breakdown of carbohydrate and will thus slow responses to treatment with juice or food, while pure glucose will be absorbed normally.

The amount of oral glucose needed to recover from hypoglycaemia may vary depending on an individual's sensitivity to glucose and the starting glucose level. Thus, an individualized approach to hypoglycaemia treatment is important. If neuroglycopenia develops, and oral treatment has not been effective or is not possible due to reduced level of consciousness, the administration of glucagon (intranasal or injectable) by the individual or a support person is indicated.

Once symptoms and glucose levels have improved, consumption of a small snack including a LGI carbohydrate in addition to fat and protein is recommended (e.g. slice of whole grain bread with unsweetened nut-butter).

Micronutrient assessment: Individuals considering bariatric surgery are at risk for micronutrient deficiencies even prior to surgery [47-49]. This risk increases further postoperatively, due to post-surgical alterations in GI anatomy, digestion, and absorption, and reduced oral intake [49]. Postoperative nausea, vomiting, and abdominal pain may further increase risk for nutrient deficiencies [50].In turn, micronutrient deficiencies can contribute to postoperative complications such as osteoporosis, anaemia (e.g. iron, B12), cognitive changes, Wernicke encephalopathy, beriberi, and neuropathies (peripheral, optic, and autonomic neuropathy) [51-56].Neuropathies can manifest as loss of sensation, muscle weakness/wasting, ataxia, areflexia, paraesthesia, numbness, and pain.51Autonomic dysfunction may potentially further impair counter regulatory hormonal responses to hypoglycaemia [57].

Current guidelines recommend measuring vitamins D, A, B1, and B12, as well as iron, calcium, zinc, copper, and folic acid at 1, 3 to 6, and 12 months following surgery, and then annually thereafter.50,58 Micronutrient deficiency risk and thus monitoring recommendations vary by surgery type [58]. Lifelong vitamin supplementation informed by monitoring is needed to prevent and treat deficiencies.

Non-nutritive therapies: Additional therapeutic approaches in combination with MNT may be required for the chronic treatment of PBH. Current pharmacologic therapy proceeds in a stepwise approach taking into account patterns and concomitant medical conditions, including dumping syndrome.

Acarbose (alpha glycosidase inhibitor) is often used as a first-line therapeutic after or together with medical nutrition therapy. Acarbose works by slowing the absorption of carbohydrates, thereby reducing the glucose spike and decreasing glucose-stimulated insulin secretion. Acarbose has been shown in head-to-head trials to significantly reduce hypoglycaemia [59,60]. Side effects can include gas, abdominal bloating, cramping, and diarrhea.

If the response to the maximally tolerated dose of acarbose is inadequate or if it is not tolerated, other medications can be considered by an experienced endocrinologist. These include diazoxide, which reduces insulin secretion, but may produce side effects including fluid retention and edema, nausea, and abdominal discomfort. Likewise, Somatisation Analogues (SSA) can be effective as they inhibit secretion of insulin and GLP-1, as well as other gastrointestinal peptides [61-65]. Short-acting formulations are administered by injection 3-4 times daily, while longer acting formulations can be administered every 3-4 weeks. Side effects can include nausea, abdominal discomfort, and diarrhea. Some individuals experience hypoglycaemia shortly after short-acting octreotide injection, likely due to inhibition of glucagon secretion. SSAs have also been shown to improve dumping syndrome [65]. Therapies under investigation include ready-to-use mini doses of glucagon [66], including a multi-dose pen [67], a glucagon closed-loop pump [68], SGLT2 inhibitors [69], and a GLP-1 antagonist, avexitide [70],Other therapies which have been used off label include GLP-1 agonists such as liraglutide [71]; unfortunately, nausea and increases in hypoglycaemia can occur in some patients. While calcium channel blockers have improved hypoglycaemia in some studies [72], a head-to-head comparison with medications including acarbose and octreotide failed to demonstrate a significant improvement in hypoglycaemia [60].

Use of a personal CGM with alarms can allow the patient to detect and treat rapidly falling glucose levels or overt hypoglycaemia before neuroglycopenia develops. Alarms are particularly helpful for those with either partial or complete unawareness of hypoglycaemia. Unfortunately, insurance coverage for CGM devices is often difficult to obtain, and self-pay can be cost-prohibitive.

For patients in whom MNT, pharmacotherapy and CGM are insufficient to control severe hypoglycaemia, additional strategies can be considered. Feeding into the remnant (bypassed) stomach via a G-tube may be considered [73-75], though hypoglycaemia can still occur if any foods are consumed orally. Reversal towards normal anatomy [76,77] can improve the frequency and severity of hypoglycaemic episodes, but does not universally resolve hypoglycaemia [78], and weight regain can occur [79,80].

Safety considerations: Hypoglycaemia can impair cognition [81], and therefore, glucose should be measured, and hypoglycaemia treated before driving or other activity that could place the individual or others at risk [81]. A wearable or smart phone medical ID app that denotes hypoglycaemia can communicate critical information to emergency responders to treat hypoglycaemia.

Individuals with PBH are recommended to keep supplies with them for glucose monitoring and acute treatment, as well as to educate friends and family about their condition. As noted above, personal CGM alarms can be used to help alert the individual of declining or low glucose levels. This is especially important for safety if the patient has reduced awareness of hypoglycaemia. Sharing of CGM patterns with a family member can provide additional safety.

Research needs: While research is ongoing to better understand the mechanisms underlying PBH and treatment approach, studies focused on identifying optimal macronutrient composition to stabilize PBH would support the work of the dietitian. In addition, the development of a validated screening tool for all pre- and post-bariatric individuals at medical or nutrition visits may be helpful to identify those at risk and/or with early disease, potentially reducing the incidence of hypoglycemia unawareness and cognitive decline that may result from recurrent hypoglycaemia.

Conclusion

PBH can compromise an individual's safety, nutrition, cognition, and quality of life. The RD is central to the implementation of a hypoglycaemia care plan. MNT is the foundational treatment for PBH, and individuals with PBH require lifetime MNT support, as well as on-going monitoring for nutritional deficiencies and supplementation needs. Assessment of patterns of hypoglycaemia may identify severe hypoglycaemia and/or unawareness, and suggest the need for further assessment and/or medication adjustments by the hypoglycaemia care team. Thus, development of a sustained therapeutic relationship between the individual and the RD is critical to preserve engagement and safety in the long-term management of PBH.

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