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**Beyond diabetes remission a step further: Post bariatric surgery hypoglycemia**

Lath D *et al.* Post bariatric hypoglycemia

Devraj Lath, Kripa Elizabeth Cherian, Thomas Vizhalil Paul, Nitin Kapoor

**Devraj Lath, Kripa Elizabeth Cherian, Nitin Kapoor, Thomas Vizhalil Paul,** Department of Endocrinology, Diabetes and Metabolism, Christian Medical College and Hospital, Vellore 632004, Tamil Nadu, India

**Nitin Kapoor,** Non Communicable Disease Unit, Nossal Institute of Global Health, Melbourne 3053, Victoria, Australia

**Nitin Kapoor,** The Baker Heart and Diabetes Institute, Melbourne 3004, Victoria, Australia

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**Corresponding author: Nitin Kapoor, MD, PhD, Professor,** Department of Endocrinology, Diabetes and Metabolism, Christian Medical College and Hospital, Main Block Ida Scudder Road, Vellore 632004, Tamil Nadu, India. nitin.endocrine@gmail.com

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**Abstract**

Postbariatric hypoglycemia is a rare but increasingly recognized complication of bariatric surgery, with significant associated morbidity, and many patients often require multimodal treatment. A mixed meal challenge test is often helpful to diagnose this condition. This manuscript highlights the underlying mechanisms that lead to this condition and the novel emerging therapeutic targets that target these mechanisms.

**Key Words:** Postbariatric hypoglycemia; Hyperinsulinemic hypoglycemia; Avexitide; GLP-1 antagonist; Obesity

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**Core Tip:** Postbariatric hypoglycemia is an uncommon complication presenting months to years after bariatric surgery (mostly in Roux-en-Y gastric bypasses) as postprandial hyperinsulinemic hypoglycaemia occurring 1-3 h after meals, and the associated neuroglycopenic symptoms can be incapacitating. Medical nutrition therapy forms the foundation of management, with pharmacotherapy and surgical interventions available for those who do not respond. An increased understanding of the implicated mechanisms has led to the development of targeted agents like avexitide, which has demonstrated good efficacy in a Phase 2 clinical trial (PREVENT) recently.

**TO THE EDITOR**

We read with interest the review by Jin *et al*[1], who discussed the potential mechanisms underlying the remarkable efficacy of bariatric surgery in inducing remission of type 2 diabetes mellitus, ranging from 33% in adjustable gastric banding to up to 95% in biliopancreatic diversion. In a recent meta-analysis involving 174772 patients compared in 16 cohort studies and 1 controlled trial, bariatric surgery was associated with a reduction in the risk of all-cause mortality by 49.2% and an increased median life expectancy of 6.1 years. These benefits were even greater among those diagnosed with type 2 diabetes mellitus[2].

Postbariatric hypoglycaemia (PBH) is an infrequent but potentially debilitating complication, with a multicenter registry-based study in Spain having reported 22 patients developing hypoglycemia following 4645 interventions, amounting to an incidence rate of 0.47%[3]. In another study using registry data, 5040 Swedish patients that underwent Roux-en-Y gastric bypass (RYGB) were matched with 10 non-surgical controls each, with no preoperative difference in the frequency of hypoglycemia or potentially related diagnoses such as confusion, seizures or syncope[4]. Following gastric bypass, 0.2% of the post-gastric bypass cohort were admitted for hypoglycemia *vs* 0.04% of the general population. Although the overall incidence is variable, these patients were at a two- to sevenfold increased risk of hypoglycemia and related diagnoses when compared to their controls. The authors also found that there was no significant increase in the risk of postbariatric hypoglycemia or related diagnoses among patients undergoing restrictive procedures, namely vertical banded gastroplasty (4366) and gastric banding (2917) when matched with controls. Patients without diabetes especially are at an increased risk of hypoglycemia following bariatric surgery *vs* those managed medically[5]. Greater frequencies of hypoglycemia (32.6% and 22.6%) are observed in gastric bypass (GBP) and sleeve gastrectomy patients subjected to a two-hour oral glucose tolerance test (OGTT)[6], with much lower rates (2.3%)[6] reported in those undergoing gastric banding[5-6]. In another study by Tzovaras *et al*[7], 29% experienced definite dumping syndrome while another 16% had symptoms suggestive of the same.

Patients undergoing bariatric surgery (especially RYGB surgery) may develop severe vasomotor symptoms of sweating, dizziness, weakness and flushing, referred to as dumping syndrome. These are attributed to the osmotic effect of rapid food entry into the intestines, release of peptide hormones like vasoactive intestinal peptide, incretins and the enteric neural response. By contrast, the development of symptoms such as confusion, decreased vision, syncope, hunger, behavioural changes, syncope and seizures are suggestive of neuroglycopenia, and these patients are found to have low plasma glucose levels 1-3 h after a meal consistent with reactive hypoglycemia[8]. This occurs months to years after bariatric surgery, and though these phenomena have been classified as early and late dumping syndrome respectively[8], some suggest the term postbariatic hypoglycemia be used instead[8-9] and that the term dumping syndrome be reserved for the vasomotor symptoms caused by rapid gastric emptying, diagnosed by an increase in pulse rate > 10/min and/or a rise in hematocrit by 3% after an OGTT. Apart from the risks of severe hypoglycemia, these patients are also more likely to regain weight due to frequent food intake.

The diagnosis of hypoglycaemia requires the documentation of low plasma glucose during the presence of symptoms and/or signs attributable to hypoglycemia, which are relieved by raising the plasma glucose concentration (known as Whipple’s triad)[10]. Postbariatric hypoglycemia following meal intake is caused by postprandial hyperinsulinemia, diagnosed by a mixed meal challenge test (MMCT) demonstrating hypoglycemia (glucose less than 55 mg/dL) accompanied by inappropriately elevated insulin (> 3.0 U/mL) and C-peptide (> 0.6 ng/mL)[9-10]. An important differential is the exclusion of a co-existing insulinoma[11-12] by cross sectional imaging or endoscopic ultrasonography, although these patients generally present with fasting hypoglycemia.

Postprandial hyperinsulinemic hypoglycemia following bariatric surgery was first described by Service *et al*[11] in a series of six patients who presented years after GBP surgery with neuroglycopenic symptoms and were found to have hyperinsulinemic hypoglycaemia. One patient was found to have an insulinoma, and the other five underwent pancreatectomy guided by intra-arterial calcium stimulation tests. Pathological examination showed islet cell hypertrophy and hyperplasia suggestive of nesidioblastosis and it was initially proposed that bypass surgery had resulted in beta cell hyperfunctioning and hyperinsulinemia. However other studies contest this finding[13], and other mechanisms proposed include an enhanced incretin effect[14], abnormal counter-regulatory hormone responses[15], altered enterohepatic circulation of bile acids[16] and changes in the microbiome[17]. The rapid transit of food from the stomach to the intestinal L cells is believed to result in an excessive release of incretins such as gastric inhibitory peptide and glucagon-like peptide 1 (GLP-1) in particular, with greater levels being observed in symptomatic patients after meals[14].

The management of PBH is complex as its mechanisms remain incompletely understood. The majority of cases exhibiting mild symptoms respond to dietary modification, and medical nutritional therapy (MNT) is the cornerstone of management. The frequent intake of smaller meals comprising carbohydrates with a low glycaemic index helps prevent hypoglycaemia[18], with the intake of meals low in protein and/or high in sugars known to trigger these episodes[19]. Various pharmacological agents have been used with some success for patients who fail MNT, by blunting the inappropriately elevated insulin secretion and ensuing hypoglycemia. These include the alpha-glucosidase inhibitor acarbose, calcium channel antagonists like nifedipine or verapamil, the beta-cell adenosine triphosphate-sensitive potassium channel agonist diazoxide (inhibits insulin secretion by hyperpolarisation) and somatostatin analogues like octreotide[20]. Refractory patients may require a gastrostomy tube placement or a restrictive procedure, with some undergoing partial or total reversal of the bypass[9,20]. Over the years, GLP-1 has become an increasingly attractive target. A recent phase 2 randomised placebo-controlled crossover study (PREVENT) employing the GLP-1 receptor antagonist avexitide [exendin (9-39)] for 28 days showed a significant decrease in the occurrence of hypoglycemia in response to a MMCT requiring rescue as well as on continuous glucose monitoring, with an improved glycemic profile[21]. In another study[22], 12 participants with PBH were randomised to receive either glucagon or a placebo from an artificial pancreas system during meals as guided by a predictive algorithm using continuous glucose monitoring. The patients who received glucagon did not require rescue glucose or develop severe hypoglycemia (< 55 mg/dL), unlike those who received the vehicle, and thus mitigating severe hypoglycemia in PBH.

Elucidation of the other proposed mechanisms may guide the development of other safe and effective therapies for PBH.

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