11 IDF. IDF framework for action on sugar. International Diabetes Federation, 2015. http://www.idf.org/sites/default/files/Framework_Sugar_1905.pdf (accessed Nov 22, 2015).

12 INSP. Opinion of the INSP regarding the proposal to reduce the special tax on sugar sweetened beverages. National Institute of Public Health of Mexico, 2015. http://www.insp.mx/notice/3848-opinion-insp-regarding.html (accessed Nov 22, 2015).

13 Seale J Jr, Regmi A, Bernstein J. International evidence on food consumption patterns. US Department of Agriculture, 2003. http://www.ers.usda.gov/media/285613/tb1904_1_.pdf (accessed Nov 22, 2015).

14 McGill R, Anwar E, Orton L, et al. Are interventions to promote healthy eating equally effective for all? Systematic review of socioeconomic inequalities in impact. *BMC Public Health* 2015; **15:** 457.

15 NHS England. Major bid to prevent illness with launch of national diabetes prevention drive. NHS England, 2015. https://www.england.nhs.uk/2015/03/12/diabetes-prevention/ (accessed Nov 22, 2015).

The rollercoaster of post-bariatric hypoglycaemia

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Bariatric surgical procedures induce substantial and sustained weight loss and improve or normalise obesity-related comorbidities, including type 2 diabetes. Surgery is superior to medical treatment for weight loss and diabetes, improves glycaemic control, reduces need for drugs, and improves lifespan.[1] Although surgical benefits are achieved with low operative mortality, long-term intestinal and nutritional complications can occur.

One challenging and sometimes severe complication of bariatric surgery is post-bariatric hypoglycaemia.[2] Patients with hypoglycaemia can present with non-specific symptoms, including a mixture of adrenergic, cholinergic, and neuroglycopenic features. Hypoglycaemia unawareness and neuroglycopenia can result in severe consequences, including impaired cognition, falls, motor vehicle accidents, loss of consciousness, and seizures. Mild, often unrecognised, hypoglycaemia can contribute to increased appetite and weight regain after surgery.

Diagnosis of post-bariatric hypoglycaemia requires documentation of low venous glucose concurrent with symptoms, with symptom relief by glucose correction (Whipple's triad). This is especially important because adrenergic and cholinergic symptoms (palpitations, light-headedness, and sweating) experienced during hypoglycaemia share substantial overlap with symptoms of dumping syndrome experienced by some post-bariatric patients. Typically, dumping-related symptoms occur very early (30 min) after eating, are not associated with concurrent hypoglycaemia, and are most prominent in the early postoperative period, resolving over time. By contrast, hypoglycaemia typically occurs 1–3 h after meals, with first symptoms developing more than 1 year postoperatively. Confirmation of hypoglycaemia, either during a spontaneous or meal-provoked episode, is crucial to distinguish these aetiologies.

Once hypoglycaemia is documented, it is important to assess the pattern and severity of hypoglycaemia. Post-bariatric hypoglycaemia typically occurs postprandially, concurrent with inappropriately high concentrations of plasma insulin. Glucose concentrations typically remain stable after overnight or prolonged fasting. If history or diagnostic testing suggest fasting hypoglycaemia, clinicians must consider additional causes for hypoglycaemia, including drug treatments, alcohol, other hormonal factors (eg, adrenocortical hormone deficiencies), or autonomous insulin secretion from an insulinoma, and if indicated, undertake diagnostic fasting in the hospital setting.

Patients with severe post-bariatric hypoglycaemia undergo profound changes in glycaemic patterns in the postprandial state. Early after meals, glucose concentrations increase rapidly, often to greater than 200 mg/dL (11·1 mmol/L), thereby triggering insulin secretion, which in turn contributes to rapid decline in glucose and subsequent hypoglycaemia.[2,3] Thus, the initial aim of treatment is to reduce postprandial glucose surges by restricting intake of high-glycaemic-index carbohydrates and slowing carbohydrate absorption with α-glucosidase inhibition with acarbose. Collectively, these approaches can reduce insulin secretion, but often yield only modest benefits in patients with severe post-bariatric hypoglycaemia. Long-term approaches targeting either incretin or insulin secretion—eg, octreotide, diazoxide, or calcium channel blockade—can be effective for some patients with post-bariatric hypoglycaemia. Personal continuous glucose monitoring helps patients to predict and detect hypoglycaemia before neuroglycopenia develops.[4] Gastric restriction or banding (to slow gastric emptying) or gastrostomy tube feeding into the bypassed stomach can provide improved glucose

stability for those requiring intensified approaches. Partial pancreatectomy was initially used to reduce insulin secretion, but is not uniformly successful and is no longer routinely recommended.

Incretin hormones probably contribute to glucose-dependent insulin secretion. Postprandial glucagon-like peptide 1 (GLP-1) is increased 10-fold in post-bypass patients, is even higher in those with post-bariatric hypoglycaemia, and is inversely associated with postprandial glucose concentration.[3] Short-term pharmacological blockade of the GLP-1 receptor attenuates insulin secretion in patients with post-bariatric hypoglycaemia.[5] Although these findings emphasise the importance of altered food delivery patterns and secretion of intestinal peptides as crucial contributors to hypoglycaemia, additional mechanisms might contribute to altered metabolism. Initial reports suggested excessive islet number or size might contribute, but this has not been reported in all series, suggesting dominance of functional dysregulation of insulin secretion. Intestinal and neural adaptations, altered gut microbiota, and increases in bile acids might be involved. Data from recent studies show that glucose effectiveness (GEZI) is increased in post-bariatric hypoglycaemia compared with in asymptomatic patients.[6] Additionally, some patients develop hypoglycaemia after physical activity, further suggesting that non-insulin-dependent mechanisms contribute to hypoglycaemia. Finally, reversal of gastric bypass is not always effective, suggesting underlying genetics or compensation that persists after surgical reversal and weight regain. Improved understanding of pathophysiology, including both insulin-dependent and insulin-independent glucose disposal (figure), could lead to novel therapeutic approaches

The prevalence of post-bariatric hypoglycaemia remains uncertain, but emerging data suggest that it might be more prevalent than initially believed. A registry-based analysis in Sweden[7] showed a two-to-seven-times increase in admissions to hospital for hypoglycaemia, confusion, syncope, and seizures in post-bariatric patients, but only a small absolute risk (0·2% of gastric bypass patients). Since most patients with post-bariatric hypoglycaemia are not admitted to hospital, this could be an underestimate of prevalence. Similar incidences were identified from self-reported diagnosis of hypoglycaemia in the BOLD study.[8] By contrast, results of a recent mail survey in the USA[9] showed that a third of bariatric surgery patients report symptoms of possible hypoglycaemia, with increased rates in women, post-gastric bypass patients, and those with longer postoperative duration, history of preoperative symptoms, or no preoperative diabetes. Biochemical investigations were not done for these patients, so it remains uncertain whether symptoms were actually related to hypoglycaemia, and prevalence estimates could be biased by increased response rates in symptomatic patients. Glucose tolerance tests have been used by some investigators,[10,11] but variable definitions of hypoglycaemia also yield variable prevalence rates (10–72%), and it remains uncertain whether responses to non-physiological glucose loads accurately represent hypoglycaemia in daily life. Similar rates of hypoglycaemia have been noted after sleeve gastrectomy.[12] Studies in which diagnostic continuous glucose monitoring was used show substantial duration of hypoglycaemia in patients with post-bariatric hypoglycaemia (eg, 30–71 min per day with sensor glucose below 55–60 mg/dL (3·33 mmol/L).[4,13,14]

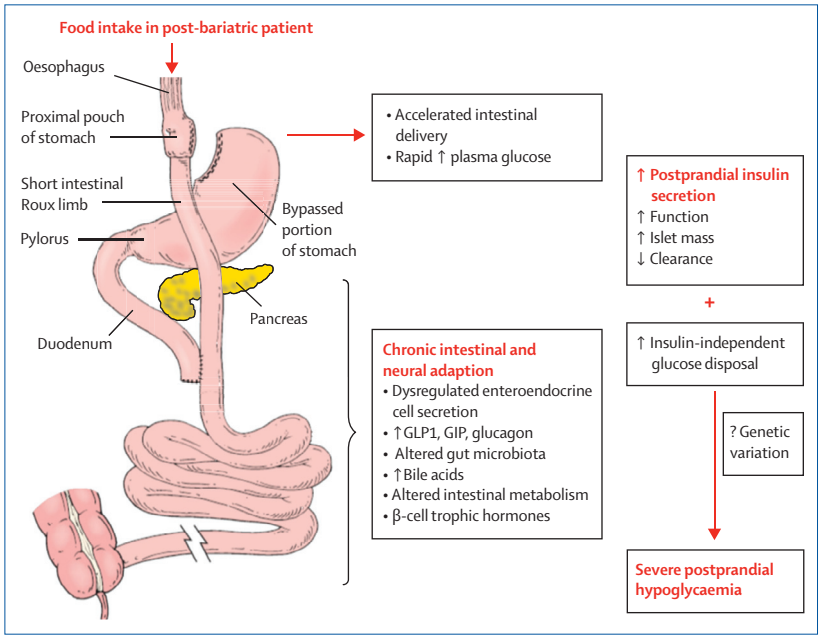

Figure: **Potential mechanisms contributing to post-bariatric hypoglycaemia**
In post-bypass patients, food quickly transits to the intestine, and plasma glucose rises rapidly. Chronic intestinal and neural adaptations, including altered intestinal and bile acid metabolism, contribute to the triggering of excessive postprandial incretin and insulin secretion. These insulin-dependent mechanisms, together with increases in insulin-dependent glucose disposal, converge to increase risk for hypoglycaemia in the postprandial state.

With bariatric surgery increasingly being used to treat epidemic obesity, clinicians will probably encounter increasing numbers of patients with hypoglycaemia presenting several years after surgery. For these patients, it is crucial to identify additional mechanisms responsible for this syndrome and to develop and optimise nutritional, self-monitoring, and pharmacological strategies to minimise the risk of hypoglycaemia. More broadly, we do not yet know whether hypoglycaemia, whether symptomatic or completely asymptomatic, could contribute to chronic weight regain, or be detrimental to long-term cognitive function. Longitudinal studies are crucial to address these key questions. Until findings from such studies are reported, clinicians should be vigilant for possible hypoglycaemia.

Several key questions remain. Can hypoglycaemia be prevented? Can we identify patients at the highest risk for this complication during the preoperative assessment? Until we better understand genetic and other factors that can increase risk, it seems prudent to carefully balance the risk versus the benefits of surgical approaches for individual patients, especially in people without type 2 diabetes or those with a history of possible hypoglycaemia uncovered during preoperative assessment. For individuals deemed to be at increased risk for hypoglycaemia, clinicians might consider favouring procedures that do not irreversibly change intestinal anatomy or function (eg, gastric banding). In the long term, it will be essential to identify mechanisms responsible for weight loss and metabolic improvement after bariatric surgery to develop surgical or pharmacological approaches that maximise weight loss and resolution of diabetes, yet minimise risk of hypoglycaemia and other nutritional or metabolic complications.

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1 Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. *N Engl J Med* 2014; **370:** 2002–13.
2 Patti ME, Goldfine AB. Hypoglycemia after gastric bypass: the dark side of GLP-1. *Gastroenterology* 2014; **146:** 605–08.
3 Goldfine AB, Mun EC, Devine E, et al. Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. *J Clin Endocrinol Metab* 2007; **92:** 4678–85.
4 Halperin F, Patti ME, Skow M, Bajwa M, Goldfine AB. Continuous glucose monitoring for evaluation of glycemic excursions after gastric bypass. *J Obes* 2011; **2011:** 869536.
5 Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. *Diabetes* 2011; **60:** 2308–14.
6 Patti ME, Li P, Goldfine AB. Insulin response to oral stimuli and glucose effectiveness increased in neuroglycopenia following gastric bypass. *Obesity (Silver Spring)* 2015; **23:** 798–807.
7 Marsk R, Jonas E, Rasmussen F, Naslund E. Nationwide cohort study of post-gastric bypass hypoglycaemia including 5,040 patients undergoing surgery for obesity in 1986–2006 in Sweden. *Diabetologia* 2010; **53:** 2307–11.
8 Sarwar H, Chapman WH III, Pender JR, et al. Hypoglycemia after Roux-en-Y gastric bypass: the BOLD experience. *Obes Surg* 2014; **24:** 1120–24.
9 Lee CJ, Clark JM, Schweitzer M, et al. Prevalence of and risk factors for hypoglycemic symptoms after gastric bypass and sleeve gastrectomy. *Obesity (Silver Spring)* 2015; **23:** 1079–84.
10 Roslin M, Damani T, Oren J, Andrews R, Yatco E, Shah P. Abnormal glucose tolerance testing following gastric bypass demonstrates reactive hypoglycemia. *Surg Endosc* 2011; **25:** 1926–32.
11 Pigeyre M, Vaurs C, Raverdy V, Hanaire H, Ritz P, Pattou F. Increased risk of OGTT-induced hypoglycemia after gastric bypass in severely obese patients with normal glucose tolerance. *Surg Obes Relat Dis* 2015; **11:** 573–77.
12 Papamargaritis D, Koukoulis G, Sioka E, et al. Dumping symptoms and incidence of hypoglycaemia after provocation test at 6 and 12 months after laparoscopic sleeve gastrectomy. *Obes Surg* 2012; **22:** 1600–06.
13 Abrahamsson N, Eden EB, Sundbom M, Karlsson FA. Hypoglycemia in everyday life after gastric bypass and duodenal switch. *Eur J Endocrinol* 2015; **173:** 91–100.
14 Kefurt R, Langer FB, Schindler K, Shakeri-Leidenmuhler S, Ludvik B, Prager G. Hypoglycemia after Roux-En-Y gastric bypass: detection rates of continuous glucose monitoring (CGM) versus mixed meal test. *Surg Obes Relat Dis* 2015; **11:** 564–69.