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COMMENTARY

Hypoglycaemia following gastric bypass surgery—diabetes remission in the extreme?

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Abstract Postprandial hypoglycaemia is increasingly recognised as a complication of gastric bypass surgery. While post-bypass hypoglycaemia is often responsive to dietary modification, a subset of individuals develop life-threatening neuroglycopenia, with loss of consciousness, seizures and motor vehicle accidents. Such patients require complex nutritional and medical management strategies to reduce postprandial insulin secretion and stabilise glucose excursions, using medications including acarbose, octreotide and diazoxide, and frequent monitoring of glucose values. In an article in this issue of *Diabetologia*, nationwide registry data from Sweden were used to assess the frequency of severe hypoglycaemia and potentially related diagnoses (e.g. confusion, syncope, seizures, accidental death) following obesity surgery. Relative risk of hypoglycaemia and related diagnoses were two- to sevenfold higher in the post-gastric bypass population, but absolute risk was small. While these data underscore that hypoglycaemia is an important complication of gastric bypass, many questions regarding frequency, pathogenesis and optimal therapy remain unanswered. Given that hypoglycaemia is usually evaluated in the outpatient setting, more precise assessments of hypoglycaemia frequency will require prospective longitudinal studies in post-bypass cohorts. Until such data are available, practitioners should have a higher awareness of symptoms consistent with neuroglycopenia in patients with a history of bariatric surgery. Understanding the beneficial and challenging metabolic consequences of bariatric surgery is a key imperative for the diabetes community, as such data may yield novel insights into mechanisms by which bariatric surgery can lead to diabetes remission.

Keywords Clinical · Gastro-entero pancreatic factors · Human · Hypoglycaemia · Insulin secretion in vivo · Insulin sensitivity and resistance · Islet cells · Islet hormones · Metabolism · Pathophysiology

Abbreviations
GLP1 Glucagon-like peptide 1
VBG Vertical banded gastroplasty

The majority of patients with type 2 diabetes are overweight or obese. Thus, such patients and their clinicians face the daily challenge of managing hyperglycaemia and obesity, or so-called 'diabesity'. Unfortunately, effective lifestyle modifications, including exercise and dietary modifications, are difficult to achieve and even more difficult to sustain. Patients therefore often ultimately require a large number of medications to control diabetes and associated illnesses as the disease progresses.

Given the limitations of medical therapies, bariatric surgery is increasingly recognised as an effective way to achieve sustained weight loss and control of type 2 diabetes and comorbidities [1, 2]. Complete or near-complete resolution of hyperglycaemia can be achieved in up to 80% of patients, particularly those with shorter duration of diabetes. While much of the data supporting these findings has been derived from non-randomised trials, it is generally accepted that procedures bypassing a portion of the proximal intestine (e.g. Roux-en-Y gastric bypass) are

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more effective than isolated gastric volume reduction (e.g. banding) [2]. Nevertheless, a randomised trial published in 2008 demonstrated that even gastric banding achieved diabetes remission in 73% of patients, as compared with only 13% treated with conventional medical diabetes and weight management strategy. Individuals treated with banding achieved a HbA_{1c} of 6% vs 7.2% in patients treated conventionally, an even more impressive finding given the reduction of medications for diabetes (and other concomitant medications) in surgically treated patients [1]. Moreover, longitudinal observational studies have demonstrated that overall long-term mortality rates, including death from diabetes, are substantially reduced following bariatric surgery [3, 4]. Such impressive findings have prompted questions of whether, in the hope of inducing sustained remission and/or reducing progression of diabetes, surgical approaches should be pursued early in the course of diabetes or at body mass index levels lower than the current guideline of 35 kg/m^2. The answers to these important questions will require long-term randomised controlled studies, some of which have been recently initiated [5, 6]. In addition, if bariatric surgery is to emerge as a key therapeutic option in our diabetes armamentarium, it will be critical to understand mechanisms responsible for improvement in glycaemic control, as well as the potential complications of these approaches.

Hypoglycaemia is increasingly recognised as a potentially devastating complication of gastric bypass surgery, which may also ultimately provide clues to mechanisms mediating improved glycaemic control [7, 8]. Typically, after gastric bypass surgery, hypoglycaemia occurs 2 to 3 h after meals, with inappropriately high insulin and C-peptide levels. In the majority of these patients, hypoglycaemia is amenable to dietary modification (including emphasis on controlled portions of low glycaemic index carbohydrates, and attention to macro- and micronutrient deficiencies) and administration of acarbose to slow carbohydrate absorption, minimise postprandial glycaemia and thus reduce the stimulus for insulin secretion. However, a subset of individuals develops severe hypoglycaemia with neuroglycopenia, manifested as confusion, loss of consciousness and, in some cases, seizures and motor vehicle accidents. For the majority of patients, even those severely affected, medical management aimed at reducing stimulus for insulin secretion is effective, with strategies built around a combination of medical nutrition and medications such as acarbose, short- and long-acting octreotide, diazoxide and calcium channel blockade. Continuous glucose-monitoring also provides patients with critical information needed to anticipate and therefore prevent severe hypoglycaemia, particularly when hypoglycaemic unawareness supervenes. Despite implementation of this complex therapeutic strategy, a small subset of neuroglycopenic patients (<10% in our referral population) continues to have life-threatening hypoglycaemia, ultimately requiring detailed functional and anatomical studies (e.g. calcium-stimulated selective arteriography), and consideration of partial pancreatectomy. Although partial pancreatectomy typically achieves improvements in symptom control and safety in this subset of severely affected patients, it carries substantial morbidity and does not fully resolve hypoglycaemia [8, 9]. Two recent case reports indicate that feeding into the bypassed stomach achieves normalisation of meal tolerance [10, 11], suggesting that reversal of bypass could be effective. However, reversal is not uniformly successful, indicating that some of the adaptive changes post-bypass may produce permanent or autonomous effects [8].

Interestingly, hypoglycaemia is typically not manifest until 2 to 3 years after bypass surgery, suggesting that it is not solely linked to the marked improvement in insulin sensitivity that occurs rapidly after surgery. Rather, post-bypass hypoglycaemia may reflect combined effects of sustained improvements in insulin sensitivity and incretin-dependent and -independent insulin secretion. Indeed, studies of patients with post-bypass neuroglycopenia [12] demonstrate that while insulin secretion is appropriately suppressed in the fasting state, plasma insulin and C-peptide levels are inappropriately high during spontaneous hypoglycaemia or that provoked by mixed meal feeding. Insulin secretion in this context may reflect the brisk early postprandial rise in glucose, further magnified by the tenfold higher elevations in postprandial levels of the incretins glucagon-like peptide 1 (GLP1) and gastric inhibitory polypeptide (GIP) compared with controls matched for either preoperative or postoperative BMI. Additional mechanisms may also contribute to the observed alterations in systemic metabolism, including not only gastric restriction and sustained weight loss, but also bypass of the duodenum, rapid transit of nutrients to the lower intestine, elevations in circulating bile acids, and intestinal and neural adaptations [2, 13].

A key question is whether hyperinsulinaemic hypoglycaemia reflects expansion of beta cell mass, beta cell functional autonomy, inappropriate adaptation to weight loss or a combination of these mechanisms. While chronic GLP1 excess in rodents reduces apoptosis and promotes islet expansion, the effects of chronic GLP1 secretion in humans remain unknown. Intriguingly, pancreatic histology from some patients with neuroglycopenia suggests the possibility of islet expansion (so-called ‘nesidioblastosis’) [7, 8]. Likewise, insulinomas have also been identified in post-bypass patients [14, 15]. By contrast, other studies have not found increased beta cell mass in patients with post-bypass hypoglycaemia compared with BMI-matched autopsy controls, but rather increased nuclear diameter, which is potentially consistent with hyperfunctional islets

[16]. Moreover, hypoglycaemia is not always fully resolved with partial pancreatectomy, indicating that functional defects may be dominant.

The question of whether severe hypoglycaemia represents an unusual response to gastric bypass, perhaps mediated by as yet unknown genetic susceptibility similar to other forms of hyperinsulinaemic hypoglycaemia [17], or an extreme response to more typical physiological changes induced by surgery remains unanswered. Nevertheless, for individual patients, this complication can be life-threatening. Thus, an important but as yet unanswered question is whether this complication of gastric bypass is frequent but suboptimally recognised, or a genuinely rare complication. Thus, the study of Marsk and colleagues in this issue of *Diabetologia* provides a welcome addition to our knowledge about the incidence of hypoglycaemia following bariatric surgery [18]. Using several nationwide registries available in Sweden, the authors examined the incidence of hypoglycaemia-related diagnoses leading to hospital admission and death in individuals who had undergone either Roux-en-Y gastric bypass (n=5,040), vertical banded gastroplasty (VBG) (n=4,366) or gastric banding (n=2,917) between 1986 and 2006. Importantly, each of the surgically treated cases was matched to a cohort of ten reference participants matched for sex and age (total n=123,230).

Several important conclusions were reached by the investigators [18]. First, the likelihood of hospitalisation for hypoglycaemia, confusion, syncope, epilepsy and seizures was significantly elevated (two- to sevenfold) following gastric bypass surgery compared with the reference population. Importantly, no increased rate of hypoglycaemia or related conditions was observed in this population prior to bariatric surgery, suggesting that these diagnoses were not related to pre-existing conditions. Second, increased rates of hypoglycaemia and related conditions were demonstrated whether or not individuals with pre-existing diabetes were included in the analysis. Third, there was no increase in hypoglycaemia-related disorders after VBG or banding procedures. This finding is consistent with the notion that exclusion of the proximal gut and increased nutrient transit to the distal gut, both features of gastric bypass but not of the solely restrictive VBG or banding procedures, are required for full expression of metabolic improvements after bariatric surgery and hypoglycaemic complications to occur. Finally, despite the higher relative risk of hypoglycaemia and related diagnoses in the post-bypass population, the absolute risk was small, with documented hypoglycaemia in only 0.2% of bypass patients and related diagnoses in about 1% of patients.

Although the study by Marsk et al. [18] is an important first step in addressing hypoglycaemia frequency following gastric bypass, it has several limitations. There was no control for body weight in the index and control groups. Furthermore, there was no propensity score matching for additional health conditions, which could likewise lead to biases. For example, pre-operative comorbidities could alter the likelihood of the care provider or patient selecting surgical intervention over medical care or gastric bypass over related procedures. Importantly, it is uncertain whether the surrogate diagnoses of confusion, syncope and seizures, or accidental death were in fact related to hypoglycaemia, given that glucose values may not have been assessed upon presentation and laboratory data were not available for review. However, it is intriguing that a large retrospective cohort study of gastric bypass patients also observed an increase in death rates due to accidents [3]. It remains to be established whether this finding could also be linked to unrecognised hypoglycaemia. In addition, the reported findings may also underestimate the true frequency of hypoglycaemia. Mild hypoglycaemia may be evaluated and treated in an outpatient setting and thus would not be ascertained in an inpatient hospital registry, whereas more severe episodes may have led to presentations not determined using the diagnostic codes assessed. To assess hypoglycaemia frequency and severity more precisely, prospective longitudinal studies of symptoms and glycaemic patterns in post-bypass cohorts will be required. Until such data are available, practitioners should have a heightened awareness of symptoms consistent with neuroglycopenia in patients with a history of bariatric surgery. It may also be clinically prudent to include detailed questioning about symptoms suggesting hypoglycaemia in the pre-operative evaluation, as this might identify patients at particularly high risk.

Does the emergence of hyperinsulinaemic hypoglycaemia following gastric bypass represent an extreme form of the improvement in systemic metabolism that is responsible for surgery-induced remission of diabetes? While uncertainty remains with regard to this point, increasing data suggest that Roux-en-Y gastric bypass and hypoglycaemic conditions are likely to be mechanistically linked. Understanding both the beneficial and challenging metabolic consequences of bariatric surgery is a key imperative for the diabetes community, as such data are likely to yield novel insights into the pathogenesis of diabetes risk and ultimately generate new avenues for treatment of obesity and type 2 diabetes.

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