A role for exogenous GLP-1 in the management of postprandial hypoglycaemia after Roux-en-Y gastric bypass?

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Abstract

Roux-en-Y gastric bypass (RYGB) is one of the most common and successful bariatric surgeries. However, more than half of RYGB-operated individuals may suffer from post-bariatric hypoglycaemia (PBH) characterised by traditional hypoglycaemic symptoms occurring 1 to 4 hours after meal intake. The mechanisms underlying PBH most likely relate to accelerated delivery of nutrients to the small intestine resulting in unretarded nutrient absorption, large elevations in postprandial plasma glucose concentrations (constituting a potent insulin secretory stimulus), and grossly elevated postprandial plasma levels of the insulinotropic gut-derived hormone glucagon-like peptide 1 (GLP-1) potentiating glucose-stimulated insulin secretion. Based on previous findings that circulating GLP-1 concentrations increased by ~100% during insulin-induced hypoglycaemia before but not after RYGB, Almby *et al.* explored whether exogenous GLP-1 may protect against PBH. They performed hyperinsulinaemic hypoglycaemic clamps with concomitant infusion of the GLP-1 analogue exenatide and saline, respectively, in individuals who had undergone RYGB surgery. Infusion with exenatide during hypoglycaemia had no plasma glucose-raising effects, did not increase the counterregulatory glucagon response, and did not affect symptom scores. In the present commentary, potentially important implications derived from the study by Almby *et al.* published in the August issue of *EJE*, are discussed in the light of previous observations on GLP-1 receptor agonist treatment in PBH. While the findings by Almby *et al.* do not provide a solution for patients with PBH, they contribute to the knowledge base needed to address the growing problem of PBH.

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Roux-en-Y gastric bypass (RYGB) is one of the most common bariatric surgeries. The procedure induces a sustained weight loss together with a reduction in obesity-related comorbidities including type 2 diabetes. The effects on postprandial glucose metabolism are evident within days or weeks after surgery – before any weight loss has occurred – and are thought to be achieved by a faster passage of nutrients to the small intestine and ensuing alterations in the secretion of several gastrointestinal hormones, acceleration of glucose absorption and

increased insulin secretion (1). Especially the remarkable increase in postprandial plasma levels of the gut-derived incretin hormone glucagon-like peptide 1 (GLP-1) – with not only a potent insulinotropic effect, but also a glucagonostatic effect – is believed to contribute to the metabolic improvements and the early remission of type 2 diabetes seen after RYGB (1).

Postprandial glycaemic excursions after RYGB are characterised by an early steep rise in plasma glucose to higher peak values than preoperatively, followed by a

fast drop to baseline values (2). In some RYGB-operated individuals, the slope by which postprandial plasma glucose concentrations drop after peaking is very steep impeding a smooth reversion to baseline concentrations. In these individuals, plasma glucose concentrations may continue to drop below 3.9 mmol/L, hereby resulting in postprandial hypoglycaemia. This post-surgical complication of RYGB is increasingly being referred to as post-bariatric hypoglycaemia (PBH) and is characterised by traditional hypoglycaemic symptoms occurring 1–4 h after meal intake (3). The clinical suspicion of PBH can be verified by documenting postprandial hypoglycaemia during continuous glucose monitoring (CGM) or during a meal provocation test. The exact prevalence of PBH is unknown but using CGM, postprandial hypoglycaemia has been demonstrated to occur in up to 75% of RYGB-operated individuals, although many of the hypoglycaemic episodes appear to be asymptomatic (4, 5).

The mechanisms underlying PBH most likely relate to the altered intestinal anatomy, which as aforementioned leads to an accelerated delivery of nutrients to the small intestine resulting in unretarded nutrient absorption. The accompanying rapid and large elevations in postprandial plasma glucose concentrations constitute a potent insulin secretory stimulus at the level of the pancreatic beta cells. Further, the ingested nutrients come into immediate contact with the mucosa of the distal jejunum where GLP-1-secreting enteroendocrine cells are much more abundant compared with the duodenum (the normal entry point of ingested nutrients into the small intestine). This results in grossly elevated (up to 20-fold) circulating postprandial plasma levels of endogenous GLP-1 (2). As the insulinotropic effect of GLP-1 is glucose-dependent and increases exponentially with increasing plasma glucose concentrations, the rapid elevation of postprandial plasma glucose combined with the grossly elevated plasma GLP-1 concentrations unleash a dramatic insulin response from the pancreatic islets clearly exceeding the need. In individuals with PBH, this insulin overshoot ultimately causes plasma glucose levels to decrease to hypoglycaemic levels (6, 7). The reason why not all RYGB-operated individuals develop PBH remains uncertain (3). Nonetheless, individuals with PBH appear to have higher postprandial GLP-1 and insulin levels compared with non-hypoglycaemic individuals, supporting the notion that an exaggerated GLP-1 response plays a role in the hypersecretion of insulin triggering PBH (8, 9).

In a study published in the August issue of *EJE*, Almby *et al.* explored whether exogenous GLP-1 may protect against PBH (10). The group previously demonstrated

that circulating GLP-1 concentrations increased by ~100% during insulin-induced hypoglycaemia in 12 obese individuals without diabetes referred to RYGB (11). This observation was puzzling as no intraluminal nutrients or other known 'GLP-1 secretagogues' were introduced during the experiment. Preliminary results from our group support that hypoglycaemia can increase circulating levels of GLP-1 in man without administration of oral or intraluminal 'GLP-1 secretagogues' (M Christensen, L Vedtofte, JJ Holst, T Vilsbøll & FK Knop, unpublished observations). The mechanisms behind this phenomenon remain obscure but may relate to a direct effect of hypoglycaemia on enteroendocrine GLP-1-secreting cells or – perhaps more likely – constitute a by-product of the massive glucagon secretion from pancreatic alpha cells during hypoglycaemia (possibly due to unspecific processing of proglucagon). Interestingly, when the abovementioned 12 individuals were subjected to the same step-wise induction of hypoglycaemia 4–5 months after surgery, they not only observed attenuated counterregulatory responses of glucagon, epinephrine, norepinephrine and cortisol, the investigators also found a much smaller GLP-1 response during hypoglycaemia, when compared with pre-surgical conditions (in accordance with the notion of GLP-1 being co-secreted with glucagon during hypoglycaemia presented above) (11). Although GLP-1 is not traditionally considered an important counterregulatory hormone and is known to exert a potent suppressive effect on glucagon secretion from alpha cells at elevated plasma glucose concentrations, the authors speculated that increased GLP-1 levels during hypoglycaemia could stimulate the secretion of glucagon. These previous findings and speculations constituted the incentives for Almby *et al.* to perform the study reported in the present issue. In this study, they performed hyperinsulinaemic–hypoglycaemic clamps with concomitant infusion of the GLP-1 analogue exenatide (0.066 pmol/kg/min) and saline, respectively, in 12 individuals (without history of type 1 or type 2 diabetes) who had undergone RYGB surgery ~12 months prior to the study. The primary objective was to test whether exogenous GLP-1 would enhance counterregulatory hormonal responses and reduce hypoglycaemic symptoms. In brief, infusion with exenatide during hypoglycaemia had no plasma glucose-raising effects, did not increase the counterregulatory glucagon response and did not affect symptom scores (10).

Almby *et al.* are to be praised for their commitment to follow-up on their previous findings and, despite the negative nature of the results, potentially important

implications with regard to previous observations on GLP-1 receptor agonist treatment in PBH may be derived from their study. The same group and others have reported reduced hypoglycaemic symptoms and improved glycaemic control in individuals with PBH during treatment with the GLP-1 receptor agonists liraglutide and exenatide when evaluated by CGM (9, 12). Considering the exaggerated postprandial GLP-1 response that supposedly contributes to PBH and the fact that GLP-1 antagonism has been shown to prevent postprandial hypoglycaemia in RYGB-operated individuals (8), this was a somewhat surprising finding, of which the possible mechanisms have been debated. As opposed to the acute postprandial elevation in endogenous GLP-1 concentrations, it has been suggested that continuous stimulation of GLP-1 receptors by exogenous GLP-1 (resulting in supraphysiological circulating GLP-1 receptor agonist concentrations) might have beneficial effects on postprandial hypoglycaemia and glycaemic variability (9). In the present study by Almby *et al.* the authors were not able to confirm their hypothesis that GLP-1 receptor agonism could reduce hypoglycaemia through an increased glucagon secretion in response to falling blood glucose concentrations. Our group recently examined the effects of 3-week treatment with the GLP-1 receptor agonist liraglutide in RYGB-operated individuals with PBH, both during CGM and in an experimental setting (13). Following a provocative liquid test meal, we found no effects of liraglutide on postprandial hypoglycaemia, and treatment with liraglutide did not affect the number of hypoglycaemic events registered during CGM; however, our results suggested a reduction in CGM-verified time in the hyperglycaemic range and in parameters of glycaemic variability. Consistent with the known side effects of GLP-1 receptor agonists, we found that treatment with liraglutide was accompanied by complaints of nausea and reduced appetite, leading us to speculate that the glycaemic and symptomatic improvements reported during treatment could be the result of reduced food intake and altered food preferences, as especially carbohydrate restriction is known to diminish postprandial hypoglycaemia after RYGB (14). Unfortunately, dietary evaluation has not been performed in relation to treatment with GLP-1 receptor agonists in individuals with PBH. The appetite-inhibiting effects of GLP-1 receptor agonists might also lead to weight loss, which is a desired effect by many individuals with PBH in whom weight regain is frequently observed (15). In other populations, GLP-1 receptor agonists – especially short-acting GLP-1 receptor agonists – reduce postprandial

glycaemia by deceleration of gastric emptying and slowing of gastrointestinal transit time (16). Given the extensive rearrangements of the gastrointestinal tract after RYGB and the rapid passage of nutrients to the small intestine, therapeutic effects on ‘pouch emptying’ seem less likely in a RYGB-operated population, but this remains to be investigated. In that perspective, a short-acting GLP-1 receptor agonist, as used by Almby *et al.* might be a better choice of treatment (16).

The present findings by Almby *et al.* contribute to the knowledge on potential therapeutic effects of treatment with GLP-1 receptor agonists in RYGB-operated individuals, but the choice of study population limits the generalizability of the results. The included participants did not have a history of hypoglycaemic complaints and PBH was not evaluated by CGM or a provocative test meal prior to study inclusion. Using CGM, studies have shown that individuals with PBH experience repeated hypoglycaemic episodes on a weekly basis (4, 5, 13), which might affect the observed counterregulatory responses since recurrent hypoglycaemia is known to attenuate counterregulation in other populations. Moreover, Almby *et al.* studied the effects of a continuous exenatide infusion in the fasting state. As PBH occurs postprandially and often is preceded by early postprandial hyperglycaemia, exenatide administered subcutaneously in connection with meal intake might have different effects on glucose metabolism in these individuals. Nevertheless, in the study alluded to above (13), we examined the effects of treatment with liraglutide in a postprandial setting in individuals with verified PBH and, in agreement with Almby *et al.* we found no increases in pancreatic glucagon levels in response to hypoglycaemia (CC Øhrstrøm, DL Hansen, UL Kielgast, JJ Holst & D Worm, unpublished observations). Thus, the mechanisms by which GLP-1 receptor agonists may ameliorate hypoglycaemic symptoms and potentially stabilise glycaemic excursions in individuals with PBH remain unknown and convincing evidence that treatment with GLP-1 receptor agonists leads to clinically detectable improvements in hypoglycaemia is still missing.

Despite the growing awareness of PBH, there are no established treatment recommendations for affected individuals besides dietary modifications. In agreement with previous studies, we recently showed that the alpha-glucosidase inhibitor acarbose and the somatostatin analogue pasireotide effectively prevented postprandial hypoglycaemia in an experimental setting, but the effects were not necessarily applicable to daily living and the treatments were associated with notable side effects (13, 17, 18). Other suggested therapeutics in

the management of PBH involve diazoxide, calcium channel blockers, sodium–glucose cotransporter-2 inhibitors, glucagon and, as discussed above, GLP-1 receptor antagonists (3, 13). Given the few available treatment options and the severe consequences associated with PBH, including the risk of syncope, seizures, motor vehicle accidents, and potentially, an increased rate of accidental deaths (3, 19), this area of research merits further investigations.

Declaration of interest

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