Hyperinsulinemic hypoglycemia after gastric bypass surgery: what's up and what's down?

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Abstract

Obesity is a global public health problem and attempts to treat this condition using life style with and without pharmacological interventions have not been successful in majority of obese individuals. To date, the most effective treatment for obesity is weight loss surgery. One of the most widely used procedures to treat obesity worldwide, Roux-en-Y gastric bypass surgery (RYGB), has shown to induce diabetes remission in addition to significant and sustainable weight loss. As the number of this procedure performed over the last two decades increased, it has become clear that a subgroup of individuals develop postprandial hypoglycemia several years after surgery. This debilitating late complication of RYGB is often associated with loss of consciousness or seizures, and in severe cases, it is only partially responsive to diet modification or other available therapeutic options. The diagnosis is often a challenge resulting in delays in receiving care in the affected individuals. Although the underlying mechanisms are under current investigations, growing evidence suggest that a combination of exaggerated meal-derived nutrient appearance to systemic circulation and altered islet and gut hormone response after eating have a role in pathogenesis of this condition. The goal of this review is to highlight new perspectives regarding this life-threatening complication of RYGB. The etiology, diagnosis, recommendation on how to distinguish from classic dumping and current available treatment based on literature review will be discussed. In addition, physiologic changes after gastric bypass predisposing to hypoglycemia syndrome will be highlighted.

INTRODUCTION

Over the last few decades, obesity and related comorbidities have become a global public health issue (WHO obesity and overweight fact sheet).¹ The increasing prevalence of obesity has called for development of various therapeutic strategies but given the complex nature of this condition resulting from genetic, epigenetic, physiological, behavioral, socioeconomic and environmental factors, attempts to treat obesity by combination of medical and life style

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CONFLICT OF INTEREST

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interventions alone have been disappointingly ineffective.^{2,3} Potent physiologic factors act to 'defend' the baseline weight^{4,5} and weight loss medications, particularly those directed toward hypothalamic pathways regulating appetite, may either lack long-term effectiveness or are associated with limiting side effects.⁶

An effective approach to sustained weight loss that gained popularity over the last two decades is bariatric surgery. Historically, Roux-en Y procedure, rerouting the gastrointestinal (GI) tract by connecting stomach to the jejunal limb of a Roux-en-Y enterostomy, was performed to treat gastric cancer⁷ or inherited disorders of lipid metabolism.⁸ A noted 'complication' at the time was sustained weight loss, which was attributed to malabsorption induced by bypassing a large part of small intestine.⁷ Eventually, this 'side effect' of surgery for primary GI disease, transitioned to being considered beneficial 'effect' of this procedure for treatment of obesity. Roux-en-Y gastric bypass (RYGB), one of the most commonly performed weight loss procedures worldwide,⁹ involves generating a 'bypass' of the upper small intestine and creation of a small stomach pouch (approximately 30 ml in volume) connected directly to the lower small intestine effecting the 'bypass'. This is achieved by dividing the stomach into the small upper pouch and closed large 'remnant'. The lower small intestine is incised with the distal end (Roux limb) then connected to the small stomach pouch effecting an alternative route to the 'bypass'. The other incised end of the upper intestine is then attached to a further lower part of the small intestine allowing for drainage of biliary-pancreatic secretions creating a 'Y limb'.

Pertinent to this review, RYGB, not only leads to sustained weight loss but also exhibits metabolic improvements including diabetes resolution¹⁰ that are at least in part independent of weight loss.¹¹ This weight loss independent effect of RYGB on glucose homeostasis seems to be exaggerated in the subgroup of individuals who develop a late complication of postprandial hypoglycemia after this procedure.^{12,13} The purpose of this review is to summarize the current understanding of the mechanisms of RYGB-related hypoglycemia and available options to treat this complication.

LITERATURE REVIEW METHOD

An electronic literature search was performed using PubMed database for relevant articles published between 1981 and 29 May 2017. The following key search terms were used: 'hypoglycemia' AND 'gastric bypass', 'hypoglycemia' AND 'Roux-en-Y gastric bypass', and 'post gastric bypass hypoglycemia'. Filters were applied to only include English language and human studies. Initial search and review was conducted primarily by the first author (AY), but was subsequently reviewed and discussed with the senior author (MS) for consensus. Initially 197 articles were identified for review. Titles and abstracts of articles were reviewed to determine relevance to the scope and objectives of review. References from bibliographies of selected articles were also reviewed for additional relevant studies, as well as other expert opinions via review articles. Sixty-four articles that were deemed relevant to incidence, definition, diagnosis, pathophysiology and treatment of RYGB-related hypoglycemia based upon the scope of our review were finally included. We also included five abstracts presented at professional research meetings that were relevant to the purpose

of our review along with one professional organization's fact sheet on obesity was also included in final review.

HOW MANY PATIENTS DEVELOP HYPOGLYCEMIA AFTER RYGB?

True prevalence of RYGB-related hypoglycemia is unknown and most likely underreported, partly due to lack of consensus in defining and diagnosis of this condition. Moreover, many patients suffering from this condition do not associate their symptoms with RYGB, leading to several years of delay in diagnosis. By the same token, many individuals with post-meal symptoms are labeled as hypoglycemic without having any documented associated low glucose concentrations.

Swedish nationwide cohort study based upon patient registries studied 5040 patients who underwent RYGB surgery between 1986 and 2006 in comparison with age- and sex-matched individual from background population.¹⁴ The investigators reported that compared with the non-surgical reference population those with RYGB had significantly higher risk of hospitalization because of hypoglycemia (hazard ratio: 2.7) or other surrogate-related conditions including confusion, syncope, epilepsy and seizures (hazard ratio: 2.8, 4.9, 3 and 7.3, respectively) based on International Classification of Diseases (ICD) codes or equivalent markers. Overall incidence of hypoglycemia in the cohort of RYGB was relatively low, 0.2% compared with 0.04% in non-surgical controls. Although they had no access to biochemical data—glucose values—during hospitalization or patients' symptomatology before their hospitalization, therefore the results may have underestimated the prevalence of RYGB-related hypoglycemia syndrome.

In another report from a single institution,¹⁵ 12 patients out of 3082 individuals who undergone RYGB between 1964 and 2006 sought medical evaluation for having symptomatic hypoglycemia. When these patients were challenged with meal tolerance test, high-carbohydrate ingestion resulted in nadir glucose levels ranging from 1.55 to 3.50 mmol l⁻¹ within 3 h from meal ingestion associated with hypoglycemic symptoms. The authors acknowledged the limitation of this study to comment on prevalence of hypoglycemia given the self-reporting nature of identified affected individuals.

A similar study relying on the self-reported hypoglycemia reviewing The Bariatric Outcomes Longitudinal Database (BOLD), 145 582 post-RYGB patients across the United States found a prevalence of 0.1%.¹⁶ When patients on diabetes medications or insulin before surgery were excluded, hypoglycemic prevalence dropped to 0.01%. The major limitation of the study was self-reporting of hypoglycemia and absence of verification.

A more recent single institution study utilized a review of patient registry for 1206 non-diabetic patients after RYBG for the time period of 2004–2014.¹⁶ Using electronic medical records, study population included those with measured blood sugar <3.33 mmol l⁻¹ regardless of associated symptoms, or any post-operative outpatient or inpatient encounter with a diagnosis of hypoglycemia using international classification of diseases codes or taking medications for treatment of hypoglycemia including glucagon, octreotide, verapamil and diazoxide, occurring at least 1 month after the surgery. Using the above definition,

cumulative incidence of hypoglycemia was 2.7 and 13.3% at 1 and 5 years after RYGB. The incidence dropped to 0.1 and 0.7% at 1 and 5 years, respectively, when more stringent criteria for hypoglycemia of glucose $<2.22 \text{ mmol l}^{-1}$ was applied or when emergency room visit or hospitalization for hypoglycemia, or gastric bypass reversal for treatment of hypoglycemia were considered. Nonetheless, interpretation of data was limited by lack of information regarding hypoglycemic symptoms associated with low glucose values and unknown timing of blood glucose measurement in relation to food intake as there was no individual chart review.

DEFINITION OF RYGB-RELATED HYPOGLYCEMIA AND HOW TO DIAGNOSE?

Hypoglycemia, in general, is defined as blood glucose concentration $<2.8 \text{ mmol l}^{-1}$ associated with symptoms of hypoglycemia that are relieved by carbohydrate ingestion (Whipple's triad).¹⁷ Hypoglycemic symptoms are broad and nonspecific in isolation but they can be categorized into those related to either glucose deprivation of central nervous system (neuroglycopenic) or activation of autonomic nervous system (autonomic). Neuroglycopenic symptoms range in severity from flushing, weakness, fatigue, drowsiness, dizziness, blurred vision to difficulty speaking, confusion, loss of consciousness and seizures. Autonomic symptoms derive from either activated adrenergic function manifested as shakiness, heart pounding and anxiety or from activated cholinergic function characterized by sweating, hunger and paresthesia.¹⁸ Hypoglycemia after RYGB is exclusively postprandial and thus differentiation of this condition from those with asymptomatic low blood glucose or postprandial symptoms suggestive of hypoglycemia but without any associated glucose abnormalities is heavily dependent on using Whipple's triad.

It has been reported that up to 10% of individuals with no previous history of GI surgery ($N = 650$) develop plasma glucose levels $<2.8 \text{ mmol l}^{-1}$ without any associated symptoms when they are challenged with 100 g of oral glucose.¹⁹ Among the non-operated patients with suspected postprandial hypoglycemia based on symptoms alone ($N = 118$), oral glucose ingestion has been shown to elicit low blood glucose levels associated with these symptoms only in $\sim 10\%$ of individuals, indicating that symptoms of hypoglycemia in majority of individuals without history of GI surgeries are not associated with low glucose levels.¹⁹

It is quite possible that meal-induced asymptomatic low blood glucose occurs much more frequently after RYGB given that bypassing foregut widens postprandial glucose excursion leading to higher peak, as well as lower nadir glucose levels.^{20–22} In fact, a large group of 36 diabetic and non-diabetic individuals several years after RYGB without any prior history of hypoglycemic symptoms at home developed low glucose levels $<3.33 \text{ mmol l}^{-1}$ following 100-g oral glucose load without any associated symptoms.²³ Evaluating patients after RYGB during their routine daily life using continuous glucose monitoring system for 5 days also has revealed that up to $\sim 70\%$ of patients after RYGB ($N = 40$) have low glucose, defined by investigators as glucose values $<3.05 \text{ mmol l}^{-1}$.²⁴ Association of these low glucose levels with symptoms or food intake, however, was not addressed in this study. Although the physiologic significance of asymptomatic postprandial hypoglycemia in the setting of GI

surgeries is still unclear, it is likely that it represents the same phenomenon in the background non-operated population,¹⁹ only more likely given the rerouted GI tract. We have, indeed, shown that, beta-cell glucose sensitivity and post-meal insulin response in individuals with asymptomatic low blood glucose ($< 3.05 \text{ mmol l}^{-1}$) after ingestion of liquid mixed meal are not different from those with normal postprandial glucose levels after RYGB²⁰ (Figure 1). Adding to the complexity of establishing diagnosis for postprandial hypoglycemia in individuals with previous RYGB is that post-meal symptoms after RYGB, collectively called dumping syndrome, are far more frequent than those in individuals without GI surgeries.²⁵ Dumping symptoms are characterized based on the time of development after eating as early and late symptoms. Early symptoms are predominantly vasomotor (palpitation, flushing, perspiration, hypotension and syncope) and GI symptoms (abdominal pain, diarrhea, borborygmus, bloating and nausea) that are developed within 15 min and late symptoms (palpitation, tremor, perspiration, aggression, fatigue, weakness, confusion, hunger and syncope) develop in 1–3 h after eating when glycemia reaches nadir levels. Therefore, hypoglycemia and late dumping have often been used interchangeably.²⁵ However, this notion that the late dumping symptoms are primarily caused by glucose abnormalities is unlikely. Maintaining glucose levels above fasting using hyperglycemic clamp failed to prevent early or late dumping symptoms such as vasomotor symptoms, fatigue, or weakness or confusion during meal tolerance studies²⁶ suggesting largely guilt by association.

To differentiate between symptoms related to post-RYGB hypoglycemia or late dumping, we use the time of onset from surgery, in that dumping usually develops shortly after RYGB when regular meal intake is reinstated, whereas the RYGB-related hypoglycemia generally manifests beyond the first year after surgery. In a cross-sectional meal study in 65 patients with and without documented hypoglycemia after RYGB, we defined dumping syndrome using Sigstad criteria²⁷ and differentiated these symptoms from autonomic hypoglycemic symptoms based on Whipple's triad, as well as the time of onset from surgery. We demonstrated that a history of dumping syndrome in this cohort did not increase the likelihood of hypoglycemia during meal studies.²⁰ Therefore, although dumping and hypoglycemia may share the common underlying mechanism—rapid nutrient passage from stomach pouch to the gut, they manifest different aspects of deregulated gut physiology. Nonetheless, given the significant overlap between the two conditions, the critical question to be addressed is which of symptoms suggestive of hypoglycemia are more specific for glucose abnormalities.

We have shown that in 65 individuals after RYGB the rate of developing nadir glucose levels $< 2.8 \text{ mmol l}^{-1}$ during meal tolerance test was similar between those with history of autonomic symptoms suggestive of hypoglycemia and those asymptomatic subjects after RYGB ($< 10\%$), whereas half of patients with prior history of neuroglycopenic symptoms developed postprandial hypoglycemia defined by Whipple's triad.²⁰ These findings suggest that neuroglycopenic symptoms rather than autonomic are more reliable diagnostic criteria to differentiate post-RYGB hypoglycemia from individuals with nonspecific dumping syndrome. It is not clear what the neurologic consequences of postprandial symptoms are without hypoglycemia in patients with GI surgeries. However, in non-operated individuals with postprandial symptoms with normal glycemia, electroencephalographic evaluation has

failed to show any abnormalities;²⁸ the implication of these findings in the cohort of patients with history of GI surgeries remained to be understood.

Altogether accurate diagnosis of postprandial hypoglycemia particularly in the individuals with RYGB requires documentation of concurrent development of symptoms, predominantly neuroglycopenic, with low blood glucose, which are largely absent at other times when glucose levels are normal. Therefore, a detailed description of medical history, time of onset post-surgery, type of symptoms whether autonomic or neuroglycopenic described by the patient or valid witnesses, relationship to food intake and sleep, as well as any documented glucose levels associated with symptoms are all essential to establish a high index of suspicion for a diagnosis.

For further confirmation, we use liquid mixed meal tolerance test and establish the diagnosis based on Whipple's triad: (1) low blood glucose concentrations ($< 2.8 \text{ mmol l}^{-1}$); (2) simultaneous neuroglycopenic symptoms and (3) symptomatic relief by carbohydrate ingestion. We do not recommend the use of oral glucose tolerance test because of the higher rates of false-positive especially in those with GI surgeries. Using mixed meal compared with oral glucose has been shown to reduce the incidence of asymptomatic postprandial hypoglycemia in individuals without GI surgeries^{19,28,29} and to increase the nadir glucose levels and narrowing glucose excursion in those after RYGB,³⁰ thus meal tolerance seems to be the procedure providing a greater specificity. Continuous glucose monitoring, which has been frequently used in the outpatient setting for the diagnosis of exogenous insulin-induced hypoglycemia, can also provide insight in the pattern of glucose excursion, both the highest and the lowest values, in the post-RYGB hypoglycemic patients. Although, it is worthy to note that the sensitivity of this diagnostic tool to detect hypoglycemia episodes in this cohort is less than that of meal studies.³¹

In patients suffering from hypoglycemia starting shortly after surgery (within weeks to months) or those individuals with fasting hypoglycemia, an evaluation to investigate for other causes of hypoglycemia, such as insulinoma, should be undertaken as warranted by the history and nature of the symptoms.³² Such a work-up may involve 72-h supervised fast and non-invasive diagnostic studies including computed tomography, magnetic resonance imaging and endoscopic ultrasonography. In cases where above-mentioned diagnostic testing does reveal a clear diagnosis, calcium-stimulated selective mesenteric angiography with hepatic venous sampling has been utilized to locate the site of excessive insulin secretion.^{33,34} This is an invasive procedure and not readily available in many medical facilities and requires special expertise in performance and interpretation.

WHAT CAUSES THIS CONDITION?

Altered systemic appearance of ingested nutrient as a result of bypassing the foregut appears to account for many changes in postprandial glucose homeostasis. After RYGB, meal ingestion leads to a larger glycemic excursion with earlier and higher peak of glucose, as well as lower nadir glucose.^{21,22} Along with altered postprandial glucose pattern, meal-induced insulin response and gut hormone secretion, mainly glucagon-like peptide 1 (GLP-1) is significantly enhanced.³⁵ Enhanced meal-induced insulin secretion after RYGB

has been attributed to rapid nutrient delivery to the gut as a result of anatomical alteration in GI tract, as well as increased insulinotropic gut peptide, GLP-1. In fact, elimination of GLP-1 action by intravenous infusion of a potent GLP-1 receptor (GLP-1r) antagonist, exendin-(9–39), has shown to diminish postmeal insulin release and β -cell glucose sensitivity in RYGB subjects compared with the non-operated controls.^{21,26,36} Postprandial glycemic effects of RYGB seem to be exaggerated in those who suffer from hypoglycemia; affected individuals have greater glucose appearance to circulation, larger meal-induced insulin and GLP-1 secretion compared with asymptomatic individuals after RYGB^{20,37} (Figure 2). Therefore, an early hypothesis proposed to explain hypoglycemia after RYGB was that augmented GLP-1-induced insulin secretion lead to hypoglycemia.^{12,37} Using intravenous infusion of exendin-(9–39) during meal or oral glucose tolerance test, we³⁵ and others³⁸ have shown that GLP-1r blockade corrects hypoglycemia in affected patients after RYGB by suppressing insulin secretion (Figure 3).

The difference in GLP-1-stimulated insulin secretion between the hypoglycemic and asymptomatic patients after RYGB is not associated with any changes in GLP-1r expression in pancreatic extracts from the two groups,³⁴ suggesting that dysregulated gut–pancreas activity as a result of increased nutrient passage from stomach pouch to small intestine rather than increased sensitivity of beta-cell to this peptide has a role in altered glucose metabolism in hypoglycemic individuals.

We have also shown that systemic glucose appearance after meal ingestion is greater in patients with the hypoglycemia syndrome compared with asymptomatic individuals³⁵ (Figure 3). Moreover, blocking GLP-1r has been shown to have trivial effect on meal-derived glucose appearance into circulation in patients with post-RYGB hypoglycemia, indicating that multiple factors must concurrently contribute to pathogenesis of this condition.

In non-surgical healthy individuals, induced hypoglycemia leads to reduction in beta-cell secretion along with enhanced α -cell hormonal release. In patients after RYGB β -cell suppression in response to glycemic reduction during hyperinsulinemic hypoglycemic clamp is blunted compared with matched non-surgical controls, suggestive of altered β -cell regulation after RYGB predisposing to relatively hyperinsulinemia during hypoglycemic conditions.^{39,40} Consistent with this finding, patients with RYGB-related hypoglycemia have larger significant delay in insulin secretory reduction following glycemic fall from the peak to the nadir levels and higher insulin secretion when glucose levels are below fasting levels compared with those without hypoglycemia after RYGB.³⁵ In addition to changes in β -cell response to hypoglycemia, α -cell regulation is also affected after RYGB. Circulatory glucagon levels after meal ingestion is increased after RYGB compared with non-surgical controls, however, no greater increase in glucagon levels were observed in patients with postprandial hypoglycemia compared with those with normal glycemia^{20,37} (Figure 4a), suggesting that counter-regulatory glucagon response is potentially impaired. Furthermore, we have shown that α -cell response to hypoglycemia during hyperinsulinemic clamp is reduced in patients after RYGB in general compared with the body mass index- and age-matched non-operated controls^{39,40} (Figure 4b). Diminished responses of β - and α -cells to

hypoglycemia after RYGB could increase the susceptibility to develop hypoglycemia after this procedure.

Other pathogenic factors, such as decreased insulin clearance after meal ingestion²⁰ (Figure 2) or increased non-insulin dependent glucose disposal (glucose effectiveness), measured during intravenous glucose infusion⁴¹ have also been proposed to explain development of this condition.

Altogether these findings indicate a multifactorial model of altered glucose metabolism in the subgroup of individuals suffering from RYGB-related hypoglycemia. Considering that widened postprandial glycaemic excursion after RYGB spans along a continuum, postprandial hyperinsulinemic hypoglycemia likely represents the extreme phenotype of the otherwise beneficial gastric bypass effect on islet cells and GI function.

WHAT THERAPEUTIC OPTIONS ARE AVAILABLE?

As reviewed, bypassing the foregut results in rapid nutrient transit to the upper intestine underlying the pathogenesis of hypoglycemia. Therefore, an integral part of treatment for the affected individuals is applying either dietary modification or medical/surgical-based interventions that diminish meal-derived glucose flux into circulation. To date, dietary modification remains to be the foremost part of the management given limited options available for treatment of this condition.

Evidence for the effectiveness of most available therapeutic options is solely based on case reports or case series rather than well-designed trials. Principles of dietary recommendations based on basic principles of normal GI carbohydrate absorption in person without history of GI surgery include decreasing carbohydrates per meal by increasing the number of meal intake to 5–6 per day, avoiding foods with high glycaemic index, and adding protein and fat to meals and snacks. Modest effectiveness of carbohydrate restriction on post-RYGB hypoglycemia has been shown by two independent investigators. In the first study, the glycaemic effects of isocaloric mixed meals containing high (80 g) vs very low carbohydrate (2 g) were compared on two separate visits in 14 patients with suspected post gastric bypass hypoglycemia based predominantly on clinical symptoms without documented hypoglycemia.¹⁵ High-carbohydrate test meal resulted in a wide glucose excursion with a range of nadir glucose levels from 1.55 to 3.44 mmol l⁻¹. Nine out of 14 subjects developed glucose 2.8 mmol l⁻¹ with high-carbohydrate meal, whereas glucose levels remained close to basal values after 2 g carbohydrate ingestion. These patients were provided some counseling regarding dietary modification to consume lower carbohydrate containing diet, and they were assessed again in a month using hypoglycemia symptom questionnaire and interview. At the follow-up visit, patients reported variable degree of improvement in symptoms (from no relief to complete resolution), suggesting that the effectiveness of this intervention varies among affected subjects. Patient compliance and practical application of such a very low carbohydrate diet in long-term clinical settings remains to be validated. In the second study, consumption of neither solid mixed meal containing 30 g of carbohydrate nor isocaloric liquid mixed meal containing 28 g of lower-glycaemic index carbohydrate elicited hypoglycemia in 14 patients with RYGB-related hypoglycemia regardless of texture

of glycemic index of the food.⁴² Although hypoglycemic status of affected individuals was not confirmed on a separate study using higher amount of carbohydrate administration investigators concluded that both low and high glycemic index meals with lower amount of carbohydrates were equally preventive against post meal hypoglycemia.

In addition to lowering the total amount of carbohydrate per meal, glucose excursion could be narrowed by manipulation of carbohydrate composition.⁴³ Substituting non-fructose carbohydrates by fructose during mixed meal study has shown to significantly diminish glycemic excursion and correct hypoglycemia in 10 affected patients after RYGB.⁴⁴ Similarly, uncooked starch has been used as part of dietary modification to treat hypoglycemia in these individuals based on findings from studies in non-surgical insulin-induced hypoglycemia in patients with diabetes.⁴⁵

Among pharmacological compounds, acarbose, an antidiabetic medication that attenuates glucose excursion, has been used frequently to treat RYGB-related hypoglycemia. Acarbose reduces postprandial glycemic peak and insulin release by inhibiting intestinal brush border enzyme, α -glucosidase⁴⁶ responsible for breakdown of starch to glucose. Eight patients with postprandial neuroglycopenic symptoms after RYGB were studied with mixed test meals with and without pre-meal administration of 100 mg of acarbose.⁴⁷ Five out of the eight patients developed low glucose levels $< 2.8 \text{ mmol l}^{-1}$ during meal tolerance test at baseline. Premeal administration of acarbose increased nadir glucose levels to normal levels in all subjects and lowered maximum to minimum blood glucose ratio. In general, however, effectiveness of acarbose in blocking carbohydrate absorption varies depending on carbohydrate composition with the largest effect on starch and sucrose absorption and minimal or no effect on maltose and glucose absorption.⁴⁸ This coupled with frequent GI side effects such as abdominal gas, bloating and diarrhea might limit its acceptance and effectiveness.

Enhanced GLP-1-induced insulin secretion after meal consumption is a major pathogenic factor. Therefore, medical interventions aiming for reduction in insulin secretion have also been explored as a treatment option. Somatostatin analogs, used for conditions such as insulinoma,⁴⁹ suppress secretion of multiple hormones involved in glucose metabolism. Therefore, although the inhibitory effects of somatostatin on insulin and GLP-1 are desirable therapeutic effect, suppression of glucagon and growth hormone may not be. In a cross-over 2-week trial of pasireotide vs placebo in nine patients with prior history of dumping, as well as symptomatic low glucose levels $< 2.8 \text{ mmol l}^{-1}$,⁵⁰ pasireotide administration has shown to narrow glucose excursion (lower peak and higher nadir glucose concentrations), reduce insulin secretion and delay gastric pouch emptying. A case report of a patient with hypoglycemia after RYGB described significant decrease in insulin and GLP-1 levels after single dose administration of octreotide before oral glucose ingestion. Although subsequent chronic lanreotide therapy resulted in symptom-free euglycemia for 4 years in this case, administration of single dose octreotide before oral glucose challenge resulted in four-to fivefold increase in glucose levels sustained above basal for duration of the study, 5 h from glucose intake, an unfavorable outcome because of near-complete suppression of insulin response.⁵¹ Also the use of these drugs is limited by GI side effects, such as diarrhea, as well

as the cost. The evidence regarding which somatostatin analogs is a better choice given duration of actions, receptor selectivity, or binding affinity is lacking.

Diazoxide, a potent vasodilator that also inhibits insulin secretion by activating ATP-dependent potassium channels in β cells, has been used for treatment of hypoglycemia after RYGB.^{52,53} Administration of diazoxide results in suppression of insulin secretion systematically, therefore, it causes fasting and postprandial hyperglycemia in non-diabetic individuals.⁵⁴ Two case reports suggested that administration of diazoxide 100–200 mg daily for a period of 9–16 months can eliminate hypoglycemic symptoms in patients with post gastric bypass hypoglycemia.^{52,53} However, tolerability of this drug is largely limited because of hyperglycemia and edema.

Calcium channel blockers have been sporadically utilized for treatment of insulinoma based on the notion that these drugs diminish insulin release through blocking β -cell voltage-dependent calcium channels.⁵⁵ The findings from administration of single dose or short-term use of these drugs on insulin secretion have been inconsistent, from mild inhibitory effect on insulin secretion^{56,57} to no effect at all.^{58,59} Nonetheless, verapamil has been used for treatment of post-RYGB hypoglycemia. A case report described some reduction in intensity and frequency of self-reported hypoglycemic episodes as a result of administration of verapamil 80 mg twice daily, in a young woman with neuroglycopenic hypoglycemia after RYGB. Although in this particular case, acarbose 50 mg tid had to be added in a month to control hypoglycemia,⁶⁰ suggesting the lack of effectiveness of verapamil alone

An investigational drug, XOMA 358 (XOMA Corporation, Berkeley, CA, USA), a human monoclonal antibody is under development and in early stages of clinical trials to be tested for the use in postprandial hyperinsulinemic hypoglycemia, as well as other conditions such as congenital hyperinsulinism.⁶¹ This IgG2 monoclonal antibody creates insulin resistance by binding to an allosteric site of insulin receptor and inhibiting its autophosphorylation and signaling via Akt,. A phase 2 study enrolled 12 patients with established diagnosis of post gastric bypass hypoglycemia. Patients were treated with a single IV infusion of XOMA 358, three different doses with 3–5 subjects in each dose cohort. Fasting glucose levels and postprandial glycemia were evaluated using continuous glucose monitoring, as well as plasma glucose measurement after liquid meal ingestion. Administration of this drug resulted in increased postprandial peak and nadir glucose levels with no data reported on the effect of this compound on the extent of glucose excursion after meal ingestion. Also, as expected targeting insulin action systematically by administration of XOMA 358 led to increased fasting glucose levels by 20%. It remains to be determined how much of fasting glucose effects of this drug would be detrimental to overall glucose control after RYGB. Further studies are planned to test long-term repeat dosing interventions.⁶²

Another therapeutic option under investigation is subcutaneous infusion of glucagon using an automated event-based open loop system similar to what was previously investigated in rescuing insulin-induced hypoglycemia in patients with type 1 diabetes.⁶³ In a recently reported study, data from glucose levels during meal studies in five patients with postprandial RYGB-related hypoglycemia were collected using a Dexcom CGM device

(Dexcom Inc., San Diego, CA, USA) and entered into a hypoglycemic prediction algorithm, which in turn prompted physician glucagon delivery (150 µg Xeris glucagon) using an Omnipod subcutaneous pump device (Insulet Corporation, Billerica, MA, USA). Investigators reported that administration of glucagon using this system prevented hypoglycemia in two of five affected individuals, although there was no control studies to address the day to day variability of glucose response to meal ingestion. Further studies are needed to establish the reliability of the hypoglycemic prediction algorithm used in this setting given a significant intra-individual variability in meal-induced glucose response.⁶⁴

The third investigational drug on the horizon is exendin-(9–39) (Eiger Biopharmaceutical, Palo Alto, CA, USA), a 31-amino-acid fragment of exenatide, which is a potent specific competitive antagonist of GLP-1 receptor. This drug was developed based on earlier studies^{35,38} (Figure 3) showing that intravenous infusion of exendin-(9–39) acutely corrects postprandial hypoglycemia by lowering insulin response with trivial effects on fasting glucose concentrations. Similar favorable glycemic responses, reversal of hypoglycemia and improvement in hypoglycemic symptoms score were reported with the use of subcutaneous exendin-(9–39).⁶⁵ Phase 2 clinical trial testing the effect of multi-ascending doses is now underway.

Surgical treatment options have also been considered in patients with life-threatening severe neuroglycopenic hypoglycemia, when adequate nutritional and medical management strategies in combination fail to provide respite. Reversal of gastric bypass with or without sleeve gastrectomy (to mitigate the associated weight regain) has been undertaken for refractory post bypass hypoglycemia but its effectiveness has not been clearly established. An analysis of published case reports and series found resolution of hypoglycemia in 13 out of 17 hypoglycemic patients. However, weight regain was reported in 4 out of 11 patients in whom post-operative weight records were available.⁶⁶ The prospect of weight regain with bypass reversal is a significant factor influencing the general acceptability of the procedure by patients. Moreover, bypass reversal procedure is likely to benefit only in those patients who have some improvement of hypoglycemia following placement and feeding through gastrostomy tube in the gastric remnant.⁶⁷ Therefore, for patients not amenable to surgical intervention often feeding through gastrostomy tube is utilized as a longer-term therapeutic maneuver for post-RYGB hypoglycemia.⁶⁸

A less morbid surgical intervention that has been tried for treatment of hypoglycemia involve placing a silastic ring or adjustable band around the gastric pouch. The proposed mechanism underlying its benefit is related to slowed nutrient delivery from stomach pouch to jejunal limb. Published case reports show resolution of symptoms in 9 out of 10 patients at short follow-up.⁶⁹ Long-term outcome is not established and band-related complications may occur.

Partial pancreatectomy was one of the earlier surgical interventional attempts for treatment of refractory neuroglycopenic hypoglycemia following gastric bypass. Although the short-term outcome of this procedure in majority of patients was symptoms relief immediately after surgery, 90% of patients had recurrence in an average of 2 years from surgery.⁷⁰

CONCLUSIONS

Hypoglycemia after gastric bypass is an unusual but serious complication of RYGB. Treatment options have been very limited and dietary modification remains to be the foremost part of the management. However, studies on the pathogenesis, strongly suggesting exaggerated secretion of GLP-1 in response to the altered gut anatomy and resulting changes in nutrient flux, offer the possibility of effective treatment of this condition with GLP-1 inhibitors, as well as any intervention that lower meal-derived nutrient appearance into circulation.

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REFERENCES

1. WHO Obesity and overweight fact sheet 311-updated 6 2016.
2. Anderson JW, Konz EC, Frederich RC, Wood CL. Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr* 2001; 74: 579–584. [PubMed: 11684524]
3. Kraschnewski JL, Boan J, Esposito J, Sherwood NE, Lehman EB, Kephart DK et al. Long-term weight loss maintenance in the United States. *Int J Obes (Lond)* 2010; 34: 1644–1654. [PubMed: 20479763]
4. Sumithran P, Prendergast LA, Delbridge E, Purcell K, Shulkes A, Kriketos A et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* 2011; 365: 1597–1604. [PubMed: 22029981]
5. Fothergill E, Guo J, Howard L, Kerns JC, Knuth ND, Brychta R et al. Persistent metabolic adaptation 6 years after ‘The Biggest Loser’ competition. *Obesity* 2016; 24: 1612–1619. [PubMed: 27136388]
6. Khera R, Murad MH, Chandar AK, Dulai PS, Wang Z, Prokop LJ et al. Association of pharmacological treatments for obesity with weight loss and adverse events. *JAMA* 2016; 315: 2424–2434. [PubMed: 27299618]
7. Mason EE. History of obesity surgery. *Surg Obes Relat Dis* 2005; 1: 123–125. [PubMed: 16925227]
8. Buchwald H, Schone JL. Gastric obesity surgery combined with partial ileal bypass for hypercholesterolemia. *Obes Surg* 1997; 7: 313–316. [PubMed: 9730516]
9. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009; 122: 248–256. [PubMed: 19272486]
10. Gloy VL, Briel M, Bhatt DL, Kashyap SR, Schauer PR, Mingrone G et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. *BMJ* 2013; 347: f5934. [PubMed: 24149519]
11. Schauer PR, Burguera B, Ikramuddin S, Cottam D, Gourash W, Hamad G et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. *Ann Surg* 2003; 238: 467–484 discussion 84–85. [PubMed: 14530719]
12. Patti ME, McMahon G, Mun EC, Bitton A, Holst JJ, Goldsmith J et al. Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. *Diabetologia* 2005; 48: 2236–2240. [PubMed: 16195867]
13. Service FJ, Thompson GB, Service FJ, Andrews JC, Collazo-Cavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. *N Engl J Med* 2005; 353: 249–254. [PubMed: 16034010]

14. Marsk R, Jonas E, Rasmussen F, Näslund E. Nationwide cohort study of post-gastric bypass hypoglycaemia including 5040 patients undergoing surgery for obesity in 1986–2006 in Sweden. *Diabetologia* 2010; 53: 2307–2311. [PubMed: 20495972]
15. Kellogg TA, Bantle JP, Leslie DB, Redmond JB, Slusarek B, Swan T et al. Postgastric bypass hyperinsulinemic hypoglycemia syndrome: characterization and response to a modified diet. *Surg Obes Relat Dis* 2008; 4: 492–499. [PubMed: 18656831]
16. Lee CJ, Wood GC, Lazo M, Brown TT, Clark JM, Still C et al. Risk of post-gastric bypass surgery hypoglycemia in nondiabetic individuals: a single center experience. *Obesity* 2016; 24: 1342–1348. [PubMed: 27225597]
17. Whipple AO, Frantz VK. Adenoma of islet cells with hyperinsulinism: a review. *Ann Surg* 1935; 101: 1299–1335. [PubMed: 17856569]
18. Towler DA, Havlin CE, Craft S, Cryer P. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 1993; 42: 1791–1798. [PubMed: 8243825]
19. Lev-Ran A, Anderson RW. The diagnosis of postprandial hypoglycemia. *Diabetes* 1981; 30: 996–999. [PubMed: 7308588]
20. Salehi M, Gastaldelli A, D'Alessio DA. Altered islet function and insulin clearance cause hyperinsulinemia in gastric bypass patients with symptoms of postprandial hypoglycemia. *J Clin Endocrinol Metab* 2014; 99: 2008–2017. [PubMed: 24617664]
21. Jørgensen NB, Jacobsen SH, Dirksen C, Bojsen-Møller KN, Naver L, Hvolris L et al. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with Type 2 diabetes and normal glucose tolerance. *Am J Physiol Endocrinol Metab* 2012; 303: E122–E131. [PubMed: 22535748]
22. Salehi M, Gastaldelli A, D'Alessio DA. Evidence from a single individual that increased plasma GLP-1 and GLP-1-stimulated insulin secretion after gastric bypass are independent of foregut exclusion. *Diabetologia* 2014; 57: 1495–1499. [PubMed: 24797288]
23. 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: 1926–1932. [PubMed: 21184112]
24. Kefurt R, Langer FB, Schindler K, Shakeri-Leidenmühler 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: 564–569. [PubMed: 25737101]
25. Van Beek AP, Emous M, Laville M, Tack J. Dumping syndrome after esophageal, gastric or bariatric surgery: pathophysiology, diagnosis, and management. *Obes Rev* 2017; 18: 68–85. [PubMed: 27749997]
26. Salehi M, Prigeon RL, D'Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. *Diabetes* 2011; 60: 2308–2314. [PubMed: 21868791]
27. Sigstad H A clinical diagnostic index in the diagnosis of the dumping syndrome. *Acta Med Scand* 2009; 188: 479–486.
28. Hogan MJ, Service FJ, Sharbrough FW, Gerich JE. Oral glucose tolerance test compared with a mixed meal in the diagnosis of reactive hypoglycemia. A caveat on stimulation. *Mayo Clin Proc* 1983; 58: 491–496. [PubMed: 6876881]
29. Charles MA, Hofeldt F, Shackelford A, Waldeck N, Dodson LE, Bunker D et al. Comparison of oral glucose tolerance tests and mixed meals in patients with apparent idiopathic postabsorptive hypoglycemia: absence of hypoglycemia after meals. *Diabetes* 1981; 30: 465–470. [PubMed: 7227659]
30. Jacobsen SH, Olesen SC, Dirksen C, Jørgensen NB, Bojsen-Møller KN, Kielgast U et al. Changes in gastrointestinal hormone responses, insulin sensitivity, and beta-cell function within 2 weeks after gastric bypass in non-diabetic subjects. *Obes Surg* 2012; 22: 1084–1096. [PubMed: 22359255]
31. Chuang J, Baum L, D'Alessio DA, Salehi M. Glycemic profile assessment using continuous glucose monitoring in patients with and without hypoglycemia after gastric bypass surgery. *Diabetes* 2012; 61 (Issue Supplement 1).

32. Mulla CM, Storino A, Yee EU, Lautz D, Sawney MS, Moser AJ et al. Insulinoma after bariatric surgery: diagnostic dilemma and therapeutic approaches. *Obes Surg* 2016; 26: 874–881. [PubMed: 26846121]
33. Goh BKP, Ooi LLPJ, Cheow P-C, Tan Y-M, Ong H-S, Chung Y-FA et al. Accurate preoperative localization of insulinomas avoids the need for blind resection and reoperation: analysis of a single institution experience with 17 surgically treated tumors over 19 years. *J Gastrointest Surg* 2009; 13: 1071–1077. [PubMed: 19291334]
34. Reubi JC, Perren A, Rehmann R, Waser B, Christ E, Callery M et al. Glucagon-like peptide-1 (GLP-1) receptors are not overexpressed in pancreatic islets from patients with severe hyperinsulinaemic hypoglycaemia following gastric bypass. *Diabetologia* 53: 2641–2645.
35. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. *Gastroenterology* 2014; 146: 669–680. [PubMed: 24315990]
36. Shah M, Law JH, Micheletto F, Sathananthan M, Dalla Man C, Cobelli C et al. Contribution of endogenous glucagon-like peptide 1 to glucose metabolism after Roux-en-Y gastric bypass. *Diabetes* 2014; 63: 483–493. [PubMed: 24089513]
37. Goldfine AB, Mun EC, Devine E, Bernier R, Baz-Hecht M, Jones DB 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: 4678–4685. [PubMed: 17895322]
38. Craig CM, Liu L-F, Deacon CF, Holst JJ, McLaughlin TL. Critical role for GLP-1 in symptomatic post-bariatric hypoglycaemia. *Diabetologia* 2017; 60: 531–540. [PubMed: 27975209]
39. Salehi M, Woods SC, D'Alessio DA. Gastric bypass alters both glucose-dependent and glucose-independent regulation of islet hormone secretion. *Obesity* 2015; 23: 2046–2052. [PubMed: 26316298]
40. Abrahamsson N, Börjesson JL, Sundbom M, Wiklund U, Karlsson FA, Eriksson JW. Gastric bypass reduces symptoms and hormonal responses in hypoglycemia. *Diabetes* 2016; 65: 2667–2675. [PubMed: 27313315]
41. 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. [PubMed: 25755084]
42. Botros N, Rijnaarts I, Brandts H, Bleumink G, Janssen I, de Boer H. Effect of carbohydrate restriction in patients with hyperinsulinemic hypoglycemia after Roux-en-Y gastric bypass. *Obes Surg* 2014; 24: 1850–1855. [PubMed: 24902654]
43. Bantle JP, Laine DC, Castle GW, Thomas JW, Hoogwerf BJ, Goetz FC. Postprandial glucose and insulin responses to meals containing different carbohydrates in normal and diabetic subjects. *N Engl J Med* 1983; 309: 7–12. [PubMed: 6343873]
44. Bantle AE, Wang Q, Bantle JP. Post-gastric bypass hyperinsulinemic hypoglycemia: fructose is a carbohydrate which can be safely consumed. *J Clin Endocrinol Metab* 2015; 100: 3097–3102. [PubMed: 26037514]
45. Axelsen M, Wesslau C, Lonnroth P, Lenner RA, Smith U. Bedtime uncooked cornstarch supplement prevents nocturnal hypoglycaemia in intensively treated type 1 diabetes subjects. *J Intern Med* 1999; 245: 229–236. [PubMed: 10205584]
46. Derosa G, Maffioli P. Mini-special issue paper management of diabetic patients with hypoglycemic agents α -glucosidase inhibitors and their use in clinical practice. *Arch Med Sci* 2012; 5: 899–906.
47. Valderas JP, Ahuad J, Rubio L, Escalona M, Pollak F, Maiz A. Acarbose improves hypoglycaemia following gastric bypass surgery without increasing glucagon-like peptide 1 levels. *Obes Surg* 2012; 22: 582–586. [PubMed: 22161170]
48. Jenkins DJ, Taylor RH, Goff DV, Fielden H, Misiewicz JJ, Sarson DL et al. Scope and specificity of acarbose in slowing carbohydrate absorption in man. *Diabetes* 1981; 30: 951–954. [PubMed: 7028548]
49. Vezzosi D, Bennet A, Rochaix P, Courbon F, Selves J, Pradere B et al. Octreotide in insulinoma patients: efficacy on hypoglycemia, relationships with octreoscan scintigraphy and immunostaining with anti-ss2A and anti-ss5 antibodies. *Eur J Endocrinol* 2005; 152: 757–767. [PubMed: 15879362]

50. Deloose E, Bisschops R, Holvoet L, Arts J, De Wulf D, Caenepeel P et al. A pilot study of the effects of the somatostatin analog pasireotide in postoperative dumping syndrome. *Neurogastroenterol Motil* 2014; 26: 803–809. [PubMed: 24750284]
51. Myint KS, Greenfield JR, Farooqi IS, Henning E, Holst JJ, Finer N. Prolonged successful therapy for hyperinsulinaemic hypoglycaemia after gastric bypass: the pathophysiological role of GLP1 and its response to a somatostatin analogue. *Eur J Endocrinol* 2012; 166: 951–955. [PubMed: 22408121]
52. Spanakis E, Gragnoli C. Successful medical management of status post-Roux-en-Y-gastric-bypass hyperinsulinemic hypoglycemia. *Obes Surg* 2009; 19: 1333–1334. [PubMed: 19551453]
53. Gonzalez-Gonzalez A, Delgado M, Fraga-Fuentes MD, Singh K, Patel A, Meacham J. Use of diazoxide in management of severe postprandial hypoglycemia in patient after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2010; 9: e18–e19.
54. Van Boekel G, Loves S, van Sorge A, Ruinemans-Koerts J, Rijnders T, de Boer H. Weight loss in obese men by caloric restriction and high-dose diazoxide-mediated insulin suppression. *Diabetes, Obes Metab* 2008; 10: 1195–1203. [PubMed: 18476985]
55. De Marinis L, Barbarino A. Calcium antagonists and hormone release. I. Effects of verapamil on insulin release in normal subjects and patients with islet-cell tumor. *Metabolism* 1980; 29: 599–604. [PubMed: 6247604]
56. Barbarino A, De Marinis L, Mancini A, Calabrò F, Massari M, D'Amico C et al. Calcium antagonists and hormone release. VI. Effects of a calcium antagonist (verapamil) on the biphasic insulin release in vivo. *Diabetes Res* 1988; 8: 21–24. [PubMed: 3066562]
57. Krempf M, Ranganatan S, Ritz P, Garnier JM, Charbonnel B. Effect of nifedipine on glucose potentiation of the acute insulin response to arginine in non-insulindependent diabetics. *Eur J Clin Pharmacol* 1991; 41: 411–415. [PubMed: 1761067]
58. Semple C, Thomson J, Beastall G, Lorimer A. Oral verapamil does not affect glucose tolerance in non-diabetics. *Br J Clin Pharmacol* 1983; 15: 570–571. [PubMed: 6860534]
59. Shamooh H, Baylor P, Kambos D, Charlap S, Plawes S, Frishman WH. Influence of oral verapamil on glucoregulatory hormones in Man*. *J Clin Endocrinol Metab* 1985; 60: 536–541. [PubMed: 3882735]
60. Moreira RO, Moreira RBM, Machado NAM, Gonçalves TB, Coutinho WF. Postprandial hypoglycemia after bariatric surgery: pharmacological treatment with verapamil and acarbose. *Obes Surg* 2008; 18: 1618–1621. [PubMed: 18566871]
61. Nath R, Johnson KW, Roessig JM, Ken D, Neale AC RM. XOMA 358, a novel treatment for hyperinsulinemic hypoglycemia: safety and clinical pharmacology from the first in human trial. *Endocrine Rev* 2015; 36 (Issue 2 Supplement).
62. Johnson K, Johnson KW, Gordon A, Neale AC, Vella A, Lee D et al. Single administration of Xoma 358, an insulin receptor attenuator improves post-meal and nighttime hypoglycemia profiles in post gastric bypass hypoglycemia (PGBH) patients. *Endocrine Rev* 2017; Vol 38 (Issue 2 Supplement).
63. Castle JR, Engle JM, Youssef JE, Massoud RG, Yuen KCJ, Kagan R et al. Novel use of glucagon in a closed-loop system for prevention of hypoglycemia in type 1 diabetes. *Diabetes Care* 2010; 33: 1282–1287. [PubMed: 20332355]
64. Mulla C Automatec event-based system for the prevention of post-bariatric hypoglycemia using a mini-dose of a stable glucagon formulation. *Endocrine Rev* 2017; 38 (Issue 2 Supplement).
65. Craig CM. Subcutaneous exendin 9–39 effectively treats post-bariatric hypoglycemia. *Diabetes* 2016; 65 (Issue Supplement 1).
66. Mala T Postprandial hyperinsulinemic hypoglycemia after gastric bypass surgical treatment. *Surg Obes Relat Dis* 2014; 10: 1220–1225. [PubMed: 25002326]
67. Spolverato G, Bhaijee F, Anders R, Salley K, Parambi J, Brown T et al. Total pancreatectomy for the management of refractory post-gastric bypass hypoglycemia. *Dig Dis Sci* 2015; 60: 1505–1509. [PubMed: 25344909]
68. McLaughlin T, Peck M, Holst J, Deacon C. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. *J Clin Endocrinol Metab* 2010; 95: 1851–1855. [PubMed: 20133462]

69. Z'graggen K, Guweidhi A, Steffen R, Potoczna N, Biral R, Walther F et al. Severe recurrent hypoglycemia after gastric bypass surgery. *Obes Surg* 2008; 18: 981–988. [PubMed: 18438618]
70. Vanderveen KA, Grant CS, Thompson GB, Farley DR, Richards ML, Vella A et al. Outcomes and quality of life after partial pancreatectomy for noninsulinoma pancreatogenous hypoglycemia from diffuse islet cell disease. *Surgery* 2010; 148: 1237–1246. [PubMed: 21134557]

Figure 1. (a) Glucose response and (b) insulin:glucose ratio during meal tolerance test in asymptomatic individuals after RYGB with nadir glucose levels below (close circle, solid line) and above 2.8 mmol l⁻¹ (open circle, dash line). Data are presented as mean $\pm$ s.e.m. (adapted with permission from reference Salehi *et al.*²⁰).

Figure 2.

Circulatory (a) glucose, (b) GLP-1 and (c) insulin levels, as well as (d) insulin secretion rates during meal tolerance test among RYGB subjects with neuroglycopenic hypoglycemic symptoms (closed circle, black line), asymptomatic individuals after RYGB (open circle, dash line), and non-surgical controls (closed square, gray line). Data are presented as mean ± s.e.m. (adapted with permission from reference Salehi *et al.*²⁰).

Figure 3. (a) Blood glucose, (b) plasma insulin and (c) insulin secretion responses to meal ingestion in RYGB subjects, with (hypoglycemic-RYGB, left panels) and without (asymptomatic-RYGB, right panels) hypoglycemia syndrome, during studies with (dashed line, white bar) and without (solid line, black bar) exendin-(9-39) infusion. Data are presented as mean $\pm$ s.e.m. (adapted with permission from reference Salehi *et al.*³⁵).

Figure 4.

Postprandial glucagon secretion during (a) meal tolerance test or (b) meal tolerance test with hyperinsulinemic hypoglycemic clamp in patients after RYGB with (black bar) and without (white bar) hypoglycemia, as well as non-surgical controls (gray bar). Data are presented as mean $\pm$ s.e.m., * $P < 0.05$ compared with RYGB groups (adapted with permission from references Salehi *et al.*^{20,39}).