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Nutritional strategies for correcting low glucose values in patients with postbariatric hypoglycaemia: A randomized controlled three-arm crossover trial

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Abstract

Aim: To evaluate the efficacy of nutritional hypoglycaemia correction strategies in postbariatric hypoglycaemia (PBH) after Roux-en-Y gastric bypass (RYGB).

Materials and methods: In a randomized, controlled, three-arm crossover trial, eight post-RYGB adults (mean [SD] 7.0 [1.4] years since surgery) with PBH ingested a solid mixed meal (584 kcal, 85 g carbohydrates, 21 g fat, 12 g protein) to induce hypoglycaemia on three separate days. Upon reaching plasma glucose of less than 3.0 mmol/L, hypoglycaemia was corrected with 15 g of glucose (G15), 5 g of glucose (G5) or a protein bar (P10, 10 g of protein) in random order. The primary outcome was percentage of time spent in the target plasma glucose range (3.9-5.5 mmol/L) during 40 minutes after correction.

Results: Postcorrection time spent in the target glucose range did not differ significantly between the interventions ($P = .161$). However, postcorrection time with glucose less than 3.9 mmol/L was lower after G15 than P10 ($P = .007$), whereas time spent with glucose more than 5.5 mmol/L, peak glucose and insulin 15 minutes postcorrection were higher after G15 than G5 and P10 ($P < .001$). Glucagon 15 minutes postcorrection was higher after P10 than after G15 and G5 ($P = .002$ and $P = .003$, respectively). G15 resulted in rebound hypoglycaemia (< 3.0 mmol/L) in three of eight cases (38%), while no rebound hypoglycaemia occurred with G5 and P10.

Conclusions: Correcting hypoglycaemia with 15 g of glucose should be reconsidered in post-RYGB PBH. A lower dose appears to sufficiently increase glucose levels outside the critical range in most cases, and complementary nutrients (e.g. proteins) may provide glycaemia-stabilizing benefits.

Registration number of clinical trial: NTC05250271 (ClinicalTrials.gov).

KEYWORDS
nutrition, postbariatric hypoglycaemia, Roux-en-Y gastric bypass

1 | INTRODUCTION

Hypoglycaemia after bariatric surgery, also known as postbariatric hypoglycaemia (PBH), is an increasingly recognized complication of bariatric surgery, particularly after Roux-en-Y gastric bypass (RYGB).[1,2] The condition typically manifests as recurrent episodes of hypoglycaemia after meals containing carbohydrates with a high glycaemic index.[3] The key pathophysiological features of PBH include excessive insulin secretion because of rapid glucose absorption and stimulation of insulinotropic factors from the gut.[4]

Dietary management is the cornerstone treatment to prevent the occurrence of PBH.[5,6] In addition, an essential part of education to improve patient safety is acute treatment of hypoglycaemia. Current guidelines, based on recommendations for managing hypoglycaemia in individuals with diabetes,[7,8] suggest correcting low glucose levels using the 'rule of 15'. This involves the consumption of 15 g of fast-acting carbohydrates or glucose.[9] Although this treatment protocol aims to increase glucose levels quickly to improve safety, rapid spikes in blood glucose can increase glucose variability and possibly even trigger later 'rebound' hypoglycaemia in PBH. Currently, there are no hypoglycaemia correction strategies tailored to the specific needs of patients with PBH. As the nature of hypoglycaemia in PBH essentially differs from that of individuals with diabetes on insulin therapy, lower doses of glucose may be more appropriate. In addition, because of its stimulatory effect on glucagon secretion,[10,11] protein also a potential corrective strategy in PBH.

The current study aimed to assess the effectiveness of alternative nutritional strategies for correcting low blood glucose levels in adults with PBH after RYGB. We hypothesized that 15 g of glucose may not be an adequate hypoglycaemia correction strategy for patients suffering from PBH and may even predispose them to rebound hypoglycaemia.

2 | MATERIALS AND METHODS

2.1 | Study design

This study was a three-arm, randomized, controlled, crossover clinical trial conducted at Bern University Hospital. After a screening and baseline visit, participants received three different interventions for hypoglycaemia correction in a random order during in-clinic visits. These visits were spaced at least 48 hours apart. All the participants provided written informed consent. This clinical trial was approved by the Ethics Commission of the Canton of Bern (BASEC ID 2021-02086) and was conducted in accordance with the Declaration of Helsinki. This clinical trial was registered at ClinicalTrials.gov (NTC05250271).

2.2 | Study population

Participants were eligible for inclusion if they were aged 18 years or older with a history of RYGB and a clinical diagnosis of PBH (symptomatic postprandial plasma or sensor glucose levels < 3.0 mmol/L, as defined by the International Hypoglycaemia Study Group[12]). The exclusion criteria were other causes of hypoglycaemia, pregnancy or lactation, medical contraindications to study procedures, drugs interfering with blood glucose regulation during the time of investigation, and inability or incapacity to follow study procedures or provide informed consent, as judged by the investigator.

2.3 | Interventions

The three interventions for hypoglycaemia correction under investigation were glucose tablets (intact Expert Dextrose, sanotact GmbH, Münster, Germany) in doses of 15 g (G15) and 5 g (G5), and one-half of a commercial low-sugar protein bar (High Protein Bar Double Chocolate Cookie, Premier Protein, Active Nutrition International GmbH, München, Germany), which contained 10 g of protein and 5 g of carbohydrates as polyols (P10). The nutritional details of the protein bars are provided in Appendix S1. Polyols, also known as sugar alcohols, are a group of reduced-calorie, low-digestible, low-glycaemic carbohydrates.

2.4 | Randomization and blinding

The order of the three interventions was allocated by simple randomization using a computer-generated sequence. The randomization list was generated before the start of the study and implemented using the randomization module in the Research Electronic Data Capture (REDCap) software. Randomization remained concealed until the interventions were assigned. Blinding of the nutritional interventions was not possible because of technical constraints. However, the participants remained blinded to the intervention until they received the hypoglycaemia correction. Additionally, patients were blinded to their glucose levels throughout the experiment.

2.5 | Procedures

After study inclusion, the participants attended a baseline visit at the clinical research facility for medical history and anthropometric assessment. On the day of the intervention, participants reported to the clinical facility after a 10-hour overnight fast and had an antecubital vein cannula fitted for frequent blood sampling. After a baseline blood draw, participants consumed a standardized breakfast consisting of bread with butter and jam, and fruit yogurt (584 kcal, 85 g of carbohydrates, of which 40 g of sugar, 21 g of fat, 12 g of protein) to induce postprandial hypoglycaemia. When plasma glucose levels fell below 3.0 mmol/L, hypoglycaemia correction was performed according to the assigned nutritional intervention. Patients were excluded from the study if their plasma glucose levels did not fall below 3.0 mmol/L during the first visit. If they did not reach this threshold during subsequent visits, hypoglycaemia correction was administered

once the plasma glucose levels stopped decreasing. Plasma glucose was sampled 5 minutes before the meal, then at 10, 20, 30, 45, 60 and 90 minutes after the start of the meal. After 90 minutes, plasma glucose was sampled every 5 minutes until 40 minutes after hypoglycaemia correction. Blood samples for insulin and glucagon measurements were collected at baseline, at the time of hypoglycaemia correction, and 15 minutes after correction. These samples were immediately centrifuged, separated and stored at −80°C until analysis. Because the primary outcome was assessed within 40 minutes after initial hypoglycaemia correction, no further corrections for ineffective hypoglycaemia correction were performed during the 40 minutes after the initial correction, except in cases of clinical signs of severe hypoglycaemia. At the end of the visit, participants were advised to ingest a meal or snack containing slowly digestible carbohydrates of their choice to allow for stable glucose levels at the time of discharge. At the end of the third interventional visit, the patients were verbally asked about their preferred hypoglycaemia correction.

2.6 | Biochemical analyses

Plasma glucose levels were measured in duplicate using a Biosen C-line glucose analyser (EKF-diagnostic GmbH, Barleben, Germany). Glucose-regulating hormones were measured using commercial immunometric assays (Elecsys Insulin assay, Roche Diagnostics GmbH, Mannheim, Germany; Mercodia AB Glucagon assay, Uppsala, Sweden).

2.7 | Outcomes

All outcomes were assessed within 40 minutes after hypoglycaemia correction. The primary outcome was the percentage of time spent in the target glucose range (defined as plasma glucose 3.9-5.5 mmol/L). Secondary outcomes were percentage of time with plasma glucose less than 3.0 mmol/L, less than 3.9 mmol/L, more than 5.5 mmol/L and more than 10.0 mmol/L, peak plasma glucose, time to euglycaemia (plasma glucose 3.9 mmol/L), proportion of participants with rebound hypoglycaemia (plasma glucose < 3.0 mmol/L following successful primary hypoglycaemia correction defined as plasma glucose ≥ 3.9 mmol/L), plasma insulin and glucagon concentrations 15 minutes after hypoglycaemia correction. Outcomes within 150 minutes after hypoglycaemia correction were not assessed because patients had lunch immediately after the inpatient visit.

Exploratory outcomes included percentage of time spent with plasma glucose 3.5-5.5 mmol/L and less than 3.5 mmol/L, time to plasma glucose of 3.5 mmol/L and of 3.0 mmol/L, proportion of participants with rebound hypoglycaemia following plasma glucose of 3.5 mmol/L and higher, and treatment failure (plasma glucose never reaching ≥ 3.0 mmol/L during 40 minutes postcorrection). Furthermore, we analysed insulin and glucagon concentrations at the time of hypoglycaemia correction, and the change between 0 and 15 minutes after hypoglycaemia correction. Finally, the patients' preference for hypoglycaemia correction was recorded.

2.8 | Sample size

Because of the lack of preliminary data, no formal sample size calculation was applicable, and we defined the sample size based on practical feasibility. Specifically, with a sample size of eight participants, the study detects an effect size (f) of 0.5 with a power of 80% at an alpha level of 5% (assuming a correlation among repeated measures of 0.6). Power was calculated for a repeated-measure analysis of variance with within-subject factors using GPower (version 3.1.9.7). New participants replaced dropouts until eight participants completed all three treatment arms.

2.9 | Statistical analyses

We preprocessed the plasma glucose values before calculating the outcomes by linearly interpolating the mean of the duplicate plasma glucose measurements. For outcomes based on time spent in specified glucose ranges, peak plasma glucose levels and hormonal responses, we assessed treatment differences using linear mixed-effects models. We used Kaplan–Meier curves to describe the time to reach specified plasma glucose levels and assessed treatment differences using Cox mixed-effects models. Visits with hypoglycaemia correction administered above these specified levels (one visit with correction at plasma glucose ≥ 3.5 mmol/L and four visits with correction at ≥ 3.0 mmol/L) were excluded from the Kaplan–Meier curves and Cox mixed-effects models. We used generalized linear mixed-effects models for the occurrence of rebound hypoglycaemia. All models were adjusted for the period effect and accounted for within-subject correlations arising from the crossover design (period was considered as a fixed effect and subjects as a random effect). In addition, we performed a sensitivity analysis in which all models were further adjusted to account for plasma glucose levels at the time of hypoglycaemia correction. In the case of a significant treatment effect (assessed using Wald chi-square tests), marginal means were compared pairwise using the Tukey method for *P* value adjustment. An identity link was used for the linear mixed-effects models, and a logit link was used for the occurrence of rebound hypoglycaemia. Statistical analysis was conducted using R version 4.2.2[13] with the packages *tidyverse* version 1.3.2,[14] *lme4* version 1.1.31,[15] *lmerTest* version 3.1.3,[16] *survival* version 3.4.0,[17,18] *coxme* version 2.2.18.1,[19] *car* version 3.1.1[20] and *emmeans* version 1.8.2.[21] Data are presented as *n* (%) for categorical variables and mean (SD) for continuous variables, unless otherwise specified. Statistical significance was set at *P* less than .05 (two-tailed).

3 | RESULTS

We recruited participants from 11 January to 13 July 2022, and the study ended when a predefined number of participants was reached. Of the 10 participants who were randomized, eight completed all three mixed meal tests. One participant did not experience hypoglycaemia

TABLE 1 Participant characteristics

Characteristic	*n* (%) or mean (SD)
N	8
Female	6 (75.0%)
Age, y	46.5 (12.5)
BMI, kg/m^2	26.0 (4.24)
Waist circumference, cm	84.9 (10.8)
HbA1c,	
%	5.4 (0.2)
mmol/mol	35.4 (2.6)
Time since surgery, y	7.0 (1.4)
Pre-RYGB BMI, kg/m^2	39.5 (2.1)
Total weight loss after RYGB, %	36.2 (12.6)
History of severe hypoglycaemia and neurological symptoms:	
None	1 (12.5%)
Loss of consciousness	3 (37.5%)
Seizure	4 (50.0%)
Hospitalization because of syncope	2 (25.0%)
Current or previous pharmacological treatment for PBH:	
Acarbose	3 (37.5%)
GLP-1 receptor agonists	1 (12.5%)
None	5 (62.5%)
Invasive treatment for PBH:	
Laparoscopic pouch resizing	3 (37.5%)
Endoscopic suturing for transoral outlet reduction	1 (12.5%)
Charlson Comorbidity Index	0.13 (0.35)

Abbreviations: BMI, body mass index; GLP-1, glucagon-like peptide-1; HbA1c, glycosylated hemoglobin; PBH, postbariatric hypoglycaemia; RYGB, Roux-en-Y gastric bypass.

during the first visit and another withdrew from the study before the first visit. The consort flow diagram is shown in Figure **S1**. One visit of one patient was excluded from the analysis of outcomes affected by an additional rescue correction 25 minutes after the initial correction (see section 3.4). Participant characteristics are reported in Table 1.

3.1 | Glucose trajectories

The plasma glucose trajectories following the three corrections are illustrated in Figure 1, and the results of the plasma glucose outcomes are shown in Table 2. There were no significant differences in the percentage of time spent in the target glucose range after the three hypoglycaemia treatments ($P = .161$). The analysis revealed a treatment effect for the time spent at less than 3.0 mmol/L and less than 3.9 mmol/L. Specifically, G15 resulted in a shorter time at less than 3.9 mmol/L than P10 ($P = .007$). Marginally non-significant differences were observed for the comparisons between G15 and G5 ($P = .083$ for time < 3.0 mmol/L and $P = .082$ for time < 3.9 mmol/L) and between G15 and P10 ($P = .059$ for time < 3.0 mmol/L). While none of the interventions led to plasma glucose values of more than 10.0 mmol/L, G15 resulted in the highest glucose peaks. In addition, hypoglycaemia correction with G15 led to the longest time with glucose values of more than 5.5 mmol/L. Results obtained by the models adjusted for plasma glucose at the time of hypoglycaemia correction were in line with the unadjusted results (Table **S1**).

Treatment effects were observed for time to euglycaemia (3.9 mmol/L) and 3.5 mmol/L or higher ($P = .04$ and $P = .003$, respectively). While pairwise comparisons did not reach statistical significance for time to euglycaemia (a marginally non-significant difference was observed for G15 vs. P10, $P = .052$), time to glycaemia of 3.5 mmol/L was shorter for G15 than for G5 ($P = .020$) and P10 ($P = .007$). Figure 2 shows Kaplan–Meier curves illustrating time to glucose values above 3.0 mmol/L, and treatment failures (plasma glucose never reaching 3.0 mmol/L during 40 minutes postcorrection). Time to 3.0 mmol/L was not statistically significantly different after the three hypoglycaemia treatments. No treatment failures occurred with G15, but did in two (29%) and three (38%) participants after G5 and P10, respectively. Rebound hypoglycaemia after reaching plasma levels of 3.9 and 3.5 mmol/L occurred in three out of eight cases (38%) after G15, but did not occur after G5 and P10 ($P = 1.00$).

Participants usually had lunch shortly after the end of the visit (at the end of the 40-minute plasma glucose collection posthypoglycaemia), which limits the interpretability of the sensor-based follow-up glucose trajectories up to 150 minutes. Therefore, the outcomes based on sensor glucose were not calculated.

3.2 | Hormonal responses

The levels of insulin and glucagon measured during the experiment are listed in Table 3. Insulin levels were highest after G15, whereas glucagon levels were highest after P10 (both $P < .001$). Hormone levels at baseline and at the time of hypoglycaemia (before correction) were comparable in all conditions.

3.3 | Participants' preferences

Of the eight participants, seven preferred hypoglycaemia correction with P10, whereas the remaining participant preferred G5. As clarified by additional comments, their responses reflected the perceived discomfort after correction with G15 and the more pleasant taste of the protein bar compared with dextrose tablets.

3.4 | Safety events

One participant required rescue correction with 5 g of additional glucose 25 minutes after the initial correction with G5 because of clinically relevant signs of neuroglycopaenia, such as sleepiness and slurred

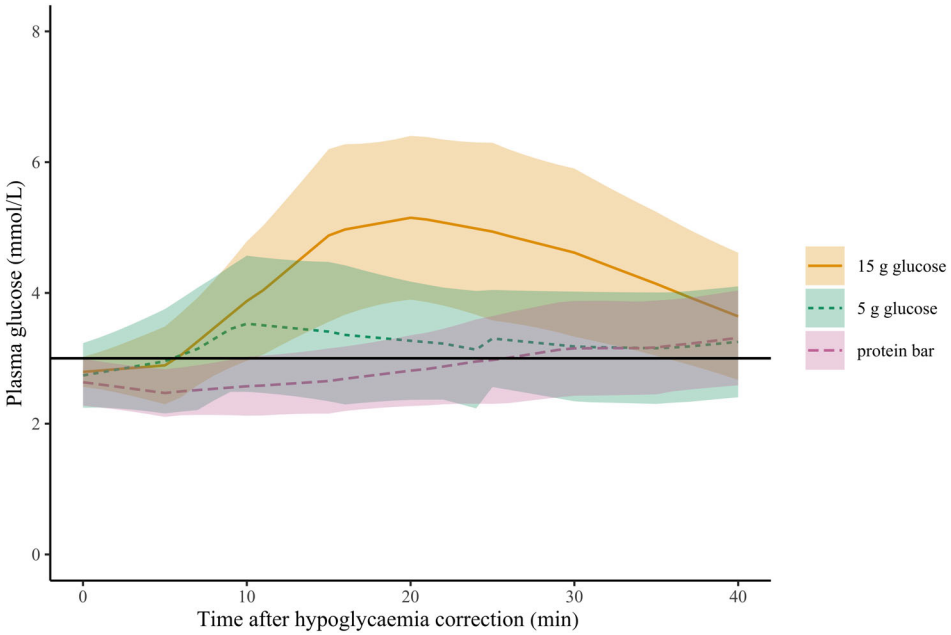

FIGURE 1 Plasma glucose trajectories during 40 minutes after hypoglycaemia correction. Mean (line) and SD (ribbon) of linearly interpolated glucose values. The solid line represents a plasma glucose value of 3.0 mmol/L.

TABLE 2 Plasma glucose outcomes during 40 minutes posthypoglycaemia correction

	Estimated mean (95% CI)			*P* value			
Outcome	G15	G5	P10	Overall	G15 versus G5	G15 versus P10	G5 versus P10
Time with plasma glucose 3.9-5.5 mmol/L, %	27.3 (9.3 to 45.2)	19.4 (0.6 to 38.3)	10.3 (−8.2 to 28.7)	.161	N/A		
Time with plasma glucose < 3.0 mmol/L, %	24.7 (−0.8 to 50.2)	53.4 (26.5 to 80.2)	58.3 (32.0 to 84.6)	.012	.083	.059	.931
Time with plasma glucose < 3.9 mmol/L, %	50.8 (29.4 to 72.2)	77.1 (54.3 to 99.9)	95.9 (73.6 to 118.2)	< .001	.082	.007	.321
Time with plasma glucose > 5.5 mmol/L, %	21.9 (14.3 to 29.6)	3.6 (−4.7 to 11.9)	−6.2 (−14.3 to 1.9)	< .001	.006	< .001	.204
Peak plasma glucose, mmol/L	5.6 (4.8 to 6.4)	3.8 (2.9 to 4.6)	3.2 (2.4 to 4.1)	< .001	.002	< .001	.449
Time with plasma glucose 3.5-5.5 mmol/L, %	43.7 (24.5 to 62.8)	29.1 (9.2 to 49.0)	28.6 (9.0 to 48.1)	.103	N/A		
Time with plasma glucose < 3.5 mmol/L, %	34.4 (12.2 to 56.7)	68.1 (45.3 to 90.8)	77.5 (55.0 to 100.1)	< .001	.002	.001	.531

Note: Results obtained from linear mixed-effects models (participant as random effect and adjusted for visit number) and estimated marginal means. Overall *P* values represent main treatment effects obtained from the ANOVA table. *P* values for pairwise marginal means were adjusted using the Tukey method. Pairwise comparisons are only reported for significant overall *P* values.

Abbreviations: ANOVA, analysis of variance; G15, hypoglycaemia correction with 15 g of glucose; G5, hypoglycaemia correction with 5 g of glucose; P10, hypoglycaemia correction with protein bar (10 g of protein).

speech. This visit was excluded from the analysis of affected outcomes (all outcomes based on plasma glucose values during the 40 minutes after the initial hypoglycaemia correction). Another adverse event occurred during the same visit, consisting of symptomatic postprandial hypotension during rapidly decreasing glucose levels (plasma glucose was ∼9.4 mmol/L and decreasing by ∼1.4 mmol/L per 5 minutes). The patient recovered fully after positioning measures were taken.

4 | DISCUSSION

In this randomized crossover clinical trial, we compared different nutritional strategies for correcting meal-induced postprandial hypoglycaemia in patients with PBH after RYGB. Although the postcorrection time in euglycaemia did not significantly differ between the ingestion of 15 g of glucose, 5 g of glucose, or a protein bar (10 g of protein), correction with 15 g of glucose led to a shorter time to reach euglycaemia and a shorter time in hypoglycaemia. However, 15 g of glucose also resulted in a longer time with glucose levels above 5.5 mmol/L, higher insulin exposure and rebound hypoglycaemia in three cases (38%). No difference in the time spent in the assessed glycaemic ranges was observed between the protein bar and 5 g of glucose. At 40 minutes postcorrection, plasma levels remained below 3.0 mmol/L in two and three participants following intake of 5 g of glucose and 10 g of protein, respectively. Nevertheless, plasma glucose was higher than that at the time of correction, and none of the participants were symptomatic. Higher glucagon levels were observed following correction with the protein bar, without any

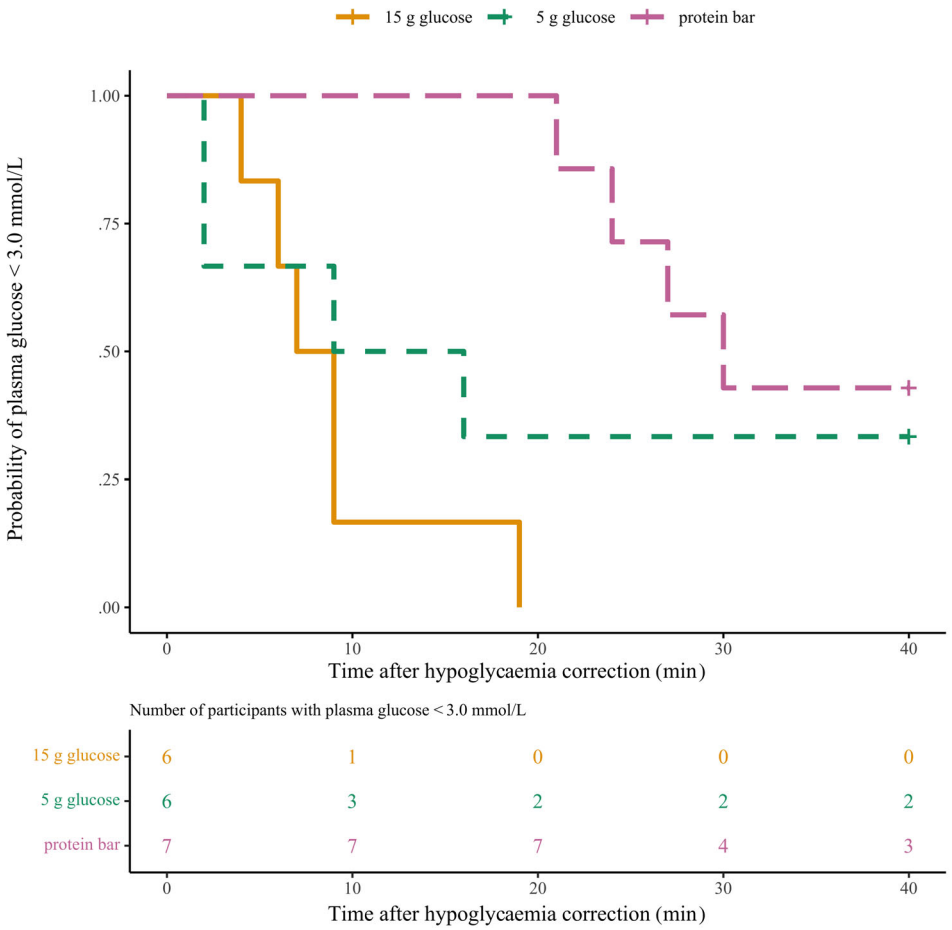

FIGURE 2 Kaplan–Meier curves of treatment failure (plasma glucose < 3.0 mmol/L). One visit with correction of 5 g of glucose was excluded because of repeated (rescue) hypoglycaemia correction, two visits with correction of 15 g glucose were excluded because plasma glucose values were just above the threshold value (3.12 and 3.07 mmol/L) by the time the hypoglycaemia correction was administered, and two visits (one with correction of 5 g of glucose and one with a protein bar) were excluded because the patient did not develop hypoglycaemia < 3.0 mmol/L during the visit.

TABLE 3 Hormonal responses to hypoglycaemia correction

	Estimated mean (95% CI)			*P* value			
Outcome	G15	G5	P10	Overall	G15 versus G5	G15 versus P10	G5 versus P10
Baseline insulin, mU/L	5.7 (3.8 to 7.7)	5.5 (3.6 to 7.5)	5.7 (3.7 to 7.7)	.918	N/A		
Insulin at hypoglycaemia, mU/L	30.1 (7.9 to 52.4)	30.4 (8.2 to 52.5)	28.0 (5.3 to 50.7)	.963	N/A		
Insulin 15 minutes after hypoglycaemia correction, mU/L	63.9 (49.7 to 78.1)	25.0 (10.8 to 39.1)	25.2 (10.7 to 39.7)	< .001	< .001	< .001	.999
Change in insulin between 0 and 15 minutes after hypoglycaemia correction, mU/L	33.8 (17.0 to 50.5)	−5.4 (−22.0 to 11.1)	−2.8 (−20.4 to 14.8)	< .001	.003	.011	.964
Baseline glucagon, pmol/L	6.4 (4.3 to 8.5)	7.7 (5.6 to 9.8)	6.9 (4.8 to 9.0)	.219	N/A		
Glucagon at hypoglycaemia, pmol/L	8.5 (3.7 to 13.2)	8.8 (3.6 to 14)	11.2 (6.2 to 16.2)	.651	N/A		
Glucagon 15 minutes after hypoglycaemia correction, pmol/L	7.4 (3.3 to 11.6)	8.0 (3.9 to 12.1)	18.5 (14.2 to 22.9)	< .001	.966	.002	.003
Change in glucagon between 0 and 15 minutes after hypoglycaemia correction, pmol/L	−1.0 (−4.1 to 2.1)	−0.8 (−4.2 to 2.6)	7.3 (4.0 to 10.7)	< .001	.995	.010	.014

Note: Results obtained from linear mixed-effects models (participant ID as random effect and adjusted for visit number) and estimated marginal means. Overall *P* values represent main treatment effects obtained from the ANOVA table. *P* values for pairwise marginal means were adjusted using the Tukey method. Pairwise comparisons are only reported for significant overall *P* values.

Abbreviations: ANOVA, analysis of variance; G15, hypoglycaemia correction with 15 g of glucose; G5, hypoglycaemia correction with 5 g of glucose; P10, hypoglycaemia correction with protein bar (10 g of protein).

increase in the two glucose-only treatments. The protein bar was the preferred treatment for seven out of eight participants.

Various pathophysiological concepts support a gradual correction of hypoglycaemia in patients with PBH. First, rapid increases in plasma glucose, as observed after correction with 15 g of glucose, may predispose to rebound hypoglycaemia, which occurred in three cases in the present study. Besides the glucose-stimulated insulin response, the vulnerability to rebound hypoglycaemia is further supported by the attenuation of counter-regulatory hormones after antecedent hypoglycaemia.[22,23] In this context, the higher glucagon exposure following the intake of 10 g of protein observed in our study may be particularly beneficial and support the notion of combining carbohydrates with proteins for hypoglycaemia correction. Additionally, proteins may serve as a source for gluconeogenesis. Second, higher insulin exposure because of an inadequately high glucose intake and rebound hypoglycaemia may predispose patients to weight regain. Associations between recurrent hypoglycaemia exposure and weight gain have not only been observed in patients with diabetes,[24] but has also been suggested as a predisposing factor for weight regain after bariatric surgery.[25] Third, the rapid correction of hypoglycaemia resulting in supraphysiological glucose levels is an important contributor to glucose variability. Glucose variability, particularly acute intra-day glucose fluctuations, has been shown to trigger oxidative stress and endothelial dysfunction in previous studies.[26–28] Increased glycaemic variability because of inadequate hypoglycaemia correction may therefore negatively impact the cardiovascular risk profile of patients with PBH.

Of note, current recommendations for hypoglycaemia correction in patients with PBH suggest to correct glucose levels below 3.9 mmol/L with 15 g of glucose and to repeat the same treatment if they are not above 4.4 mmol/L after 15 minutes.[9] Our findings and the above-mentioned considerations, however, suggest the possibility of a more gradual hypoglycaemia correction strategy, with lower amounts of rapidly available carbohydrates potentially combined with proteins to stabilize glucose dynamics. Our data did not clearly indicate a superior treatment, but the three treatments exhibited marked differences in several aspects. As such, appropriate treatment may vary depending on the patient's glucose-insulin phenotype (e.g. glucose absorption kinetics, insulin sensitivity, magnitude of insulin exposure, counter-regulation to hypoglycaemia) and situative factors (e.g. activity level). Therefore, the selection of a hypoglycaemic treatment strategy may require individual consideration, underscoring the need for personalization.

Because none of the tested strategies was unequivocally superior to the others, the most appropriate method may not have been captured by the study. Our findings lead us thus to speculate that 10 g of glucose or 10 g of protein combined with 5 g of glucose would lead to a lower proportion of participants experiencing treatment failures at 40 minutes post-correction while avoiding rebound hypoglycaemia. Alternatively, glucose may be combined with other carbohydrates, such as fructose (e.g. in the form of sucrose), which has a slower and more sustained effect on glycaemia.[29,30] Such strategies are in line with the common practice of combining carbohydrates with high and low glycaemic indices.

In addition, the threshold to apply corrective actions should be reconsidered in PBH patients, as bariatric surgery alters glucose and insulin kinetics and, consequently, postprandial nadir glucose values.[31,32] In our study, we implemented a threshold of less than 3.0 mmol/L as this level does not occur under physiological conditions in individuals without diabetes and is currently recognized as defining clinically significant hypoglycaemia.[12] As glucose levels continued to rise 15 minutes after correction, we recommend waiting for at least 20 minutes before further action is considered. Symptoms may not be reliable indicators of repeated corrections. Instead, trend arrows in continuous glucose monitoring systems accompanied by capillary glucose testing may provide important decision support to avoid both persistent hypoglycaemia and overshoot hyperglycaemia.

The strengths of the present study include the randomized crossover design and experimental procedures resulting in standardized solid meal-induced hypoglycaemia, which is representative of postprandial hypoglycaemia experienced under real-life conditions. The treatment strategies were chosen based on current recommendations,[9] feasibility in daily life and underlying hypotheses. However, this study had several limitations. The sample size was small and predominantly female, the follow-up period was short, and there was intra-individual variability in meal-induced glucose dynamics despite identical stimuli, as reported in other investigations.[33]

In conclusion, recommendations to correct hypoglycaemia with 15 g of glucose should be reconsidered for patients with PBH after RYGB. Instead, a lower dose of glucose appears to be sufficient to increase glucose levels outside the critical range in most cases. Although preferred by patients, protein bars as a hypoglycaemia treatment method seem to require added low amounts of rapidly available carbohydrates for sufficient hypoglycaemia correction. Although our study may provide a rationale for using lower amounts of rapid-acting carbohydrates for hypoglycaemia correction in patients with PBH after RYGB, the clinical heterogeneity of PBH requires tailoring such strategies to individual needs. Additional larger studies are required to further elucidate the personalized approach for PBH.

AUTHOR CONTRIBUTIONS

Conceptualization: KAS, DH and LB. Data curation: KAS. Formal analysis: KAS, CTN and DH. Funding acquisition: SM and LB. Investigation: KAS, AFe, CS and JG. Methodology: KAS, CTN, DH and LB. Project administration: KAS and AFe. Resources: LB. Supervision: SM, ZS, AFa, DH and LB. Validation: KAS and CS. Visualization: KAS. Writing – original draft: KAS and LB. Writing – review and editing: AFe, CS, FP, JG, CTN, SM, ZS, AFa and DH.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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