


ORIGINAL ARTICLE

Diabetes/Lipids/Obesity/Metabolism

Defining Clinical Characteristics of Individuals With and Without Post-Bariatric Hypoglycemia After Gastric Bypass

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Context: Post-bariatric hypoglycemia (PBH) is a complication of bariatric surgery including Roux-en-Y gastric bypass (RYGB). It remains unclear why only some individuals develop PBH.

Objective: To identify clinical characteristics distinguishing post-RYGB individuals with PBH, versus without symptomatic hypoglycemia (RYGB non-hypo).

Design and Setting: Cross-sectional observational study in academic referral centre. Adults 18–70, without current diabetes, were recruited into three groups: (1) PBH ($n = 39$); (2) RYGB non-hypo ($n = 25$); and (3) individuals without history of upper gastrointestinal surgery ($n = 17$). Outcome measures included between-group differences in medical history and medication use, and survey-based scores for hypoglycemia, dumping syndrome, and autonomic symptoms.

Results: PBH participants were 92% female, age 53.4 ± 11.9 y, BMI 31.2 ± 5.6 kg/m², versus RYGB non-hypo (100% female, age 53.2 ± 10.5 y, BMI 32.2 ± 8.0 kg/m²) and controls (65% female, age 44.5 ± 14.6 y, BMI 30.8 ± 6.3 kg/m²). 87% of PBH reported level 3 hypoglycemia, with emergency visits in 28% and vehicle accidents in 8%. Reduced hypoglycemia awareness was reported by 82%; 13%–17% were classified as unaware (modified Clarke/Gold scores). Preoperative hypoglycemia symptoms and family history were reported by 26% and 18% of PBH. PBH had significantly higher survey scores for hypoglycemia, dumping syndrome, and autonomic symptoms, and higher self-reported neuropathy, autonomic neuropathy, orthostatic hypotension, reflux esophagitis, intestinal dysmotility, and IBS (all $p < 0.05$ vs. RYGB non-hypo). Gabapentin and PPI use was more frequent in PBH.

Conclusion: High rates of IBS, dumping symptoms, and orthostatic hypotension suggest disordered autonomic regulation as a potential contributor to PBH. Self-reported preoperative symptoms and family history of hypoglycemia suggest possible preoperative differences in glucose metabolism in PBH.

Ashna Grover and Maryam Farahmandsadr have contributed equally.

1 | Introduction

Bariatric/metabolic surgery remains the most potent approach for management of obesity and related medical conditions, yielding both weight loss and improved glycemic control and remission of type 2 diabetes (T2D) [1]. Mechanisms contributing to improved metabolism after bariatric surgery include weight loss and improved insulin sensitivity, increases in insulin and incretin hormone secretion, and reductions in food intake and obesity-related inflammation [2]. Unfortunately, with improvements in glucose metabolism after bariatric surgery comes risk for post-bariatric hypoglycemia (PBH) [3]. PBH can occur after multiple upper gastrointestinal procedures, including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, fundoplication, gastrectomy, and esophagectomy. PBH usually develops at least 1 year or more postoperatively, typically occurring within 1–3 h after meals, and with greater severity after ingestion of high glycemic index carbohydrates. While the prevalence of PBH differs according to assessment methodology, up to 38% of individuals post-RYGB report symptoms consistent with hypoglycemia [3, 4]. CGM has demonstrated that 75% of patients experience asymptomatic low sensor glucose levels after RYGB [5]. Unfortunately, repeated hypoglycemia can lead to hypoglycemia unawareness [6, 7] further impairing safety due to neuroglycopenia.

PBH is characterised by rapid emptying of glucose from the stomach or gastric pouch into the intestine, resulting in rapid rise in glucose after meal ingestion and exaggerated postprandial levels of glucagon like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and other peptides. Together these result in exaggerated postprandial insulin secretion with subsequent rapid drop in glucose to hypoglycemic levels [2]. Additional contributors may include altered bile acid metabolism [8], altered gastrointestinal motility [9], increased insulin-independent glucose uptake [10], and decreased counterregulatory hormone secretion [11]. The presence of autonomic dysfunction in some severely affected patients [12] raises the possibility that alterations in neural control of gastrointestinal function and metabolism could contribute to PBH. However, why only some individuals develop PBH after RYGB remains unclear. Predictors of hypoglycemia identified in prior studies include younger age, female sex, and use of antidepressant medications [3]. Further predictive factors include history of preoperative symptoms suggestive of possible hypoglycemia, lower HbA1c, lower BMI, greater surgical weight loss, and absence of preoperative diabetes [3, 13–15]. Preoperative metabolic testing has revealed earlier glucose peak and small but significant increases in insulin secretion during oral glucose tolerance testing in those who subsequently develop PBH [14, 16].

To identify additional clinical factors that distinguish post-RYGB patients with and without PBH, we assessed medical history and utilised validated surveys of hypoglycemia symptoms and related disorders, in participants with (1) PBH, (2) post-RYGB without hypoglycemia, and (3) no history of gastrointestinal surgery.

2 | Methods

Study protocol was approved by Joslin Diabetes Center Committee on Human Studies and registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov)

(NCT04428866). All participants provided voluntary informed written consent. Data were collected between February 2020 and May 2023.

This was a cross-sectional observation study, based on information gathered during the first visit of larger study aimed to elucidate mechanisms of PBH. Three groups of participants age 18–70 were recruited: (1) PBH after RYGB, previously diagnosed on the basis of Whipple's triad (hypoglycemia symptoms, plasma/capillary glucose below 54 mg/dL (3 mmol/L), and symptom relief with glucose elevation), and history of neuroglycopenia, recruited from Joslin Hypoglycemia Clinic and by advertisement; (2) RYGB without symptoms of hypoglycemia (RYGB non-hypo), with RYGB at least 1 year previously, recruited by social media advertisement (TrialFacts) and (3) group with similar weight, but no history of upper gastrointestinal surgery, hypoglycemia, or diabetes, recruited by advertisement (Craigslist).

The surgery timeline ranged from 1.5 to 25 years before recruitment for the study. The first patient enrolment date was 26 February 2020, while the earliest surgical date was 1 November 1997, and latest surgical date was 1 April 2021.

Exclusion criteria included current diabetes or use of diabetes medications (except acarbose), major systemic illness, arrhythmia, hypertension, active coronary artery disease, fasting hypoglycemia, insulinoma, pregnancy, active alcohol or substance abuse, and recent steroid or investigational drug exposure.

This report summarises data collected during visit 1 of this study, which was a screening visit and included detailed patient history, exam, and completion of questionnaires related to hypoglycemia. (Data from Visit 2, 3 and 4 will be described in upcoming papers). After informed consent was obtained, a detailed history and physical exam were performed by licensed clinicians, including extensive medical (including hypoglycemia-related symptoms) and surgical history, assessment of body composition via impedance plethysmography (Tanita TBF-215), and EKG. Laboratory testing included glycated haemoglobin (HbA1c), complete blood count, comprehensive chemistry, urinalysis, and pregnancy test if applicable.

Surveys completed by participants in the PBH group included the Hypoglycemia Fear Survey II (HFS-II) to assess fear of hypoglycemia and impact on daily life. This included two subscales, the Behaviour (HFS-B) and Worry (HFS-W), assessing behaviours to avoid hypoglycemic episodes and specific concerns about hypoglycemic episodes [17]. The Gold score, modified Clarke Hypoglycemia Awareness Questionnaire, and DAFNE hypoglycemia awareness tool [18, 19] were used to assess hypoglycemia awareness in PBH. All participants also completed the Edinburgh Hypoglycemia Symptom Scale (EHSS) [20] and dumping syndrome rating scale (DSRS) [21]. Rome IV criteria for diagnosis of irritable bowel syndrome (IBS) were assessed [22]. The COMPASS 31 questionnaire was used to assess autonomic symptoms [23]; this scale measures autonomic system symptoms through 31 patient-reported questions within six weighted domains: orthostatic intolerance [10 points]; vasomotor [six points]; secretomotor [seven points]; gastrointestinal

[28 points]; bladder [nine points] and pupillomotor [15 points]. A higher score indicates worse autonomic dysfunction.

Sample size for the broader study was calculated using data from our prior analysis of glucagon counterregulation after RYGB. We aimed to detect a significant 30% difference in the change in glucagon levels from baseline to hypoglycemia for the three-group comparison, and estimated power > 0.81 (0.99 for AUC glucagon) and $\alpha = 0.05$ (3-way ANOVA) with a sample size of 16 per group. Hence, we budgeted for sample size of 20 per group, allowing screen failure and dropout rates of 20%. For this report, sample sizes are greater, as some participants only completed visit 1 and elected not to complete the more intensive clinical measurements in visits 2–4. Additionally, due to recruitment issues during the pandemic, we offered an option of remote participation wherein some participants with PBH only completed visit 1, to allow a larger visit 1 database. We now present our findings as a descriptive study with characterisation of the different cohorts.

2.1 | Data Analysis

Analyses were performed using STATA version 18. Distributional properties of the data were examined, and normality was evaluated using the skewness kurtosis test. Continuous variables were expressed as mean \pm standard deviation and categorical variables as frequency (percentages). Between-group differences were evaluated using ANOVA for continuous variables, chi-square test or Fisher's exact test for categorical variables, and Tukey HSD for post-hoc testing. A *p*-value less than 0.05 was considered statistically significant.

3 | Results

3.1 | Participant Recruitment and Demographics

Ninety-five individuals were recruited for study participation (consort diagram, Figure 1). Six were excluded (five lost to follow-up after initial contact, one new-onset pregnancy) and four were excluded due to screen failure (high HbA1c and use of diabetes medication, sleeve gastrectomy, low haematocrit, ambiguous hypoglycemia symptoms). Of the 85 eligible participants, data were available from 81 participants at the time of analysis within three study groups (PBH, $n = 39$; RYGB non-hypo, $n = 25$; and nonsurgical controls, $n = 17$) (Table 1). Some participants elected to participate only in remote activities; comparison of in-person and remote participants is provided in Table S1.

PBH participants were 92% female, with mean age 53.4 ± 11.9 years, BMI 31.2 ± 5.6 kg/m², $38.9 \pm 9.2\%$ body fat; RYGB non-hypo were 100% female, age 53.2 ± 10.5 years, BMI 32.2 ± 8.0 kg/m², $40.4 \pm 7.8\%$ body fat; and controls were 65% female, age 44.5 ± 14.6 years, BMI 30.8 ± 6.3 kg/m², $35.1 \pm 11.9\%$ body fat. Consistent with the increased prevalence of females who undergo bariatric metabolic surgery [24], sex distribution differed between combined surgical (PBH + RYGB non-hypo) and control groups ($p = 0.0003$) but did not differ

between PBH and RYGB non-hypo. Age was greater in PBH versus controls ($p = 0.037$) but did not differ between PBH and RYGB non-hypo.

3.2 | Surgical History

PBH and RYGB non-hypo had similar duration of postoperative follow-up at the time of data analysis. Self-reported postoperative complications, revisional surgeries, pancreatitis, and vitamin deficiencies were numerically higher in the PBH group versus RYGB non-hypo but differences did not reach statistical significance (Table 1). Although surgical data were available only for a subset of participants ($n = 25$ for PBH, $n = 13$ for RYGB nonhypo), there was no statistical difference between the length of Roux and biliopancreatic (BP) limbs between groups per available surgical operative reports (Figure S1).

3.3 | Hypoglycemia Symptoms and Severity

Hypoglycemia symptom history was obtained using qualitative questions and quantified using the Edinburgh Hypoglycemia Symptom Score survey (possible range: 18–126 points). Mean EHSS score was significantly greater in PBH (63.1 ± 23) versus RYGB non-hypo (19.6 ± 3.6 , $p < 0.001$). Multiple individual components of EHSS score were also significantly greater for PBH versus RYGB non-hypo ($p < 0.02$ for all, Table 2).

3.4 | Hypoglycemia Awareness

Eighty-two percent of individuals with PBH reported reduced or absent perception of symptoms of hypoglycemia on qualitative assessment. Quantification of these relationships using the Gold Score and modified Clarke Hypoglycemia Awareness questionnaire revealed mean Gold score of 2.78 ± 0.33 in PBH (range 1–7) [25], with 52% of PBH participants classified as 'aware', 30% as 'indeterminate', and 17% as 'unaware'. Likewise, the Modified Clarke Score classified 61% of PBH as 'aware', 26% as 'indeterminate', and 13% as 'unaware' (Figure 2). Hypoglycemic symptoms were self-reported by PBH participants to occur at mean glucose 58 ± 11 mg/dL (3.22 ± 0.61 mmol/L).

3.5 | Impact of Hypoglycemia on Quality of Life

The Hypoglycemia Fear Survey II (HFS-II) [26] was used to assess the impact of hypoglycemia on quality of life of patients with PBH, including impact on behaviour, what activities they avoid, and frequency of hypoglycemia worry. Mean scores for HFS-B, HFS-W, and total were 17.5 ± 13.0 (range 0–47), 35.3 ± 20.4 (range 3–71), and 52.8 ± 31.3 (range 7–118), respectively. In addition, 87% reported hypoglycemic events requiring the assistance of others, and 28% reported emergency room visits for hypoglycemic episodes. Motor vehicle accidents related to hypoglycemia were reported by 8%, while 73% reported hypoglycemia had resulted in modification of driving habits. Sixty-one percent reported that hypoglycemia had a negative impact on employment status or productivity.

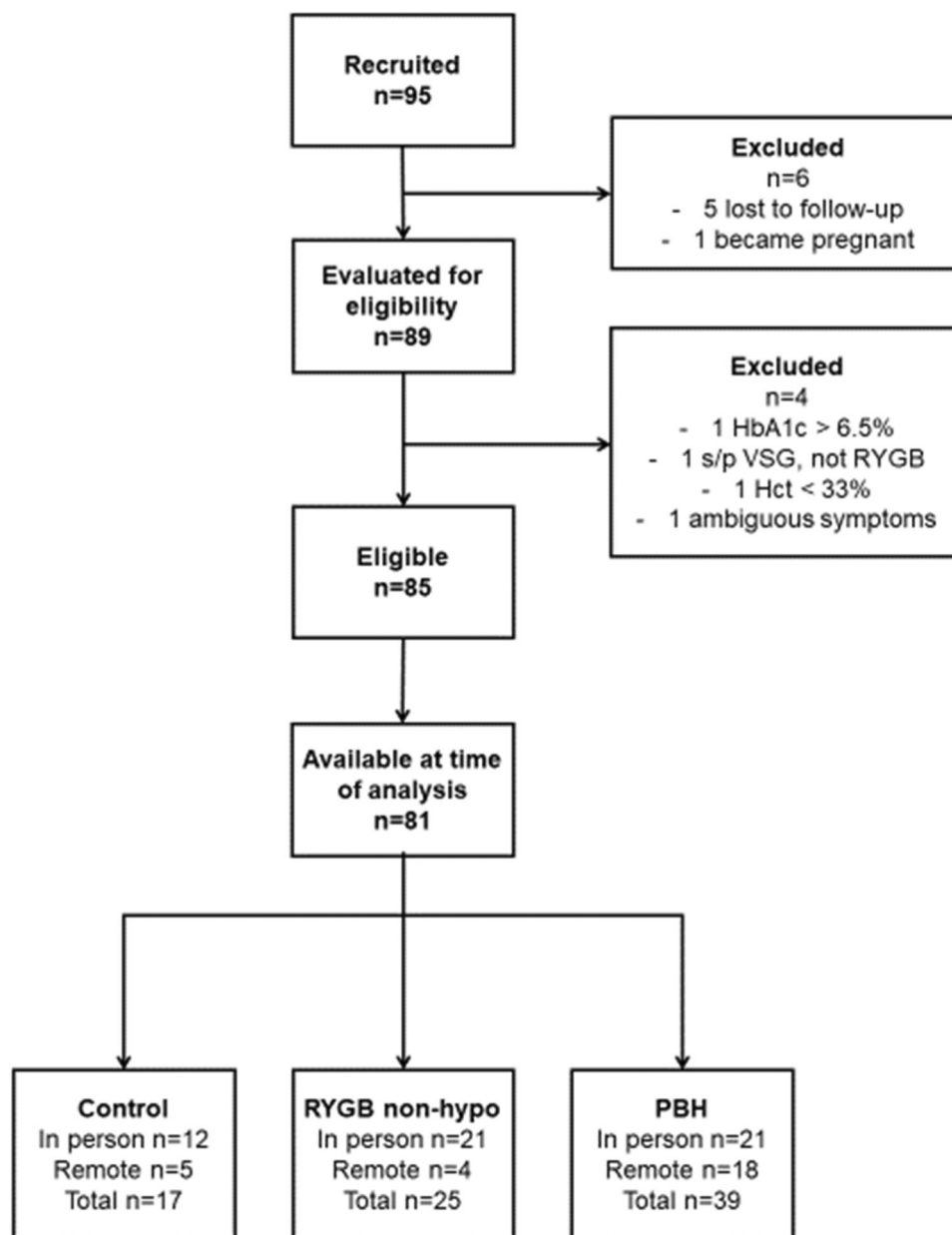


FIGURE 1 | Consort diagram.

3.6 | Preoperative Personal or Family History of Hypoglycemia

Twenty-six percent of participants with PBH reported history of hypoglycemia symptoms that preceded bariatric surgery (not evaluated medically), while 18% reported family history of hypoglycemia.

3.7 | Dumping Syndrome Symptoms

To determine whether early dumping symptoms were more common in PBH, the DSRS Score (9–63 points) was assessed (Table 3). Individuals with PBH had a significantly higher total DSRS score (26.4 ± 14.5) versus RYGB non-hypo (12.7 ± 5.7) or control (11.6 ± 6.3) (ANOVA $p < 0.001$). Tukey's post hoc test revealed significant differences for PBH versus RYGB non-hypo

and for PBH versus control for total score ($p < 0.001$) and all subscores ($p < 0.05$) except cold sweat.

3.8 | Autonomic Symptoms

Autonomic symptoms are commonly associated with hypoglycemia. Conversely, reductions in autonomic symptoms may reflect hypoglycemia-associated autonomic dysfunction or via additional mechanisms not directly related to hypoglycemia [12]. We administered the COMPASS 31 questionnaire to assess autonomic symptoms separate from hypoglycemia, within six domains, including orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor dysfunction. Scores range from 0 to 100, with higher scores indicating more severe autonomic symptoms. As shown in Figure 3, the PBH group had significantly higher scores than

TABLE 1 | Demographic and clinical characteristics of participants.

	PBH (n = 39)	RYGB Non-Hypo (n = 25)	Control (n = 17)	P
Age (years)	53.4 (11.9)	53.2 (10.5)	44.5 (14.6)	0.034 ^a
Sex (Male/Female, %)	8/92	0/100	35/65	0.001
Time Since Surgery (years)	9.4 (6.2)	10.9 (6.7)	-----	0.35
Preoperative BMI (kg/m ²)	43.9 (9.1)	46.6 (6.7)	-----	0.23
Current BMI (kg/m ²)	31.2 (5.6)	32.2 (8.0)	30.8 (6.3)	0.81
Body fat (%)	38.9 (9.2)	40.4 (7.8)	35.1 (11.9)	0.2
History of T2D preoperatively (%)	37.3	9.52	-----	0.26
Postoperative complications (%)	41	24	-----	0.16
Revisional surgeries (%)	23	8	-----	0.18
History of pancreatitis (%)	5	0	-----	0.52
History of vitamin deficiencies (%)	76	72	-----	0.66

Note: P values are derived from ANOVA for continuous variables, and chi-square or Fisher's exact test for categorical variables. Data are presented as mean (SD) for continuous variables and as percent for categorical variables.

Abbreviations: PBH, post-bariatric hypoglycemia after RYGB; RYGB Non-Hypo, no symptoms of hypoglycemia after RYGB; Control, no gastrointestinal surgical history.

^ap < 0.05 by post-hoc analysis for PBH versus controls.

TABLE 2 | Edinburgh Hypoglycemia Symptom Scale (EHSS) and subscales for postsurgical participants.

	PBH (n = 38)	RYGB non-hypo (n = 24)	P
Confusion	4.47 (2.02)	1 (0)	< 0.001
Sweating	4.71 (2.08)	1.12 (0.44)	< 0.001
Drowsiness	3.97 (2.22)	1.45 (1.17)	< 0.001
Weakness	4.18 (2.01)	1 (0)	< 0.001
Dizziness	4.00 (1.93)	1 (0)	< 0.001
Heat sensation	4.03 (2.12)	1.16 (0.48)	< 0.001
Difficulties to speak	3.66 (2.22)	1 (0)	< 0.001
Palpitations	3.57 (2.01)	1 (0)	< 0.001
Difficulties to concentrate	4.68 (2.03)	1.04 (0.20)	< 0.001
Cold sensation	2.05 (1.87)	1.04 (0.20)	0.011
Diplopia	2.29 (1.84)	1 (0)	0.001
Blurred vision	2.97 (2.07)	1 (0)	< 0.001
Hunger	2.66 (2.06)	1.04 (0.20)	< 0.001
Nausea	2.74 (1.97)	1.33 (0.76)	0.001
Fear	2.97 (2.17)	1 (0)	< 0.001
Tiredness	4.68 (2.00)	1.41 (1.05)	< 0.001
Tingling in the lips	1.89 (1.72)	1 (0)	0.014
Shivering/trembling	3.61 (1.95)	1 (0)	< 0.001
Total score	63.05 (23.20)	19.62 (3.64)	< 0.001

Note: Mean and standard deviation are presented; p-values are derived from an independent samples t-test.

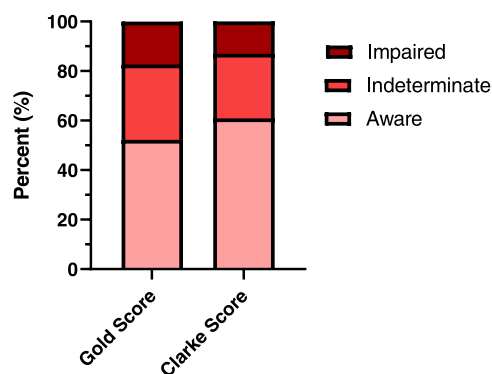


FIGURE 2 | Hypoglycemia awareness in participants with PBH (n = 23). The left bar indicates the Gold score (aware, n = 12, indeterminate, n = 7, impaired, n = 4), while right bar indicates the Clarke score (aware, n = 14, indeterminate, n = 6, impaired, n = 4). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/terms-and-conditions)]

the other two groups for both total and subscores (ANOVA $p < 0.001$), indicating greater severity or frequency of symptoms. Likewise, categorical analysis of the COMPASS-31 survey score (using cutoff of > 16, based on a validation study in patients with diabetes) [27], revealed that one of 14 (7%) individuals in the control group, 6 of 25 (24%) in the RYGB non-hypo group, and 29 of 39 (74%) in PBH met criteria for autonomic dysfunction. Chi-squared test showed a significant difference among all three groups ($\chi^2 = 25.99$, $df = 2$, $p < 0.0001$). Pairwise comparisons indicated no significant difference between Control and RYGB non-hypo ($p = 0.38$), but significant differences between Control and PBH ($p < 0.0001$) and between RYGB non-hypo and PBH ($p = 0.0001$). These results were also paralleled by increased self-reported prevalence of neuropathy and autonomic neuropathy in PBH versus either RYGB non-hypo or control groups (all $p < 0.05$, Table 4).

We additionally analysed the data to clarify whether autonomic neuropathy diagnosis or symptoms might be related

TABLE 3 | Dumping syndrome rating scale (DSRS) score and subscores.

	<i>PBH (n = 38)</i>	<i>RYGB non-hypo (n = 24)</i>	<i>Control (n = 17)</i>	<i>P (ANOVA)</i>
Total score	26.4 (14.5)	12.7 (5.7)	11.7 (6.3)	< 0.001^{a, b}
Tiredness	3.6 (2.4)	1.7 (1.4)	1.8 (1.4)	< 0.001 ^{a, b}
Palpitations	2.9 (2.2)	1.3 (0.9)	1.00 (0.00)	< 0.001 ^{a, b}
Sweating/heat sensation	3.4 (2.5)	1.4 (0.8)	1.1 (0.5)	< 0.001 ^{a, b}
Cold sweat	2.0 (1.7)	1.2 (0.7)	1.00 (0.00)	0.013 ^b
Need to lie down	3.8 (2.6)	1.7 (1.3)	1.5 (1.1)	< 0.001 ^{a, b}
Diarrhoea	2.9 (2.3)	1.6 (1.3)	1.3 (1.2)	0.006 ^{a, b}
Nausea and/or vomiting	3.1 (2.3)	1.4 (0.8)	1.3 (1.2)	< 0.001 ^{a, b}
Abdominal cramping	2.9 (2.5)	1.4 (0.9)	1.4 (1.5)	0.004 ^{a, b}
Fainting, weakness, shivering	2.4 (1.8)	1.1 (0.4)	1.2 (0.7)	< 0.001 ^{a, b}

Note: Mean and standard deviation are presented. P values in the final column are derived from one-way analysis of variance (ANOVA). Superscript within the final column indicates results of Tukey's post-hoc analysis.

^a $p < 0.05$ by Tukey's post-hoc analysis for PBH versus RYGB non-hypo.

^b $p < 0.05$ for PBH versus controls.

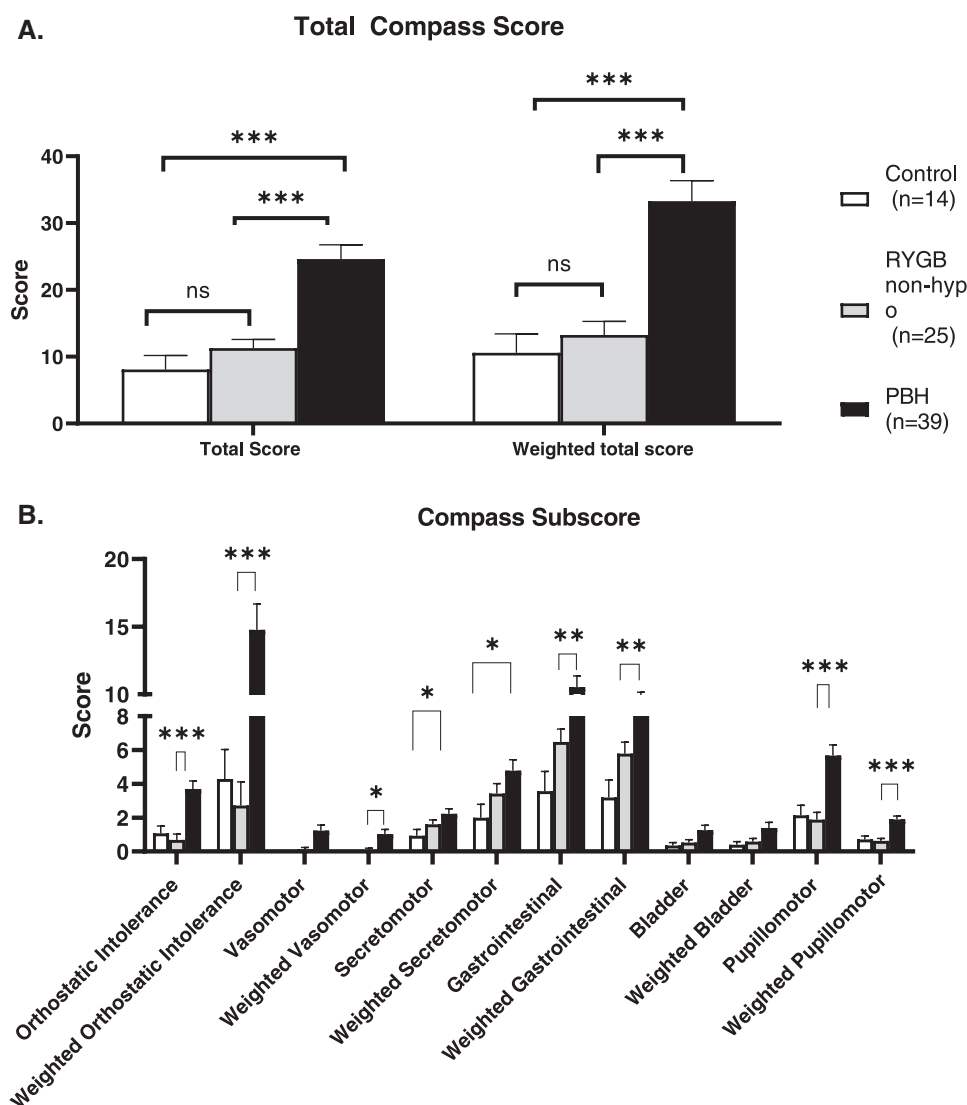


FIGURE 3 | (A) Total autonomic symptom prevalence, as assessed by Compass 31 survey. For weighted score, each domain is weighted based on its relevance to autonomic function. Total score is significantly higher for PBH as compared to RYGB non-hypo and control group (ANOVA $p < 0.001$). (B) Compass domain subscores. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$, based on Tukey HSD post-hoc test.

TABLE 4 | Self-reported prevalence of selected medical conditions (% of group).

	<i>PBH (n = 39)</i>	<i>RYGB Non-Hypo (n = 25)</i>	<i>Control (n = 17)</i>	<i>P</i>
Neuropathy ^a	44	0	0	< 0.0001 ^{*,c}
Autonomic Neuropathy ^a	18	0	0	0.017 [*]
Orthostatic Hypotension ^a	31	4	6	0.008 [*]
Postural Orthostatic Tachycardia Syndrome (POTS) ^a	5	0	0	0.33
Reflux Esophagitis ^b	67	40	12	0.001 ^{*,c}
Altered Gastric Emptying ^a	46	13	6	0.001 ^{*,c}
Intestinal Dysmotility ^b	46	12	0	0.001 [*]
Irritable Bowel Syndrome (IBS) ^a	46	4	18	0.001 [*]
Cholecystectomy ^b	56	40	6	0.002 ^{c,d}
Depression ^b	79	72	41	0.02 ^c

*indicates significant difference for PBH versus RYGB non-hypo.

^aFisher's exact test was used for conditions.

^bwhile X2 was used for variables.

^cindicates significance for PBH versus control.

^dindicates significance for RYGB non-hypo versus control.

TABLE 5 | Medication use (% of group).

	<i>PBH (n = 39)</i>	<i>RYGB Non-Hypo (n = 25)</i>	<i>Control (n = 17)</i>	<i>P</i>
Multivitamins ^a	64	80	41	0.036 ^c
Gabapentin ^b	21	4	0	0.051
Proton pump inhibitor ^b	33	12	0	0.005
SSRI ^b	26	24	11	0.53
SNRI ^b	5	12	0	0.41
Tricyclic antidepressants ^b	3	4	6	0.78
Beta-blockers ^b	5	4	0	1.00
Tramadol ^b	5	0	0	0.67

Note: For Tukey's post hoc test, * indicates $p < 0.05$ for PBH versus RYGB non-hypo.

^aindicates Chi-square testing used.

^bindicates Fisher's exact test used.

^cIndicates $p < 0.05$ significance for RYGB non-hypo versus control.

to the presence of diabetes in the preoperative state. Two of seven participants with self-reported autonomic neuropathy in the PBH group had a history of preoperative diabetes (28.6%). Of those who met survey criteria, none of the controls had a history of diabetes, while one of six (17%) of RYGB non-hypo had history of diabetes preoperatively, and seven of 29 (24%) in PBH had history of diabetes preoperatively. Chi-square analysis did not show significant differences between groups.

3.9 | Concomitant Medical Conditions

Self-reported prevalence of orthostatic hypotension, reflux esophagitis, altered gastric emptying, intestinal dysmotility, IBS, and depression was higher in PBH versus either RYGB non-hypo or control groups (all $p < 0.05$, Table 4). In addition, history of cholecystectomy was more common in both PBH and

RYGB non-hypo surgical groups versus controls, but did not differ between PBH and RYGB non-hypo.

3.10 | Medication Use

There were significant differences in patterns of specific medication classes between groups (Table 5). Sixty-four percent of PBH reported using multivitamins, versus 80% in RYGB non-hypo and 41% in controls (chi-square $p = 0.036$). Additionally, 21% of PBH participants reported using gabapentin, versus 4% of RYGB non-hypo and none of controls ($p = 0.05$). Likewise, use of proton pump inhibitors (PPIs) was greater in PBH (33%) versus RYGB non-hypo (12%) or controls (0%, $p = 0.005$). There were no significant between-group differences in use of anti-seizure medications, laxatives, anti-psychotics, anti-cholinergic, sleep medications, steroids, calcium channel blockers, thyroid hormone, and hormonal contraceptives (all $p > 0.05$).

3.11 | Vital Signs

Systolic blood pressure, measured in the supine position, was significantly lower in the PBH group as compared with RYGB non-hypo and control group ($p < 0.049$, Table S2). There was no significant difference in other vital signs.

3.12 | Laboratory Data

Laboratory data in each of the three study groups (Table S3) showed that mean haemoglobin (Hgb) and haematocrit (Hct) levels were lower in both surgical groups as compared with controls (ANOVA $p = 0.03$ and 0.01 , respectively). White blood count, platelet count, HbA1c, glucose, creatinine, total bilirubin, alkaline phosphatase, and AST were similar in all three groups (all $p > 0.05$).

4 | Discussion

Clinical characteristics of those who develop PBH versus those who remain asymptomatic remain poorly understood. We now report results of a descriptive, symptom-based clinical evaluation to identify potential differences in history between post-RYGB patients who develop hypoglycemia and those who do not, and to identify clinical characteristics which might be helpful for preoperative risk assessment.

Consistent with clinical practice, participants with PBH experienced severe hypoglycemia with neuroglycopenia and had significantly higher EHSS score (both total and subdomain scores) compared with RYGB non-hypo. Hypoglycemia unawareness was substantial, with Gold and modified Clarke scores indicating impaired awareness in 17% and 13% of PBH participants, respectively. Mean self-reported glucose associated with symptoms was 58 ± 11 mg/dL (3.22 ± 0.61 mmol/L), suggesting a wide range of glucose levels at which symptoms occurred. Reduced awareness can be associated with rapid onset of neuroglycopenia, level 3 hypoglycemia requiring assistance of others, and emergency room visits. These may contribute to reduced quality of life in PBH as seen in the increased scores in HFS-II.

The precise aetiology of high prevalence of hypoglycemia unawareness in PBH is still unclear, but it may be linked to hypoglycemia-associated autonomic failure. In this setting, the autonomic nervous system fails to induce sympathetic and parasympathetic symptoms in response to hypoglycemia, and counterregulatory hormone response is reduced. Reduction in warning symptoms allows neuroglycopenia to ensue, as in patients with diabetes [6]. Hypoglycemia unawareness has been described in the general post-bariatric population, even in those reporting no hypoglycemia history. In one study, 48% of randomly selected post-RYGB individuals experienced asymptomatic hypoglycemia after a liquid mixed meal, with reduced peak cortisol [28]. Similarly, counterregulatory responses to insulin-induced hypoglycemia are reduced as early as 6 months after bariatric surgery [29]. Until we understand and can address mechanisms responsible for impaired counterregulation, therapeutic use of continuous glucose monitoring to

improve awareness has been shown to reduce hypoglycemia frequency [30].

Careful review of medical history to identify possible predictors of hypoglycemia revealed that 26% of participants with PBH reported preoperative hypoglycemia symptoms, while 18% reported family history of hypoglycemia. It is challenging to ascertain whether these were accurate diagnoses, given that hypoglycemia symptoms are nonspecific, and most individuals or their family members had not had formal medical evaluation to define hypoglycemia. Likewise, those in the RYGB non-hypo group may have underreported preoperative symptoms, possibly due to limited awareness of the condition [31]. However, a recent study of the Longitudinal Assessment of Bariatric Surgery (LABS) cohort found that hypoglycemia symptoms, reported preoperatively, were the dominant predictor of postoperative hypoglycemia, with a 10-fold greater relative risk [3]. Therefore, it is possible that some individuals are predisposed to developing hypoglycemia even before surgery, potentially due to baseline differences in glucose metabolism and/or genetic variation. At this time, we suggest that bariatric surgery candidates should be screened for symptoms of hypoglycemia during the preoperative evaluation process, to identify those at higher risk for PBH and to guide decision-making.

We found numerically higher rates of self-reported postoperative complications, revisional surgeries, pancreatitis, and vitamin deficiencies in PBH versus RYGB-nonhypo. While these could potentially contribute to metabolic differences or neuropathic complications, these differences were not statistically significant and will require evaluation in future larger studies.

Our evaluation revealed higher dumping syndrome scores in those with PBH, indicating more severe postprandial symptoms such as lightheadedness, palpitations, and fatigue (early dumping syndrome). This is consistent with the known impact of RYGB on gastric emptying. Indeed, hypoglycemia has been considered a late component of dumping syndrome, and these conditions share multiple elements of pathophysiology [32]. However, differences are noted clinically; many patients with PBH report symptoms of early dumping occurring early in the postoperative period which resolved with time, whereas hypoglycemia occurs usually at least > 1 year postoperatively. Given the significant effect of dumping syndrome in reducing quality of life after bariatric surgery [33], further comprehensive longitudinal studies are necessary to define these complex relationships.

Our evaluation revealed high rates of self-reported neuropathy, autonomic neuropathy, orthostatic hypotension, intestinal dysmotility, and IBS in PBH versus RYGB non-hypo. Between-group differences were particularly striking for autonomic symptoms, scored via the Compass 31 survey. Participants with PBH had higher total Compass 31 scores and higher subscores for orthostatic intolerance, vasomotor symptoms, gastrointestinal, and pupillomotor symptoms, as compared with both RYGB non-hypo and control groups. It remains uncertain whether these findings reflect hypoglycemia-associated autonomic failure [12] or autonomic dysfunction as a component of more generalised peripheral and autonomic neuropathy. Bariatric surgery has been linked to both peripheral and autonomic neuropathy potentially due to micronutrient deficiencies [34].

It is possible that preoperative diabetes could be associated with pre-existing or postoperative development of neuropathic symptoms, but our data do not demonstrate significant differences in the percentage of preoperative diabetes between those with and without autonomic neuropathy symptoms. Regardless of aetiology, autonomic dysfunction could contribute to impaired counterregulation, thereby worsening hypoglycemia. Generalised intestinal dysmotility (downstream of gastric emptying) could also contribute to exaggerated bile acid responses and GLP-1 secretion in the postprandial state, as suggested by recent computer modelling [8]. Moreover, orthostatic hypotension and intestinal dysmotility could yield additional postprandial symptoms not directly linked to hypoglycemia [31]. Longitudinal studies of peripheral and autonomic function in postsurgical patients will be essential to determine whether neuropathy is associated with and/or contributes to PBH pathogenesis, or whether both reflect common postoperative mechanisms.

We observed that self-reported depression is higher in patients who underwent bariatric surgery compared to the control group and could contribute to the poor quality of life in individuals with PBH [35]. We acknowledge that self-reported diagnoses are suboptimal, and depression criteria were not formally assessed. In addition, antidepressant usage was not significantly different in either bariatric surgery group compared to the control group, despite previous association of hypoglycemia with use of these medications in the larger LABS cohort, followed longitudinally [3].

Additional medications also have the potential to exacerbate hypoglycemia in the post-bariatric patient. There was higher frequency of gabapentin use for pain management in PBH, potentially linked to increased self-reported diagnoses of neuropathy. Although hypoglycemia is not commonly reported as a side effect of gabapentin, some studies and case reports suggest an association [36]. Gabapentin activation of gamma-aminobutyric acid type A (GABA_A) receptors, which stimulate insulin release, may increase risk of hypoglycemia [37]. We observed prevalent use of PPIs, likely due to reflux esophagitis, in PBH; some studies report modest impact of PPIs to modulate glycemia [38].

Bariatric surgery can cause nutrient deficiencies due to altered food intake and reduced absorption [39], contributing to lower haemoglobin and ferritin levels [40]. Indeed, both the RYGB non-hypo and PBH groups had lower haemoglobin and haematocrit levels, despite reported intake of multivitamins, compared to controls.

Strengths of our study include detailed medical history and use of validated surveys to quantify symptoms of hypoglycemia and autonomic disorders. Limitations of our study include referral bias, given that PBH patients were recruited from a hypoglycemia-focused outpatient clinic which typically evaluates patients with more severe hypoglycemia. Some components of the history were self-reported and thus may be affected by recall bias. Inclusion of remote participants may have affected symptom reporting. The control group was matched for weight, but not for gender, with a significantly higher proportion of males, potentially limiting comparison with the surgical groups. Furthermore, there was a higher prevalence of preoperative history of T2D in PBH group than in RYGB non-hypo

group, which could contribute to between-group differences. It is possible that this was particularly relevant for differences in neuropathy and autonomic symptoms, which can be a complication of diabetes. We also acknowledge that the COMPASS 31 questionnaire for assessing autonomic symptoms has not been specifically validated in bariatric patients to date.

In summary, our data highlight several distinct elements of medical history and symptoms in individuals with PBH as compared with those who remain asymptomatic post-RYGB. Firstly, hypoglycemia severity, fear of hypoglycemia, and impact on daily life was substantial in PBH, potentially linked to reduced hypoglycemia awareness. Secondly, those with PBH had higher dumping syndrome scores, confirming previous associations and highlighting common pathophysiology between these conditions. Thirdly, self-reported diagnosis of neuropathy and survey-based autonomic neuropathy symptom scores were higher in PBH, including symptoms of orthostatic hypotension and gastrointestinal dysmotility which could suggest common underlying mechanisms or contribution of autonomic dysfunction to impaired counterregulatory responses and hypoglycemia. Finally, our finding that some patients had hypoglycemia symptoms even before surgery and may have family history of hypoglycemia-like symptoms hints at an at-risk phenotype, also identified in the large LABS cohort [3]. Until we understand whether genetic and other factors underlie risk for PBH, our data suggest the importance of assessing patients thoroughly before surgery to anticipate risk of PBH and guide therapeutic decision-making for the patient and care team alike.

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