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ORIGINAL CONTRIBUTIONS

Impact of Postprandial Hypoglycemia on Weight Loss After Bariatric Surgery

Eleni Rebelos[1] · Diego Moriconi[1] · Marco Scalese[2] · Francesca Denoth[2] · Sabrina Molinaro[2] · Valeria Siciliano[2] · Marco Anselmino[3] · Stefano Taddei[1] · Ele Ferrannini[2] · Monica Nannipieri[1]

Abstract

Introduction Postprandial hypoglycemia (PPHG) is a well-known complication after bariatric surgery (BS). However, it is not known whether PPHG affects weight loss after BS.

Aims To assess the impact of PPHG on weight loss after BS in subjects without and with type 2 diabetes mellitus (T2D).

Methods Data from 338 subjects who had undergone gastric bypass (RYGB) or sleeve gastrectomy (LSG) and were followed up for at least 2 years were analyzed. At each follow-up visit, the patient's anthropometric and biochemical characteristics were recorded and the Edinburgh Questionnaire was performed to evaluate the presence of PPHG symptoms.

Results *Before surgery*: younger age and lower BMI predicted PPHG after BS ($p = 0.02$ and $p = 0.0008$, respectively). Also, the baseline OGTT indicated that subjects who developed PPHG had an earlier glucose peak and more often had low glucose levels at 2 h compared with the no-PPHG group ($p = 0.03$ and $p = 0.004$, respectively). *After surgery:* Mild-to-moderate PPHG occurred equally after RYGB and LSG (38% vs 25%, p = ns when accounting for confounders), and in T2D who achieved remission and those who did not (29.5% vs 28.6%, ns). At the 2-year follow-up, occurrence of PPHG was independently associated with smaller weight loss ($p = 0.0006$).

Conclusions Mild-to-moderate PPHG is a frequent complication after bariatric surgery and results in smaller weight loss after 2 years. Age, baseline BMI, and an earlier glucose peak during OGTT predict PPHG after bariatric surgery.

Keywords Postprandial hypoglycemia · Bariatric surgery · RYGB · Sleeve gastrectomy · Weight loss

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CHO	Carbohydrates
CGM	Continuous glucose monitoring
γGT	Gamma-glutamyltransferase
eGFR	Estimated glomerular filtration rate
EPIC	European Prospective Investigation into Cancer and Nutrition
HbA_{1c}	Glycosylated hemoglobin
HDL	High-density lipoproteins
IQR	Interquartile range
LD	Late dumping syndrome
LDL	Low-density lipoproteins
LSG	Laparoscopic sleeve gastrectomy
MMT	Mixed meal test
NGT	Normal glucose tolerance
OGTT	Oral glucose tolerance test
PPHG	Postprandial hypoglycemia
PTH	Parathyroid hormone
RYGB	Roux-en-Y gastric bypass
T2D	Type 2 diabetes mellitus
BS	Bariatric surgery

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✉ Eleni Rebelos
eleni.rebelos@utu.fi

[1] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[2] CNR Institute of Clinical Physiology, Pisa, Italy

[3] Unit of Bariatric Surgery, AOUP, Pisa, Italy

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Introduction

Bariatric surgery (BS) is the most effective treatment for long-term weight loss and reduction of obesity-related metabolic disturbances in severe obesity. However, individuals treated with Roux-en-Y gastric bypass (RYGB) are exposed to an increased risk of postprandial hypoglycemia (PPHG), which may lead to adverse events and impaired quality of life [1–3]. In fact, 1 to 3 years after RYGB, ~30% of patients develop mild-to-moderate PPHG symptoms, which resolve with dietary modification [4]. Regarding laparoscopic sleeve gastrectomy (LSG), similar percentages of PPHG using oral glucose tolerance testing (OGTT) have been reported [5]. PPHG usually occurs 2–4 h after the ingestion of a meal and is attributed to the rapid delivery of glucose to the jejunum, which acts as a strong stimulus for insulin secretion and subsequent hypoglycemia [6]. The incidence of severe episodes requiring hospitalization is reported in less than 0.5% of the operated patients [7], but the incidence of symptoms suggestive of PPHG—according to the Edinburgh Questionnaire or the presence of low plasma glucose values (< 50 mg/dl) after a glucose challenge—can reach and exceed 30% [4, 5]. Moreover, using continuous glucose monitoring (CGM) in 15 subjects who underwent RYGB, Abrahamsson et al. reported that they spent 2.9% of the monitoring time in hypoglycemia (mainly in the postprandial phase). As discussed by the authors, CGM tends to slightly underestimate glucose levels, and thus, the incidence of hypoglycemic events may have been overestimated [8].

Studies on the predictors of PPHG after BS have yielded mixed results. Whereas in some studies the occurrence of PPHG was found to be unrelated to age, gender, and preoperative or postoperative body mass index (BMI) [9, 10], a recent paper by Nielsen et al. [11] reported that younger age and lower post-surgery BMI are strong predictors of PPHG. Furthermore, Lee et al. [12] described an association between PPHG and the presence of preoperative hypoglycemic symptoms, female gender, and longer time since surgery. Most studies report that PPHG develops in patients with normal preoperative glucose tolerance (NGT), and it has been suggested that patients with type 2 diabetes mellitus (T2D) are protected from the development of PPHG on account of their impaired β-cell function and decreased insulin sensitivity [3]. However, recently our group and others have shown that PPHG after BS occurs also in T2D patients [13, 14].

As far as weight loss is concerned, whereas it is well established that in the general population PPHG is a risk factor for increased food intake and weight gain [15], its effect on weight loss in subjects who have undergone BS—and experience frequent PPHG—has not been elucidated. The lack of conclusive data on whether PPHG affects weight loss after BS is attested by the fact that PPHG has been thought both to contribute to weight loss and to promote weight regain. More specifically, it has been suggested that PPHG and/or early dumping syndrome after ingestion of simple carbohydrates could contribute to major weight loss after RYGB due to aversion to such foods [16, 17]. On the other hand, it has been argued that asymptomatic PPHG may spontaneously divert the diet of the affected patients towards high-calorie foods, thus becoming the so-called sweet eaters.

Against this background, we hypothesized that postoperative PPHG would decrease weight loss due to carbohydrate craving and a higher calorie intake after PPHG events. In addition, we sought to determine which baseline parameters may predict PPHG after BS.

Methods

Study Design/Study Population

We collected pre- and post-BS data from all the subjects who were regularly followed at our outpatient clinic for metabolic control. In the preoperative setting, the registered data consisted of anthropometric and biochemical characteristics and, in 204 subjects, also of a standard, 2-h oral glucose tolerance test (OGTT). Post-BS data regarding the presence of symptoms suggestive of PPHG and the patients' alimentary pattern were also recorded. Subjects were screened before surgery to exclude secondary causes of obesity and to verify their eligibility for BS. Further exclusion criteria were as follows: (a) previous BS, (b) treatment with pharmacologic agents that can induce hypoglycemia, (c) use of psychiatric medications known to affect body weight, and (d) severe medical conditions (cirrhosis, end-stage renal failure, malignancy, connective tissue diseases, endocrine diseases). An OGTT was performed on 204 patients that did not have T2D diagnosis before surgery. Based on the American Diabetes Association criteria [18], 28 patients had newly onset T2D and started treatment with metformin, whereas 92 patients had T2D at baseline and were treated with metformin only (42%), combination of metformin and dipeptidyl peptidase-4 inhibitors (45%), or basal-bolus insulin therapy (13%). All subjects underwent RYGB or LSG at the Bariatric Surgery Unit of Pisa's University Hospital between August 2008 and February 2014. Selection of the intervention was personalized according to the patient's characteristics (age, BMI, treatment) and co-morbidities (gastroesophageal reflux disease, *H. pylori*, iron/vitamin deficiencies, anemia, non-alcoholic steatohepatitis) after multidisciplinary evaluation (internist and surgeon). The Ethics Committee of Pisa University approved the present study (number 2360). Prior to enrolment, each participant gave written consent. The study was performed in accordance with the Declaration of Helsinki.

Follow-up Visits

After surgery, patients were followed by planned visits at 45 days, 3 months, 6 months, and every 6–12 months thereafter, depending on their general status (symptoms, weight loss, metabolic control). During these visits, anthropometric (weight, blood pressure, cardiac frequency) and biochemical measurements were recorded. In addition, a questionnaire adapted to the Edinburgh Hypoglycemia scale was performed in order to screen for 11 symptoms of PPHG [19]. These symptoms were sweating, palpitations, shaking, hunger, confusion, drowsiness, odd behavior, speech difficulty, incoordination, nausea, and headache. If the patient experienced ≥ 3 symptoms suggestive of PPHG during the whole period since the last visit, she/he was asked additional questions regarding the macronutrient composition of her/his meals and the temporal relationship between the onset of the symptoms and meal termination. Thus, a subject was assigned to the PPHG group after careful evaluation of the following criteria: (a) symptoms suggestive of low blood glucose levels, (b) the onset of symptoms 1 h after and within 4 h from the start of the last meal, (c) the macronutrient content of the last meal prior to the start of symptoms, (d) capillary glucose levels < 3.33 mmol/L, and (e) remission of symptoms after eating carbohydrates. A subject fulfilling all five criteria was assigned to the PPHG group.

Severity of PPHG

PPHG episodes requiring medical assistance, hospitalization, or both were considered severe [4]. All other episodes that were resolved after simply consuming carbohydrates were considered mild-to-moderate.

OGTT Confirmation

All patients reporting symptoms suggestive of PPHG were encouraged to undergo a 5-h diagnostic OGTT.

EPIC Questionnaire

Subjects also completed a semi-quantitative diet questionnaire validated in the Italian language, EPIC, developed by the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which assesses dietary habits in terms of macronutrient consumption and estimates the contribution of specific nutrients to daily calorie intake through standard portion(s) [20]. EPIC investigates separately main food categories: starters, main courses, fruits/vegetables, drinks, and sweets. Moreover, the frequency of consumption of each food group is subdivided into days, weeks, and months. Based on caloric and macronutrient content, foods were grouped into category 1: bread, breakfast cereals, rusks, breadsticks, pizza, pasta, rice, and potatoes; category 2: low-, medium-, and high-calorie cookies, brioches, industrial sweet snacks, ice cream, pies, yogurt, fresh fruit, orange squash, grapefruit squash, fruit juice, tea and herbal tea, coffee, chocolate spread, jam, marmalade, sugar, and honey; category 3: cheese and dairy products; category 4: vegetables; category 5: legumes; category 6: eggs, red meat, sausages, cold cuts, white meat, and fish; category 7: milk; and category 8: sweetened drinks, carbonated or not.

Calculations

Insulin sensitivity was estimated using the oral glucose insulin sensitivity (OGIS) index, which has been validated against the euglycemic hyperinsulinemic clamp [21].

Statistical Analysis

Continuous variables were expressed as mean ± SD or median (interquartile range (IQR)); categorical variables were expressed as percentages. The comparison between continuous variables in patients with PPHG events and in those patients without PPHG events was performed by Student's t test or the Wilcoxon test, as appropriate. The comparison between categorical variables was performed by the χ^2 test. To assess the association of weight loss with PPHG and the type of surgery, a linear logistic regression analysis, adjusted for gender and age, was used separately for each year of follow-up (2, 3, 4, and 5 years). Moreover, the association of PPHG with the macro-categories of food was investigated separately for the first and second years of follow-up by first performing a univariate logistic regression and then a multivariate logistic regression adjusted for all $p < 0.1$ from univariate tests (operation type, gender, and age). The association between PPHG and consumption of CHO was tested by a univariate analysis. A $p \leq 0.05$ was considered statistically significant. Statistical analyses were done using JMP version 13.0 (SAS Institute, Cary, NC, USA). The figures were created using GraphPad.

Results

Before Surgery

A total of 338 subjects were evaluated; their disposition is shown in Supplementary Figure 1. Of them, 261 underwent RYGB and 77 underwent LSG. Since the decision on the intervention was personalized according to each patient's characteristics and co-morbidities, subjects undergoing LSG turned out to be older ($p < 0.0001$) and to have higher total cholesterol levels ($p = 0.05$) and worse renal function ($p = 0.01$) (Supplementary Table 1).

Subjects who developed PPHG ($n = 119$), compared with those who did not ($n = 219$), had lower BMI before surgery ($p = 0.0008$) and were younger ($p = 0.02$). There was no difference in the incidence of PPHG between women and men. Subjects who developed PPHG had lower fasting glucose at baseline (95 ± 30 vs 105 ± 44 mg/dL, $p = 0.02$) and a tendency for lower Hb_{A1c} (6.1 ± 0.9 vs 6.4 ± 1.4, $p = 0.099$). The better glycemic control in the PPHG group was driven by a lower percentage of T2D. When restricting the analysis to subjects without T2D, there were no significant differences in fasting glucose or HbA_{1c} between PPHG and no-PPHG (Table 1).

In the 204 subjects who had baseline OGTT data, subjects developing PPHG after surgery more frequently had the glucose peak at 30 min and decreasing glycemias thereafter (22/77 vs 20/127, in the PPHG and no-PPHG groups respectively, $p = 0.028$). This result became stronger after excluding T2D subjects (22/64 PPHG vs 19/105 no-PPHG, $p = 0.017$). Moreover, 2-h plasma glucoses < 3.33 mmol/L occurred only in the PPHG (Fig. 1).

After Surgery

In the whole dataset, 92 subjects had symptoms attributable to early dumping syndrome, and of them, only 39 subjects also developed PPHG. Of the 119 subjects in the PPHG group, 43 presented PPHG 1–1.5 years after BS, 47 subjects at 1.5–2 years, and 29 at 2 years post surgery. In a univariate analysis, PPHG occurred more frequently in patients undergoing RYGB compared with LSG (38% vs 25%, respectively, $p = 0.03$). However, after accounting for confounders such as baseline BMI, age, and gender, there was no difference in the incidence of PPHG between the two surgeries. PPHG occurred both in T2D and in non-diabetic subjects, with no difference in incidence between the two groups (Table 2).

OGTT Confirmation

Out of the 119 subjects reporting PPHG symptoms, 48 received a 5-h OGTT, which in 46 cases confirmed the presence of PPHG (symptoms and plasma glucose < 3.33 mmol/L). Only two subjects with T2D had glucose levels between 3.33 and 3.88 mmol/L and also reported symptoms; these subjects were also considered suffering from PPHG.

PPHG Impact on Weight Loss

One year after BS, both groups experienced major weight loss, with no difference between PPHG and no-PPHG (− 14.4 ± 4.8 vs − 15.4 ± 5.8 BMI units, respectively, $p = 0.4$). During the second year post surgery, the rate of weight loss was lower in the PPHG than in the no-PPHG group (− 0.4 vs 1.2 BMI units). This resulted in greater weight loss in the no-PPHG compared with the PPHG at 2 years (− 17.2 ± 6.3 vs − 14.7 ± 5.2 BMI units, $p = 0.0006$). In a multivariate model, age ($p = 0.0003$), baseline BMI ($p < 0.0001$), RYGB ($p < 0.0001$), and occurrence of PPHG ($p = 0.008$), but not gender, were independently associated with weight loss at 2 years. The negative impact of PPHG on weight loss was confirmed when restricting the PPHG group to only those who had both symptoms and a positive OGTT ($n = 48$) in a

Table 1 Anthropometric and biochemical characteristics of the study population at baseline and 2-year follow-up (FU) (entries are mean ± SD or median (IQR) if non-normally distributed)

	No-PPHG		PPHG		p_g	p_t	p_{g*t}
	Baseline	Two-year FU	Baseline	Two-year FU			
M/W	50/169		24/95		0.6		
Age (years)	48 ± 11	50 ± 11	45 ± 10	47 ± 10	0.02	-	-
BMI (kg/m^2)	47.8 ± 7.4	30.6 ± 5.3	44.5 ± 6.3	29.8 ± 5.6	0.008	< 0.0001	0.0006
T2D/no-T2D	65/154	10/209	27/92	4/115	0.2	0.9	-
Fasting glucose (mmol/L)	105 ± 44	87 ± 15	95 ± 30	87 ± 18	0.02	< 0.0001	0.1
HbA_{1c} (%)	6.0 (1.0)	5.6 (0.5)	5.9 (0.6)	5.55 (0.57)	0.08	< 0.0001	0.4
OGIS (mL min^{-1} kg^{-1})	315 (79)	-	331 (93)	-	0.09	-	-
Total cholesterol (mg/dL)	192 (49)	176 (45)	197 (49)	193 (55)	0.2	0.0001	0.2
HDL cholesterol (mg/dL)	45 (16)	61 (17)	46 (19)	61 (20)	0.9	< 0.0001	0.2
LDL cholesterol (mg/dL)	116 (42)	97 (42)	121 (43)	108 (45)	0.1	< 0.0001	0.5
AST (U/L)	20 (12)	21 (9)	20 (8)	19 (9)	0.09	0.5	0.6
ALT (U/L)	24 (20)	19 (13)	23 (19)	20 (12)	0.6	0.004	0.4
γGT (U/L)	23 (18)	13 (10)	24 (18)	15 (10)	0.9	< 0.0001	0.6
eGFR (mL min^{-1} 1.73 m^{-2})	94 ± 21	99 ± 23	97 ± 20	99 ± 25	0.8	< 0.0001	0.1

p_g, group effect; p_t, time effect; p_{g*t}, time*group interaction

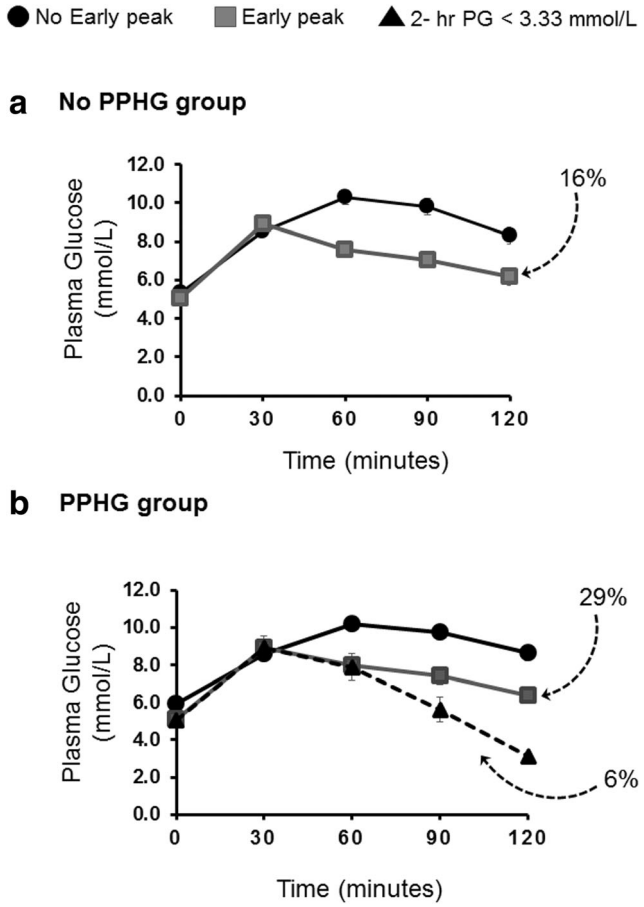

Fig. 1 Baseline OGTT plasma glucose levels in individuals without (A) or with PPHG (B). In both groups, the gray line with squares represents tests showing an early peak; the numbers indicate the corresponding early peak incidences (16% in the no-PPHG vs 29% in the PPHG group). The dotted black line with triangles in the PPHG group indicates those OGTTs where 2-h plasma glucose levels were < 3.33 mmol/L already at baseline; no such case was present in the no-PPHG group

univariate analysis (17.2 ± 6.3 vs 13.8 ± 5.1 BMI units, $p = 0.0005$) as well as a multivariate analysis ($p = 0.045$). Of note, even though all confirmed PPHG subjects were advised to modify their diet, 69% of the subjects still continued reporting PPHG symptoms (even though more rare) after a longer follow-up period, and only 31% of them reported complete resolution of their symptoms.

Table 2 Type of surgery, glucose tolerance, and post-surgical remission of T2D according to PPHG

	PPHG	No-PPHG	*p* value
RYGB/LSG, *n*	100/19	161/58	0.03*
T2D/non-diabetic, *n*	27/92	65/154	0.17
T2D-R/T2D no-R, *n*	23/4	55/10	0.97

*This difference was lost when adjusting for age, gender, and baseline BMI

T2D-R, T2D remission; *T2D no-R*, no remission

Macronutrients Consumption and Risk of PPHG

In a univariate analysis, 1 year after surgery, subjects in the PPHG group were consuming more complex carbohydrates compared with those in the no-PPHG group, but there was no difference in the consumption of simple carbohydrates. At 2 years, the PPHG group was consuming more simple carbohydrates compared with the no-PPHG group (Table 3). These findings were confirmed by a multivariate logistic regression: after adjusting for macronutrient categories, type of surgery, age, and gender at 1 year, the risk of developing PPHG was increased by 33% by the consumption of 1000 kcal/week of nutrients included in category 1 (slowly absorbed complex carbohydrates). At 2 years, the risk of developing PPHG was increased by 43% by the consumption of 1000 kcal/week of nutrients included in category 2 (simple carbohydrates).

Discussion

The present study combined careful collection of cases of mild-to-moderate PPHG, their follow-up data on weight loss, and the alimentary patterns of patients presenting PPHG symptoms. The major finding is that the occurrence of PPHG has an independent negative effect on weight loss achieved after BS. An additional finding is that baseline OGTT features, such as early glucose peak and tendency to having PPHG at baseline, predict PPHG after surgery. Of note, the negative impact of PPHG on weight loss was confirmed when the analysis was restricted to those subjects who had both symptoms of PPHG and a confirmatory OGTT, and persisted after a longer follow-up period at 3 and 4 years.

The negative impact of PPHG on post-surgical weight loss is in agreement with the notion that PPHG may contribute to weight regain after BS [22]. Banerjee and colleagues studied 50 subjects undergoing RYGB and reported no difference in weight loss between those coded as having PPHG and those who were not, only on the basis of reported symptoms [23]. In contrast, Raverdy et al. studied subjects undergoing RYGB and reported that weight loss in the PPHG group is higher than that in the no-PPHG group [24]. However, in this large study, the baseline BMI was not reported and was not included as a covariate; a different BMI at baseline would have affected the weight loss trajectory. In our study, baseline BMI was a strong predictor of post-surgical weight loss (Fig. 2), as is generally the case with every weight-reducing intervention [25].

Ideally, PPHG-predictive OGTT should be protracted to 3–5 h after glucose ingestion. In our study, the baseline OGTT used the standard 2-h format to categorize glucose tolerance and was extended to > 2 h only in a minority of cases (data not shown). Despite this limitation, we confirmed that plasma

Table 3 Carbohydrate consumption at the first and second years of follow-up (entries are mean ± SD)

	PPHG		No-PPHG		*p*	
	1 year	2 years	1 year	2 years	1 year	2 years
Complex CHO intake (Mcal/week)	4.78 ± 2.20	4.85 ± 2.06	4.00 ± 1.72	4.70 ± 2.06	0.04	0.7
Simple CHO intake (Mcal/week)	1.20 ± 1.02	1.66 ± 1.13	1.32 ± 1.11	1.26 ± 0.96	0.5	0.03

CHO, carbohydrate

glucose levels < 3.33 mmol/L detected within 2 h of glucose ingestion did predict PPHG after BS. This finding is in agreement with previous reports by us and others, showing that subjects who develop PPHG after BS have lower glucose nadir values on the baseline OGTT [26] or report symptoms of PPHG already before surgery [12]. Another finding from the OGTT is that subjects who developed PPHG at baseline had more frequently an early peak of plasma glucose at 30 min and a rapid decrease thereafter, suggesting an accelerated gastrointestinal transit, which BS exacerbates [14]. We have previously shown that the earlier glucose peak in the PPHG group is associated with a higher insulin output during the first hour of the OGTT, suggesting better β-cell function [26].

Younger age and lower starting BMI were also independent predictors of PPHG. Since BMI is well correlated with insulin resistance [27], this finding suggests the presence of enhanced insulin sensitivity in the PPHG group. Previously, we have shown that higher insulin sensitivity before surgery—as assessed by OGIS—is a predictor of PPHG after both RYGB and LSG [26]. However, other studies have yielded negative or opposite results. In a large study, Lee et al. failed to detect any association between insulin resistance by HOMA-IR and the incidence of PPHG [12]. Moreover, in a recent study using the intravenous glucose tolerance test and minimal modelling, Patti et al. showed that PPHG subjects had similar insulin sensitivity as those who did not present PPHG [28]. A study using the euglycemic clamp technique in a large, well-characterized cohort of bariatric patients may be needed to settle the controversy. On the other hand, our previously reported finding that subjects who develop PPHG have better β-cell glucose sensitivity concurs with Patti et al. [28] and Raverdy et al. [24] who suggest that PPHG is more likely to present in subjects with higher preexisting β-cell function at a time when insulin sensitivity is restored due to weight loss.

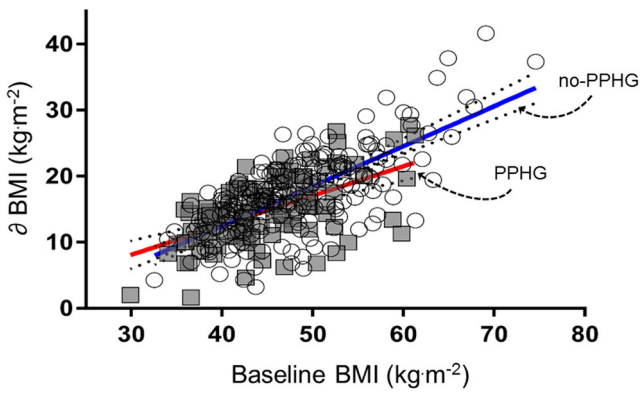

Fig. 2 Association between baseline BMI and change of BMI (∂BMI) 2 years after surgery in subjects in the PPHG group (*squares*) and the no-PPHG group (*circles*). The slope in the former is significantly ($p = 0.02$) less steep than that in the latter group

From the analysis of the EPIC questionnaire, we found that at 2 years post surgery, subjects reporting PPHG were consuming more simple carbohydrates compared with those not reporting PPHG. This change in the alimentary pattern may be indicative of a decreased adherence to the dietary recommendations, which could facilitate the development of PPHG. Alternatively, it could also suggest that the occurrence of PPHG leads to higher consumption of carbohydrates in order to overcome the hypoglycemic event.

Approximately, $^{1}/_{3}$ of our study population reported mild-to-moderate PPHG that did not require any medical treatment apart from dietary adjustments. Severe PPHG requiring hospitalization occurred in only one RYGB patient; this result is in line with previously published epidemiology [4] and with the notion that severe PPHG occurs only after RYGB [29]. One other salient finding of our study was that PPHG occurred with a similar incidence after both RYGB and LSG. Previous studies have shown a higher incidence of PPHG after RYGB than after LSG [30]. Against this prevalent concept, in a randomized, 1-year follow-up trial, Capristo et al. found no difference between RYGB and LSG in the incidence of PPHG (defined as a glycemia < 3.1 mmol/L) [29]. Randomized clinical trials with a longer follow-up are warranted in order to definitely answer whether there is or (against the prevalent idea) there is no difference in the incidence of PPHG between the two interventions.

We also showed that PPHG may occur irrespective of glucose tolerance, in accordance with Natoudi et al. [13] who reported PPHG occurring also in subjects with T2D in remission. We expand on this finding by describing PPHG in subjects with T2D who did not achieve remission after surgery [31]. Of note, all these subjects were in good glycemic control with diet only and were not being treated with any hypoglycemic agent.

The strengths of our study are the relatively large size, the long follow-up, and the detailed clinical characterization of

the study population with frequent follow-up visits. Our study has also limitations. Most importantly, the initial detection of PPHG was based on a combination of symptoms and the alimentary context. However, the diagnostic OGTT performed in roughly half of them confirmed the presence of PPHG in all cases. Moreover, we chose to use OGTT, instead of a mixed meal test (MMT), which would have represented a more physiologic test to diagnose PPHG. In turn, a drawback of MMT is that it is not standardized across different studies, having several mixed meals being used. All in all, in clinical practice, clinicians have to identify hypoglycemic episodes based solely on symptoms [32]. However, PPHG may be asymptomatic [8], which also means that the current study may underestimate the incidence of PPHG after BS.

In conclusion, our study shows that mild-to-moderate PPHG occurs frequently after BS irrespective of glucose tolerance and that subjects who suffer from PPHG lose less weight compared with those who do not have PPHG. An OGTT performed before surgery provides important information that can predict PPHG after surgery, and should be considered in all candidates for BS. Close follow-up of patients after surgery is warranted in order to detect early episodes of PPHG, which may decrease the weight loss efficacy of surgery.

Authors' Contribution E. R., D.M., and M.N. collected and analyzed data, reviewed literature, and drafted the manuscript. M.S., F.D., S.M., and V.S. analyzed data. M.A. operated the patients. M.A., S.T., E.F., and M.N. reviewed the manuscript. All authors approved the final version of the manuscript. M.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Compliance with Ethical Standards

The Ethics Committee of Pisa University approved the present study (number 2360). Prior to enrolment, each participant gave written consent. The study was performed in accordance with the Declaration of Helsinki.

Conflict of Interest The authors declare that they have no conflict of interest.

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