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Medical and surgical treatment of postbariatric hypoglycaemia: Retrospective data from daily practice

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Abstract

Aim: To evaluate medical and surgical treatment of postbariatric hypoglycaemia (PBH) in daily practice.

Materials and Methods: Retrospective data were extracted from medical records from four hospitals. PBH was defined by neuroglycopenic symptoms together with a documented glucose <3.0 mmol/L in the postprandial setting after previous bariatric surgery. Data were scored semiquantitatively on efficacy and side effects by two reviewers independently. Duration of efficacy and of use were calculated.

Results: In total, 120 patients were included with a median follow-up of 27 months with a mean baseline age of 41 years, total weight loss of 33% and glucose nadir 2.3 mmol/L. Pharmacotherapy consisted of acarbose, diazoxide, short- and long-acting octreotide and glucagon-like peptide-1 receptor agonist analogues (liraglutide and semaglutide) with an overall efficacy in 45%-75% of patients. Combination therapy with two drugs was used by 30 (25%) patients. The addition of a second drug was successful in over half of the patients. Long-acting octreotide and the glucagon-like peptide-1 receptor agonist analogues scored best in terms of efficacy and side effects with a median duration of use of 35 months for octreotide. Finally, 23 (19%) patients were referred for surgical intervention. Efficacy of the surgical procedures, pouch banding, G-tube placement in remnant stomach and Roux-en-Y gastric bypass reversal, pooled together, was 79% with a median duration of initial effect of 13 months.

Conclusions: In daily practice, pharmacotherapy for PBH was successful in half to three quarters of patients. Combination therapy was often of value. One in five patients finally needed a surgical procedure, with overall good results.

KEYWORDS
bariatric surgery, cohort study, hypoglycaemia, observational study, real-world evidence

1 | INTRODUCTION

Improved insulin secretion, mediated by gastrointestinal hormones, together with increased insulin sensitivity, plays an important role in

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the beneficial effect of bariatric surgery on type 2 diabetes improvement and remission.[1] These effects on glucose metabolism could, however, also be partly responsible for the development of postprandial hyperinsulinaemic hypoglycaemia, more often called postbariatric hypoglycaemia (PBH). Most bariatric patients experience some degree of postprandial low blood sugar, usually 1-2 h after a meal, which is probably a physiological consequence of the changes induced by the surgery. There is, however, a small number of patients who experience a low blood sugar with severe neuroglycopenic symptoms, which interfere with daily life, sometimes even leading to accidents and hospital admissions.[2,3]

First-line treatment of PBH is dietary advice consisting of frequent small, carbohydrate-low and protein-rich meals reducing the hyperglycaemic excursion shortly after a meal.

When dietary advice fails, pharmacotherapy with acarbose and somatostatin analogues is recommended in a recent guideline on dumping syndrome issued by an international consensus panel of multidisciplinary experts.[4] The panel endorsed the statement that dumping syndrome can be divided into early and late dumping. Early dumping contains symptoms appearing within 1 h postprandially. Late dumping consists of a number of symptoms developing 1-3 h after a meal characterized by hypoglycaemia. The recommendations, however, are based on short studies with a limited number of patients and without combination therapy. There are also limited data on surgical treatment of PBH as published in a literature review in 2021.[5] With this in mind, we conducted a retrospective, multicentre, observational study of medical and surgical treatment of PBH to give an overview of real-world data with regard to efficacy, side effects and duration of treatment results.

TABLE 1 Patient characteristics, surgical procedures and hypoglycaemia data

Patients	N = 120
Female, n (%)	102 (85)
Age (years)	41 [33-49]
BMI (kg/m^2)	42.6 [38.4-46.4]
Total weight loss (%)	34 [26-41]
T2D, n (%)	22 (18.3)
Cholecystectomy (%)	45 (37.5)
Type of surgery (%)	
RYGB	82 (68)
OAGB	34 (28)
Sleeve gastrectomy	3 (2.2)
SADI	1 (0.8)
Time surgery – first hypoglycaemia (months)	16 [10-30]
Glucose nadir at diagnosis (mmol/L) (±SD)	2.32 ± 0.53
Median [IQR$_{25-75}$]	2.3 [2.0-2.8]
Glucose measurement device (%)	
SMBG	78
CGM/FGM	10
MMT	12

Note: Mean and median glucose nadir are calculated from the lowest values obtained during a documented period of hypoglycaemia from each individual patient defining the diagnosis postbariatric hypoglycaemia. Values are mean ± SD; median IQR$_{25-75}$ or n (%) of subjects.
Abbreviations: BMI, body mass index; CGM, continuous glucose measurement (masked); FGM, flash glucose measurement; MMT, mixed meal test; OAGB, one anastomosis gastric bypass; RYGB, Roux-en-Y gastric bypass; SADI, single anastomosis duodeno-ileal bypass; SMBG, self-measured blood glucose; T2D, type 2 diabetes mellitus.

2 | MATERIALS AND METHODS

2.1 | Data acquisition

Four internists (LDH, MMO, VAG, APB) from four hospitals in The Netherlands, one university and three large teaching hospitals, involved in the daily care of patients with postbariatric metabolic complications, have each kept a list of patients who were referred by bariatric surgeons because of postbariatric hypoglycaemic symptoms. The number of bariatric procedures in the hospitals varied between 500 and 1000 per year. From the lists the electronic medical records were selected based on medical and or surgical treatment of PBH. PBH was defined by postprandial neuroglycopenic symptoms [difficulty in speaking, blurred vision, confusion, drowsiness, impaired consciousness, coma, seizures, (traffic) accidents], and a measured glucose value of <3.0 mmol/L after previous bariatric surgery.[6,7] Both symptomatic and asymptomatic patients were included provided they met the criteria above. Glucose was measured either by finger prick, with a continuous glucose measurement device or as venous sample during a mixed meal test (Table 1). Patients with ongoing hypoglycaemic episodes, despite adequate dietary advice given by a registered dietician from the bariatric centre, were eligible for the study. The final number of patients per hospital was 59, 36, 18 and seven.

Some patients used more than one drug both at the same time as well as in the course of their treatment. This gave the opportunity to evaluate both individual drugs as well as combinations.

Data were extracted from the medical records by two reviewers (LDH, SHW) independently and the scores were compared. In case of discrepancy the data were reassessed by both reviewers together leading to a consensus.

Efficacy, measured as reduction of hypoglycaemic events, was first scored semiquantitatively by converting the physician notes into four groups, given as the percentage reduction of hypoglycaemic events: 100%, 50%-100%, 20%-50% and 0%-20%. More than 50% reduction in hypoglycaemic events was considered sufficiently effective. Second, we categorized the patient reported experience of the drug effect during the consultation into five categories: no hypoglycaemic events anymore, almost no hypoglycaemic events, an acceptable decrease, a non-acceptable decrease and no decrease in hypoglycaemic events. No and almost no hypoglycaemic events were considered as sufficient efficacy. Side effects were scored as none, yes but acceptable and yes but not acceptable. The duration of

efficacy was calculated in months from start of a drug to the date a decrease in effect was noted. Duration of use of medication was calculated in months until the medication was stopped, until follow-up was ended or until February 2022. In case of combination therapy, we scored the efficacy after the addition of the second drug and compared this score with the one with the first drug as monotherapy.

Patients from whom an e-mail address could be retrieved, were invited to fill in an online questionnaire relating to the impact of PBH and of the treatment on quality of life. They were asked about frequency of current PBH events and impact in daily life, whether current treatment was adequate and if there were side effects. Furthermore, we asked whether they would have had decided to have the bariatric surgery if the knowledge of their current situation with PBH had been available at that time.

The study was conducted in accordance with the WMA Declaration of Helsinki on medical research involving humans. The Regional Ethical Review Board Medical Center Leeuwarden (RTPO-Leeuwarden) judged the study not to be subjected to legislation concerning medical scientific research on humans. Written informed consent was obtained from the study participants. The study was registered in the Dutch Trial Register: NTR 9491.

2.2 | Statistics

Continuous data are presented as mean and SD or median [interquartile range] where appropriate. Categorical data are presented as number (n) and percentage (%). The t-test was used for normally distributed variables and the Mann-Whitney U-test for skewed distributed variables. A Kaplan-Meier analysis was performed for the calculation of the duration of drug use because a substantial number was censored at 1 February 2022. The Mantel-Cox test was used for analysis of differences between the Kaplan-Meier curves. Statistical analyses were performed in IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). GraphPad Prism, version 8 (Graphpad Software Inc., La Jolla, CA, USA) was used for graphic presentations.

3 | RESULTS

3.1 | Patients

The extracted data were retrieved during the period between January 2013 and February 2022.

Clinical characteristics of 120 patients are shown in Table 1. This study population is comparable with the general bariatric population with the majority of women, an average age of 41 years, preoperative body mass index of 43 kg/m^2 and a postoperative total weight loss of 33%.[8] Preoperative prevalence of type 2 diabetes (18%) was somewhat lower and previous cholecystectomy (37%) higher compared with an average bariatric Roux-en-Y gastric bypass (RYGB) population, as both are known to confer protection from and increase the risk for PBH, respectively.[9,10] RYGB was the most performed surgical procedure, followed by one-anastomosis gastric bypass. The median time from the surgery to the first hypoglycaemic event was 16 months and the mean glucose nadir 2.3 mmol/L, which was recorded mostly by a self-measured blood glucose. Median total follow-up time of patients was 27 (12-49) months.

3.2 | Pharmacotherapy

Drugs used [median daily dose (IQR)] were as follows: acarbose [150 (150-300) mg], diazoxide [200 (100-400) mg], short-acting octreotide [150 (150-150) µg], long-acting octreotide (octreotide LAR©) [25 (20-30) mg/4 weeks], liraglutide [1.8 (0.6-1.8) mg] and semaglutide (1.0 mg/week). Acarbose was used most often as the first-line drug (99 of 107). Diazoxide (six of 14), short-acting octreotide (four of 14) and long-acting octreotide (five of 23) were first in line in a minority of cases. The glucagon-like peptide-1 (GLP-1) receptor agonist analogues have not been used as first-line drugs.

Most patients used either one (51 patients, 42%) or two drugs (32, 26%) consecutively during the whole treatment period, but 37 (31%) used three or more different medications with five (4%) patients adding up to five different medications during the retrospective observation period. Combination therapy with two drugs at any point during the study period was used by 30 (25%) patients. At the time of the data acquisition 33 of 97 (34%) did not use any drug for PBH anymore. The remaining 23 (19%) patients received a surgical intervention because of the insufficient effects of pharmacotherapy. In total, 15 of those 23 who had surgical intervention for PBH remained without medication after a median follow-up of 38 months.

3.3 | Monotherapy

Table 2 summarizes the efficacy, side effects, duration of effect and use during treatment with monotherapy. Sufficient efficacy (>50% hypoglycaemia reduction) ranged from 45% to 75% and no or almost no hypoglycaemic event from 29% to 78%. Both long-acting octreotide and GLP-1 analogues were superior both in terms of reduction of hypoglycaemic events as well as from the patients' perspective. This translated in the longest effect duration of both drugs. Side effects were most prevalent with diazoxide and least with lira- and semaglutide. Figure 1 shows the Kaplan-Meier curves of medication use for four drugs. The combination of efficacy and side effects resulted in a median use of 35 months for the long-acting octreotide. A median number of months for GLP-1 analogues could not be calculated as more than 50% were still using the medication at the time of the closure of data acquisition. The curves were significantly different from each other ($p < .001$).

3.4 | Combination therapy

A combination of two drugs was used 51 times with improvement in 29 (57%) and even complete resolution of hypoglycaemic events in nine (17%) of the cases.

TABLE 2 Efficacy, duration of effect and duration of use of monotherapy

Percentage reduction of hypoglycaemic events	100% (%)	50%-100% (%)	20%-50% (%)	0%-20% (%)	Duration initial effect (months)	Duration usage (months)
Acarbose (n = 107)	21	35	20	24	7 [3, 20]	19 [5, 39]
Diazoxide (n = 14)	20	25	20	35	2 [1, 6]	2 [1, 8]
Short-acting octreotide (n = 14)	8	38	16	38	1[a] [1, 4]	1[a] [1, 4]
Long-acting octreotide (n = 23)	5	68	22	5	18 [6, 36]	35 [12, 54]
Liraglutide (n = 13) Semaglutide	8	62	8	15	19 [8,31]	NA NA

Patients' perspective	No hypo event (%)	Almost no hypo (%)	Acceptable (%)	Not enough (%)	No decrease (%)
Acarbose (n = 107)	17	23	21	31	6
Diazoxide (n = 14)	10	25	20	35	10
Short-acting octreotide (n = 14)	7	22	25	15	31
Long-acting octreotide (n = 23)	4	43	28	22	0
Liraglutide (n = 13) Semaglutide	8	70	0	7	15

Side effects	None (%)	Yes, acceptable (%)	Yes, not acceptable (%)
Acarbose (n = 107)	62	16	22
Diazoxide (n = 14)	25	15	60
Short-acting octreotide (n = 14)	35	21	43
Long-acting octreotide (n = 23)	42	29	29
Liraglutide (n = 13) Semaglutide	70	23	7

Note: Values are median [IQR], or percentages.
[a]Seven patients changed the subcutaneous formulation into the LAR preparation within 2-4 months.

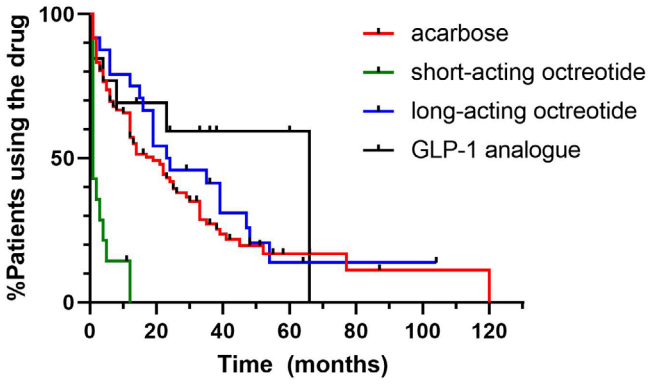

FIGURE 1 Percentage of Patients using various drugs in time. Black dots represent those censored either at last documented follow-up or at the time of the closing of data acquisition (1 February 2022). GLP-1, glucagon-like peptide-1

Acarbose was the drug most often used to which a second one was added, usually because of insufficient efficacy. The addition of diazoxide to acarbose improved efficacy in four of 14 (29%) patients, but in all the side effects were unacceptable. The addition of short-acting octreotide to acarbose improved efficacy in eight of 13 (61%) with complete resolution of hypoglycaemic events in four (30%) patients. Short-acting octreotide was stopped in two patients because of side effects. The combination of acarbose with long-acting octreotide gave improvement of efficacy in eight of 12 (67%) patients with complete or near complete resolution of hypoglycaemia in five (41%). One (8%) patient stopped long-acting octreotide because of side effects. The addition of liraglutide to acarbose gave improvement in seven of 11 (63%) patients, all with near complete resolution. One (9%) patient stopped liraglutide because of side effects. In one patient, semaglutide was added with clear improvement.

3.5 | Surgery

During the follow-up, 23 of 120 (19%) patients were referred because of persistence of hypoglycaemic episodes that interfered too much with daily life. In total, 30 procedures were performed because seven patients had two procedures each (Table 3).

The number of consecutive drugs used before surgery were: one in four patients, two in six, three in three, four in six, five in two, six in one and seven in one.

TABLE 3 Effects of surgery for postbariatric hypoglycaemia on hypoglycaemic events

Percentage reduction of hypoglycaemic events	100%	50%-100%	20%-50%	0%-20%	Duration of initial effect (months)[a]	Δ Weight (kg)[a]
Banded bypass (n = 13)	9	3	0	1	4-36	+1/−8
G-tube feeding in remnant stomach (n = 11)	5	2	1	3	5-83	0/+4
RYGB reversal (n = 5)	4	0	0	1	11-48	+24/+55
Part pancreatectomy (n = 1)	1[b]				6	+1

[a]Minimum-maximum.
[b]Developed diabetes.

The most often performed procedure was a banded bypass (Minimizer adjustable band and Minimizer gastric ring; Bariatric Solutions GmbH, Stein am Rhein, Switzerland) (n = 13, 43%), followed by G-tube (Flowcare) feeding in the stomach remnant (n = 11, 37%) and RYGB reversal (n = 5, 16%). Overall, the initial success was good with complete resolution of hypoglycaemic events in 63% of the procedures and 50%-100% reduction in 16%, leaving 21% of procedures not enough or not successful enough. Median duration of the initial effect was 13 months (6-30) with a median total follow-up time of 38 (26-57) months. Banded bypass, G-tube placement and RYGB reversal were sufficiently effective (>50% reduction in hypoglycaemia) in 12 of 13 after banded bypass, seven of 11 after G-tube placement and four of five after RYGB reversal.

3.6 | Predictors of treatment success or failure

We looked at possible predictors of treatment success or failure by dividing the population into those who needed one versus more drugs to control their hypoglycaemia and into those with and without surgery for PBH. Age, body mass index at surgery, total weight loss, time between surgery and first hypoglycaemia and glucose nadir were all not significantly different in the various groups. An earlier onset of hypoglycaemic events after bariatric surgery tended to be present in those without surgery as the final solution for PBH (median: 17.7 vs. 24.1 months, $p = .077$).

3.7 | Online questionnaire

The online survey was sent to 93 patients and completed by 67 (72%) (Table S1). Mean time between last change of medication and survey was significantly shorter for respondents of the survey compared with non-respondents of the survey (33 ± 25 vs. 54 ± 30 months, $p < .001$). The average number of drugs used during the observation period was also more in the respondents compared with the non-respondents (2.5 ± 1.2 vs. 1.8 ± 0.9, $p < .001$). Two of three respondents still experienced hypoglycaemic events and nearly half reported limitations in daily life. In total, 19 (22%) would have declined bariatric surgery with the current knowledge, given their perceived severity of PBH. One in three currently experienced moderate or severe side effects of the medication for hypoglycaemia. Nine (39%) patients who had surgery for hypoglycaemia completed the survey. Eight of them still had hypoglycaemic events, three used medication and three experienced side effects because of the surgery.

4 | DISCUSSION

This retrospective observational study on medical and surgical therapy for PBH is to our knowledge the largest in terms of numbers of patients and duration of follow-up and the only one providing real-world data with modern pharmacotherapy.

Overall efficacy of medication, both defined as more than 50% reduction of hypoglycaemic events and as a combination of no or almost no hypoglycaemic events, ranged from 45% to nearly 80% depending on type of drug. Both long-acting octreotide and the GLP-1 analogues performed best with the least side effects.

Table 4 summarizes all known studies on medication for PBH and is used for comparison with our data.

Acarbose was used by most patients as first-line treatment according to recommendations by most experts.[4] Acarbose, an inhibitor of the enzyme alpha-glucosidase, present at the luminal border of the small intestinal cells, delays the breakdown of oligosaccharides into glucose thereby delaying absorption of glucose leading to a reduced response of insulin secretion thereby preventing or mitigating a postprandial hypoglycaemia.[13,15] The sufficient efficacy score was modest (40% and 45% respectively) and side effects, usually diarrhoea and flatus were unacceptable in one of five patients. The median duration of initial effect was 7 months and acarbose use was on average 19 months. The modest effect is in agreement with the study by Vilarrasa et al. who described 22 patients, treated with acarbose with a partial response (>50% reduction) in only four patients.[19] Smaller studies (n = 4-8) with short follow-up (<1 month) showed improvement either in symptoms or with continuous glucose measurement in approximately 60% of patients with side effects in 20%. Diazoxide, a specific adenosine triphosphate-dependent potassium channel agonist of beta-cells, inhibits secretion of insulin and stimulates glucose release by the liver.[42] Common side effects are hypotension, palpitations and oedema. Efficacy in our cohort ranged from 35% to 45%; however, in most patients the medication was stopped, often within 1 month, because of side effects. Only a few patients were able to tolerate the drug. Only eight cases have been reported in the literature with partial response in four patients and complete in one.[19,21,22]

TABLE 4 Medical treatment for PBH: current literature

Author, year	Surgery, number, inclusion	Study type	Dose, route	Test, outcome	Result
	Acarbose				
McLoughlin[11] 1979	Vagotomy with/without gastric procedure, 10 with dumping complaints	Placebo-controlled, cross-over	100 mg oral 1 dose	50 g OGTT, glucose nadir, number with glucose <3.5 mM	Glucose nadir: Placebo: 2.8 mM; 100 mg: 3.9 mM Number with glucose <3.5 mM: 5/10; 0/10
Speth[12] 1983	B-II gastrectomy, 7 vagotomy, pyloroplasty, 2 glucose <3.0 at OGTT	Placebo-controlled, cross-over	50 and 100 mg once at the start of the meal	Meal test, glucose nadir Number with hypo (value not defined)	Glucose nadir: Placebo: 2.6 mM; 50 mg: 3.2 mM; 100 mg: 3.2 mM Number pts with hypo: 8/9; 2/9; 2/9
Moreira[13] 2008	RYGB, 1, case report	Observational	50 mg TID	Clinical: subjective symptoms	Acarbose added to verapamil with substantial clinical improvement
Hanaire[14] 2010	RYGB, 1, case report	Observational	50 mg TID	CGM, glucose <3.0 mmol/L	No hypoglycaemic episodes after start acarbose
Ritz[15] 2012	RYGB, 8 symptomatic PBH	Non-randomized	50-100 mg TID	CGM, av 5 days % time <3.3 mM	Reduction from 2.5% to 0.18% of time spent <3.3 mM
Valderas[16] 2012	RYGB, 5 neuroglycopenia + glucose <2.8 mM	Non-randomized	100 mg once	MMT, ensure plus 200 ml, glucose >2.8 mM	5/5 glucose >2.8 in MMT
Frankhouser[17] 2013	RYGB, 4 symptomatic	Observational	50 mg, TID	Clinical: Subjective symptoms	4 complete response, 1 stopped: side effects
Mordes[18] 2015	RYGB, 4 symptoms + glucose <3.0 mM with SMBG or OGTT	Observational	25-50 mg, 6 times (2 pts with nifedipine 30 mg)	Clinical: patients reports	1 complete 2 partial response 1 intolerant
Vilarrasa[19] 2016	RYGB, 19 DS 2, BP diversion 1 Severe hypo, <3.0 mM	Retrospective Case series	50 mg, TID	Clinical response	4/22 (14%), partial response (50% reduction)
Øhrstrøm[20] 2019	RYGB, 11, symptomatic glucose <3.5 mM	Observational	50 mg 4-6 times, 1 week	Blinded 7-day CGM, % time <3.9 mM, MMT: glucose nadir	CGM: av reduction from 48 to 5 min time <3.9 mM MMT: Glucose nadir: 3.4-3.9 mM
	Diazoxide				
Spanakis[21] 2009	RYGB, 1 symptomatic, SMBG 1.9 and 2.7	Case report	50 mg, 2 times	Clinical: patient report	Complete resolution of symptoms
Gonzales-Gonzales[22] 2013	RYGB, 1 symptomatic, SMBG 2.2 mM, OGTT 2.3 mM	Case report	100 mg, 2 times	Clinical: patient report	Partial resolution, glucose occasionally 3.3 mM
Vilarrasa[19] 2016	RYGB, 19, DS 2, BP diversion 1 Severe hypo, <3.0 mM	Retrospective Case series: 6	170 mg/day av	Clinical response	3/6 (50%) partial response (50% reduction)
	Octreotide				

TABLE 4 (Continued)

Author, year	Surgery, number, inclusion	Study type	Dose, route	Test, outcome	Result
Hopman[23] 1988	Part gastrectomy, 5 HS vagotomy, 1 Glucose <3.0 at OGTT	Randomized, cross-over placebo controlled	50 μg s.c.	OGTT Glucose nadir, hypoglycaemia: <3.0 nM	Glucose nadir: Placebo:1.9; octreotide: 7.5 mM No hypoglycaemia after octreotide
Tulassay[24] 1989	B-II gastrectomy, 8 Symptoms 7 hypo at OGTT	Randomized, cross-over placebo controlled	50 μg s.c.	OGTT Glucose nadir	Glucose nadir: Placebo: 1.8; octreotide: 6.5 mM No hypoglycaemia after octreotide
Primrose[25] 1989	Gastrectomy, RYGB, gastrectomy-jejunostomy, 3	Randomized, cross-over placebo controlled	50 and 100 μg s.c.	OGTT	3/3 no hypoglycaemia after octreotide
D'Cruz[26] 1989	Vagotomy + gastroenterostomy, 1 pt, symptomatic, hypo with OGTT	Case report	50 μg, 2 times	MMT and clinical: patients report, after 3 weeks	Resolution of hypoglycaemia in MMT and at home (SMBG)
Geer[27] 1990	Gastrectomy, RYGB, 2 with hypo at MMT	Randomized, placebo controlled	100 μg s.c.	MMT: solid	2/2 no hypoglycaemia after octreotide
Gray[28] 1991	Dumping complaints, 9; vagotomy and pyloroplasty, 3; vagotomy and antrectomy, 2; RYGB, 2; selective vagotomy, 1	Randomized, cross-over, placebo controlled	100 μg s.c. single dose	MMT Glucose <3.3 mM	Hypoglycaemia: 4/9 after placebo, 0/9 after octreotide
Hasler[29] 1996	Dumping complaints, 8; subtotal gastrectomy, B-II, 5; antrectomy, B-I, 1; subtotal gastrectomy, RYGB, 1; gastrojejunostomy, 1	Randomized, cross-over, placebo controlled	50 μg octreotide single dose s.c.	OGTT	Glucose nadir: Placebo: 8/8 < 3.3 mM, 2/8 < 2.2 mM Octreotide: 8/8 > 3.3 mM
Vecht[30] 1999	Vagotomy, antrectomy, B-I 7: early and late dumping	Case-series	Single dose 25 μg 3 times 25-50 μg	OGTT, 50 g Clinical follow-up >3 months	OGTT: Glucose nadir: 2.9 vs. no hypo Clinical: 5/7 symptom free
Didden[31] 2006	Part gastrectomy, 16 Early and late dumping	Case series	3 times 50 μg s.c. LAR 10-20 mg	Clinical follow-up >7 years	On average 50% efficacy and 50% stopped: side effects, s.c. and LAR
Arts[32] 2009	Upper GI surgery, dumping complaints, hypoglycaemia, 29 8 partial gastrectomy 10 RYGB 8 Nissen fundoplication 3 part oesophagectomy	Cohort study	50 μg octreotide 3 times s.c. for 3 days followed by 20 mg octreotide LAR i.m./4 weeks	OGTT baseline, after 3 times 50 μg octreotide, after 3 months octreotide LAR 20 mg i.m. Dumping severity score QuoL: SF-36	Glucose nadir/hypo (<3.3) after OGTT: Baseline: 3.0 mM/24/29 Octreotide s.c.: 5.4 mM/3/29 Octreotide LAR: 3.8 mM/10/29 Decrease in DSS Improvement in QuoI
Myint[33] 2012	RYGB, 1	Case report	100 μg octreotide single dose Lanreotide	OGTT	No hypoglycaemia in OGTT after octreotide No hypoglycaemic events for 4 y during lanreotide therapy

(Continues)

TABLE 4 (Continued)

Author, year	Surgery, number, inclusion	Study type	Dose, route	Test, outcome	Result
Vilarrasa[19] 2016	RYGB, 19 DS 2, BP diversion 1 Severe hypo, <3.0 mM	Retrospective Case series	50-100 μg s.c. 2 times 13 pts	Clinical response	5/13 (38%) partial response (50% reduction) 3/13 (23%) complete response
	Pasireotide				
De Heide[34] 2014	RYGB, neuroglycopenia, 1	Case study	Pasireotide 300 μg s.c. vs. octreotide 100 μg s.c.	MMT	Glucose at 180 min: After octreotide: 2.0 mM After pasireotide: 3.5 mM
Tack[35] 2018	RYGB, 38 Gastrectomy, 5 Neuroglycopenia and glucose SMBG <2.8 mM or OGTT <3.3	Single arm, dose escalation, 3 months s.c. followed by (LAR) 3 months, followed by extension 6 months	Pasireotide 50-200 μg t.i.d., s.c. Pasireotide LAR 10-20 mg, extension: max 60 mg/4 weeks i.m.	OGTT	Glucose >3.3 mM: 3 months s.c.: 26/43 (60.5%) RYGB subgroup: 22/38 (57.5%) 3 months LAR: 12/33 (36.4%)
Øhrstrøm[20] 2019	RYGB, 11 PBH, SMBG <3.3 mM, CGM	Intervention as part of 5 different medications for PBH	Baseline and pasireotide 300 μg s.c. 30 min before MMT	MMT,	MMT: Baseline: mean nadir: 3.4 mM; 9/11 nadir <3.9 mM Pasireotide: mean nadir: 7.2 mM, no hypoglycaemia
Øhrstrøm[36] 2020	RYGB, 5 PBH, SMBG <3.3 mM, CGM	Open label intervention, dose escalation	Baseline and pasireotide 75, 150 and 300 μg s.c. 30 min before MMT	MMT	Glucose nadir: Baseline 3.4 mM 75, 150, 300: 6.2, 8.1, 8.9 mM All doses: glucose >3.9 mM in MMT
	Liraglutide				
Abrahamsson[43] 2013	RYGB, 5 PBH, SMBG <3.0 mM	Observational	Liraglutide 1.2-1.8 mg s.c.	Outpatient clinical data CGM (1 patient)	No symptomatic hypoglycaemia in follow-up, return of hypo after temporarily stop No hypoglycaemia in CGM registration (1 patient)
Øhrstrøm[20] 2019	RYGB, 11 PBH, SMBG <3.3 mM, CGM	Intervention as part of 5 different medications for PBH	Liraglutide 1.2 mg once daily, 3 weeks	MMT Blinded 7-day CGM	MMT: no change in [glucose] at different points, less negative iAUC of glucose CGM: Lowest interstitial glucose: 3.0 mM vs. 2.7 No difference in % time in glucose <3.9 or 3.0 mM
	Avexitide[a]				
Craig[37] 2021	RYGB, 17 PBH, SMBG <3.0 mM	Randomized, placebo-controlled, cross-over	Avexitide 30 mg s.c. twice daily Avexitide 60 mg s.c. once daily Both for 14 days	MMT with rescue glucose iv if glucose <2.8 with neuroglycopenia or glucose <2.2 mM	MMT: Baseline: 47% needed rescue

TABLE 4 (Continued)

Author, year	Surgery, number, inclusion	Study type	Dose, route	Test, outcome	Result
				Blinded CGM	Avexitide (30, 60 mg):24, 12% needed rescue Increase in glucose nadir: 21, 26% compared with baseline SMBG: Reduction 40, 60% of glucose <2.8 mM CGM: reduction in time <2.8 mM: 30, 60 mg: 50, 24%
	Verapamil				
Moreira[13] 2008	RYGB, 1 SMBG <2.8 mM	Case report	Verapamil twice daily 80 mg	Clinical data	Improvement in number and severity of hypoglycaemic events
Øhrstrøm[20] 2019	RYGB, 11 SMBG <3.3 mM, CGM	Intervention as part of 5 medications for PBH	Verapamil 120 mg once daily	MMT, Blinded 7-day CGM	No effect on hypoglycaemia
Vilarrasa[19] 2016	RYGB, 19 DS 2, BP diversion 1 Severe hypo, <3.0 mM	Retrospective Case series	Verapamil 80 mg Plus nifedipine 20 mg n = 10	Clinical response	5/10 (50%) partial response (50% reduction)
	Glucagon				
Mulla[38] 2020	RYGB, 12 PBH	Randomized, placebo-controlled cross-over	Closed loop: glucose-responsive automated glucagon delivery system	MMT	5/12 glucose <3.1 mM after placebo 12/12 glucose >3.1 after glucagon
	SGLT-2 inhibitors				
Ciudin[39] 2021	RYGB, 21 PBH	Prospective, pilot baseline and intervention	Canaglifozin 300 mg once daily for 2 weeks and once before test	OGTT 100 g	Baseline: glucose at 30 and 180 min: 12 and 2.1 mmol/L Canaglifozin: glucose at 30 and 180 min: 8.9 and 3.4 mmol/L Baseline: 20/21 glucose <2.8 mmol/L Canaglifozin: 2/21 glucose <2.8 mmol/L
Carpentieri[40] 2022	RYGB, sleeve, 7 women Positive hypoglycaemia symptom score	Prospective, pilot, intervention	Empagliflozin 25 mg, once daily for 2 days and just before the MMT	MMT (ensure plus, 200 ml)	Empagliflozin vs. baseline: Fasting glucose: 4.8 vs. 4.6 mM ($p = .022$) Nadir glucose: 3.6 vs. 3.1 nM ($p = .179$): NS AUC-gluc: 10.9 vs. 7.8 mmol/h/L (0.045)

(Continues)

TABLE 4 (Continued)

Author, year	Surgery, number, inclusion	Study type	Dose, route	Test, outcome	Result
	Pramlintide				
Sheehan[41] 2022	RYGB, 14 pts with PBH	Prospective, pilot, intervention	69 μg s.c. av t.i.d.	MMT CGM	Meal test: no significant difference CGM: minimal shortening of time with glucose <3.9 mM

Abbreviations: av, average; B-I, Bilroth-I; B-II, Bilroth-II; BP, biliopancreatic; CGM, continuous glucose monitoring; DS, duodenal Switch; DSS, dumping severity score; HS, High Selective; LAR, Longacting repeat; MMT, mixed meal test; NS, not significant; OGTT, oral glucose tolerance test; PBH, postbariatric hypoglycaemia; pts, patients; QuoL, quality of life; RYGB, Roux-en-Y gastric bypass; s.c., subcutaneous; t.i.d., three times a day.

[a]Still under study, not available for clinical use.

The limited usability of diazoxide has also been described in the consensus statement.[31] The somatostatin analogues octreotide and pasireotide are used much more often for PBH. These analogues act through multiple mechanisms, including decreasing pouch emptying, slowing of small bowel propulsion, inhibiting release of gastrointestinal hormones, such as GLP-1 and inhibiting insulin release. Octreotide also inhibits glucagon release in contrast to pasireotide and can in some patients lead to hypoglycaemia.[34] The side effects that occur most often are pain at injection sites, diarrhoea and abdominal pain at the start of the treatment. Contrary to most literature, long-acting octreotide proved to be more efficacious (50%-75%) than the subcutaneously administered short-acting formulation (30%-45%) in our cohort.[4] Side effects were also less with the long-acting formulation and seven patients changed from the subcutaneous to the long-acting formulation shortly after the start. The initial treatment effect was maintained on average for 1.5 years and the duration of use was nearly 3 years, supporting a good balance between efficacy and side effects. The GLP-1 analogues, liraglutide and semaglutide, were most successful in terms of efficacy (70%-80%) and with the least side effects (30%, with 7% unacceptable); however, the number of users was small and the follow-up time short. In the literature, only five cases of PBH treated with liraglutide are available.[43] The postulated mechanisms involve increased secretion of glucagon from pancreatic alpha-cells as well as suppression of insulin release by beta-cells at low blood sugars with longstanding GLP-1 receptor stimulation.[43] However liraglutide 1.2 mg for 3 weeks was not able to prevent a meal-induced hypoglycaemic event.[20] Therefore, it is probable that other mechanisms such as reduction of appetite and potentially change in macronutrient preferences may play a role.[44,45] These mechanisms could also explain the improvement in glycaemic variability during continuous glucose measurement.[20] Side effects are mainly decreased appetite, nausea and diarrhoea, usually decreasing in time.

Combination therapy was used 51 times by 30 (25%) patients, mainly the combination of acarbose with either octreotide or a GLP-1 analogue. With improvement in 57% of cases and complete resolution of hypoglycaemic events in 17% it is worthwhile to try. To our knowledge, no literature on combination therapy for PBH exists, except for a few case reports.[13,18] Our data suggest that the efficacy of most medications decreases in time. This could be because of less adherence to dietary measures when hypoglycaemic events are in better control or to changes in disease course of PBH. Therefore, it should be emphasized that, before initiation of new medication, adherence to dietary recommendations is key.

Nearly one in five patients in our cohort were referred for surgical treatment because of inadequate control of PBH with diet and medication. A few of them declined more than one or two pharmacological options and preferred a surgical solution. The surgical procedures, pouch banding, G-tube feeding in remnant stomach, and RYGB reversal were initially quite successful with long-lasting total or near total remission of hypoglycaemic events in most patients. The results of RYGB reversal are comparable with an 80% success rate in a literature review in 2021.[5] Weight regain is the most often occurring side effect and can be substantial. Performing a gastric sleeve resection during

reversal surgery may be an option to counteract weight gain, although a clear recommendation remains to be established. Placing a gastrostomy tube in the remnant stomach for feeding proved successful in the majority of patients who opt for this procedure with five of 11 having complete and two near complete resolution of hypoglycaemic events. A meal test study showed a complete reversal of the exaggerated incretin and augmented insulin response after administration of the same standard liquid meal via the G-tube in the remnant stomach compared with the oral route.[46] Placement of a 20 French Flocare G-tube with a 15 balloon is done laparoscopically. After adhesiolysis, a check whether the remnant stomach can be tension-free attached to the abdominal wall is performed. The G-tube is then inserted through the abdominal wall and placed in the outer curvature of the stomach. With the use of absorbable V-loc the stomach is attached to the abdominal wall. After G-tube placement a short trial of water administration is applied. Different feeding strategies, all about 1000 kcal/24 h, are used (for 12 h at night, six times a day intermittently or continuous feeding). The procedure is not without risks or complications and needs adequate patient selection and instruction and close follow-up by a multidisciplinary team.[47] Placing a band or minimizer ring around the proximal part of the pouch resulted in complete resolution of hypoglycaemic events in nine and near complete resolution in three of 13 patients. The ring was overall well tolerated. To our knowledge, no literature has been published on this procedure. Partial pancreatectomy is effective in 54% of patients according to the review by Xu et al. while sometimes causing insulin-dependent diabetes.[5] In addition, a retrospective cohort study in patients treated with partial pancreatectomy for non-insulinoma pancreatogenic hypoglycaemia (48 of 75 postbariatric) found a recurrence risk of hypoglycaemia of 87% with a median time to recurrence of 16 months.[48] These data underscore the rationale for not pursuing partial pancreatectomy. Currently, partial pancreatectomy is not recommended by most experts.

In the cross-sectional analysis by means of the questionnaire, the impact on quality of life for many with PBH became apparent. One in five would not have opted for bariatric surgery if they knew what was ahead of them, a similar percentage gave their current lives an unsatisfactory grading and half of all patient in this study experienced regular to daily limitations. These findings are in agreement with our previous research and show that the impact of PBH is profound.[49]

The strengths of this study are the large number of patients, the long follow-up and the possibility of evaluating combinations of drugs in a real-world setting. Furthermore, an estimation of duration of the effect could be derived from the medical records as well as duration of use, which gives an indication of the balance between efficacy and side effects. There were also some limitations. First, the inclusion of patients in the cohort was not based on a solid test but relied on a more practical definition, as there is still debate on the clinical setting and the cut-off for glucose values.[6,7] Second, the semiquantitative score is a subjective interpretation of the written findings in the medical records. However, the independently scored results by the two authors showed a high level of agreement initially, varying between 85% and 90%. Furthermore, compared with the standard data collection during prospective studies, these findings from the medical records give a reflection of daily practice: medicine-based evidence. Third, the retrospective collection of data up to a fixed time point can give an underestimation of duration of the initial effect and of the use of medication as some patients were followed for a relatively short period when the data were collected. More than half of the total cohort was still using medication at the time of the data collection. Fourth, the order of prescription of different drugs was not the same in the hospitals but was based on the doctor's preference. A prospective study using a fixed order of drugs for PBH could give a better estimation of the efficacy and side effects of the different drugs. Fifth, the online questionnaire was filled in by slightly more than 50% of all patients and the results of the survey may be biased by a relative overrepresentation of respondents that they used more drugs that were also different and had more recent changes in medication.

In conclusion, medical therapy for PBH in daily practice is effective in 45%-75% of patients with long-acting octreotide and the GLP-1 analogues having the best results and least side effects. Combination therapy by adding either long-acting octreotide or a GLP-1 analogue to acarbose can be of value. The decrease in efficacy of medication over time can tilt the benefit to harm ratio, giving a need for regular evaluation of continuing the medication and analysing causes such as less adherence to a low carb diet. One in five patients were referred for surgical options. One in five of the respondents of the survey would have declined bariatric surgery if they had had the knowledge of their hypoglycaemic events today, stressing the impact of PBH in daily life.

AUTHOR CONTRIBUTIONS

Loek J. M. de Heide performed the study design, data collection, data analysis and manuscript preparation. Marloes Emous was involved in the study design and manuscript preparation. André P. van Beek designed the study, collected and analysed the data and was involved in the preparation of the manuscript. Sterre T. Wouda performed data collection and analysis. Vincent J. T. Peters. Mirjam M. Oosterwerff and Victor A. Gerdes also collected data. The final version was approved by all authors.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests

PEER REVIEW

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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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