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van Furth, A Marrit; de Heide, Loek J M; Emous, Marloes; Veeger, Nic; van Beek, André P

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Original article

Dumping Syndrome and Postbariatric Hypoglycemia: Supporting Evidence for a Common Etiology

A. Marrit van Furth, B.Sc.[a,*], Loek J. M. de Heide, M.D.[b], Marloes Emous, M.D., Ph.D.[b,c], Nic Veeger, M.D., Ph.D.[d], André P. van Beek, M.D., Ph.D.[a,b]

[a]*Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[b]*Centre for Obesity Northern Netherlands, Medical Center Leeuwarden, Leeuwarden, The Netherlands*
[c]*Department of Surgery, Medical Center Leeuwarden, Leeuwarden, The Netherlands*
[d]*Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

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Abstract

Background: Dumping syndrome (DS) and postbariatric hypoglycemia (PBH) are frequent complications of bariatric surgery. Previously known as "early and late dumping," these complications have been separated due to differences in their onset and behaviors.

Objectives: To investigate a potentially common etiology of DS and PBH using an analysis of a mixed meal test (MMT) study.

Setting: A large teaching hospital in the Netherlands.

Methods: From all patients who underwent bariatric surgery in 2008–2011, a random selection completed an MMT (n = 47). Patients scored complaints related to DS and PBH with a standardized questionnaire at several time intervals. The groups were divided into patients with (DS+; n = 22) and without (DS-; n = 25) an increase in DS symptoms after the start of the MMT. Glucose and gut hormone levels were compared. Hypoglycemia was defined as a blood glucose level below 3.3 mmol/L.

Results: The DS+ group had lower blood glucose values compared to the DS- group, which reached significance at 90 and 120 minutes ($P < .05$). For the DS+ group, glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and satiety were higher at various time intervals ($P < .05$) compared to the DS- group. No differences were found for insulin and hunger score. GLP-1 and PYY were correlated with symptoms of DS.

Conclusion: Patients with DS complaints had lower postprandial glucose values. GLP-1 and PYY values were elevated in the DS+ group early and late during the test. These hormones also correlated with DS. These findings support the hypothesis of a common etiology of DS and PBH and a role of GLP-1 and PYY in both complications. (Surg Obes Relat Dis 2021;17:1912–1918.)

Keywords: Dumping syndrome; Postbariatric hypoglycemia; Bariatric surgery; Gastric bypass; GLP-1; PYY

Bariatric surgery has proven to be the most effective long-term treatment for weight reduction and obesity-associated morbidities [1]. However, it is frequently complicated by dumping syndrome (DS) and postbariatric hypoglycemia (PBH), also known as "early and late dumping" [2]. The prevalence of DS and PBH depends on the type of

*Correspondence: A. Marrit van Furth, B.Sc., University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, The Netherlands.

E-mail address: a.m.van.furth@student.rug.nl (A.M. van Furth).

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surgery, definition, and diagnostic test used. DS has been reported in 19% to 42% of patients and PBH in 12% to 72% [3–5].

While DS and PBH started with similar nomenclature, they have been separated due to several differences. DS typically develops directly after bariatric surgery, whereas PBH takes months to years to occur [6]. DS complaints start within the first hour after a meal. The symptoms attributed to DS are mainly gastrointestinal complaints (i.e., abdominal pain, bloating, nausea, and diarrhea) and vasomotor symptoms (e.g., sweating, flushing, palpitations, tachycardia, hypotension, dizziness, and, rarely, even syncope) [6]. In contrast, PBH is defined by a hypoglycemic event, usually starting 1 to 3 hours after a meal. It presents with hypoglycemia-related symptoms (drowsiness/unconsciousness, irritability, confusion) and adrenergic symptoms (sweating, palpitations, hunger, tremor) caused by vagal and sympathetic activation [7]. These hypoglycemic episodes can occur several times a day [8]. Not surprisingly, patients with early and late dumping had significantly lower scores on questionnaires measuring their quality of life (RAND-36, a widely used health related quality of life survey) and anxiety and depression (HADS, a hospital anxiety and depression scale) compared with patients without dumping [5].

The pathophysiological mechanisms contributing to these phenomena are still incompletely understood. The current theory is that early dumping is caused by rapid delivery of food to the small intestine, resulting in osmotic fluid shifts from the intravascular compartment to the intestine [5]. PBH is thought to occur in the setting of high weight loss after bariatric surgery, when increased insulin sensitivity is combined with increased insulin secretion by beta cells, leading to a hyperinsulinemic hypoglycemic event, the principal hallmark of PBH [9]. The pivotal role of glucagon-like peptide-1 (GLP-1) in PBH is emphasized, as the GLP-1 antagonist exendin 9-39 prevents hypoglycemia in people with severe symptoms [10].

In our previous questionnaire study, we showed that patients were more likely to develop DS complaints after a primary Roux-en-Y gastric bypass (pRYGB; 19%) than after sleeve gastrectomy (SG; 9%) [4]. Furthermore, 40% of patients developed PBH complaints after revisional RYGB (rRYGB), compared to 31% after pRYGB. A hypothesis is that rRYBG after earlier gastric banding can, by damaging vagal nerve fibers, cause more complaints of PBH [4]. Furthermore, in a meal test we found that DS was related to active GLP-1, the key hormone in the pathophysiology of PBH [11]. Also, some literature suggests that DS and PBH are more related than is currently assumed. For example, somatostatin analogues, which suppress the release of GLP-1 from the L-cells, also decrease DS complaints [3]. Moreover, acarbose, a first-line medication for PBH that reduces the rate of glucose absorption, has been shown to also reduce DS complaints [12]. Lastly, in a recent study in 11 women with PBH after gastric bypass surgery, hormone excursions associated with PBH appeared to be related to symptoms of DS [13].

Altogether, this raises the possibility that an overlap exists between DS and PBH and that both are occurring within the same dumping disease spectrum. Therefore, the aim of the current study was to further explore the relationship between DS and PBH, using data from our previous meal test study in a group of patients after RYGB [11].

Methods

Study population

For this retrospective cohort study, a preexisting database was used. This database was created in our previous study of a cohort of nondiabetic patients aged 18–75 years who underwent pRYBG between 2008 and 2011 in the Medical Centre Leeuwarden. From the entire eligible cohort (550 patients), a representative random sample of 140 patients was selected with the random sample function in SPSS. These patients were approached by telephone, and 51 were willing to participate. From these participants, we excluded 4 more patients for reasons described previously (Fig. 1) [14]. Results from this population on DS and on PBH have been previously published separately [11,14]. The Regional Ethical Review Board of the Medical Center Leeuwarden had approved the mixed meal test (MMT) study protocol (ISRCTN 4160409912). Written informed consent was obtained from all participants.

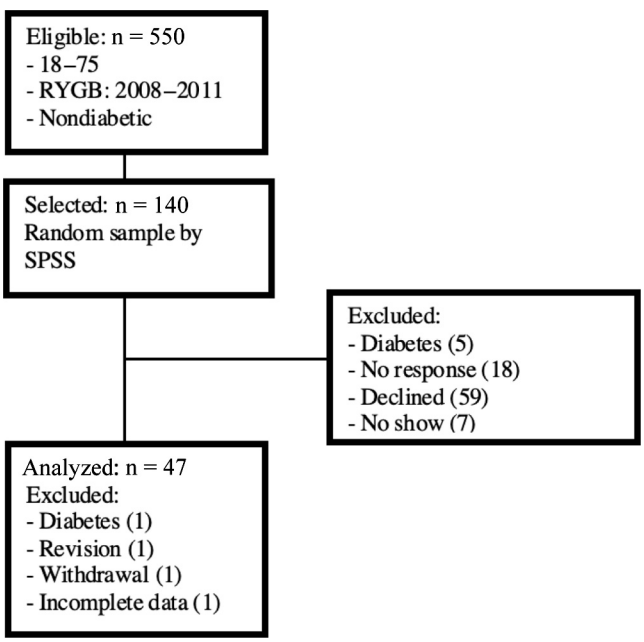

Fig. 1. Flowchart of the selection process. RYGB = Roux-en-Y gastric bypass.

Surgical technique

All patients' operations were in the Medical Centre Leeuwarden, where 3 bariatric surgeons used the standardized operation technique that has been described previously [5]. In short, for the pRYGB technique, a pouch of 30 to 60 cm^3 was created with an antecolic-antegastric Roux-en-Y reconstruction. The biliopancreatic limb was measured at a length of 80 cm after the ligament of Treitz, and the alimentary limb length was 150 cm. Linear stapling was used to divide the loop between the 2 anastomoses. Moreover, the surgeons tried to prevent dissection of the branches of the vagal nerve by strict perigastric dissection as they entered the lesser sac to create the pouch [5].

Questionnaires

The dumping severity score developed by Arts et al. [3] was used for assessment of the severity of DS and PBH symptoms. Patients were asked to score 8 commonly perceived complaints relating to DS and 6 complaints relating to PBH. The symptoms regarding DS consisted of 4 abdominal symptoms (abdominal pain, diarrhea, bloating, and nausea) and 4 autonomic symptoms (sweating, flushing, dizziness, and palpitations). The PBH complaints included 4 adrenergic symptoms (sweating, palpitations, hunger, and tremor) and 2 neuroglycopenic symptoms (drowsiness/unconsciousness and irritability). This questionnaire used a 4-point Likert scale. Patients were asked to grade the intensity (0 = absent; 1 = mild; 2 = moderate; and 3 = severe) of the complaints.

DS definitions

No formal diagnostic criteria exist for DS and PBH. For the purpose of this study, we divided the patients into groups based upon whether they did (DS+) or did not (DS-) experience an increase in DS complaints 30 minutes after initiation of the test meal (Fig. 2). The DS complaints were calculated as the sum of the individual components of the 8 DS symptoms, with the intensity score ranging from 0 to 3. The incremental score was determined by subtracting the baseline DS score at 0 minutes from the cumulative DS score at 30 minutes. PBH was defined as a glucose concentration of less than 3.3 mmol/L during the meal test [11]. PBH symptoms were scored as mentioned in the Questionnaires subsection.

MMT

After an overnight fast, the patients consumed a 200-mL liquid meal (Ensure Plus, Abbott) containing 300 kcal, 12.5 g of protein, 40.4 g of carbohydrate (of which 13.8 g were sugar), 9.84 g of fat, and 154.9 g of water as previously described [11]. Responses were measured by collecting blood samples, heart rate, and blood pressure

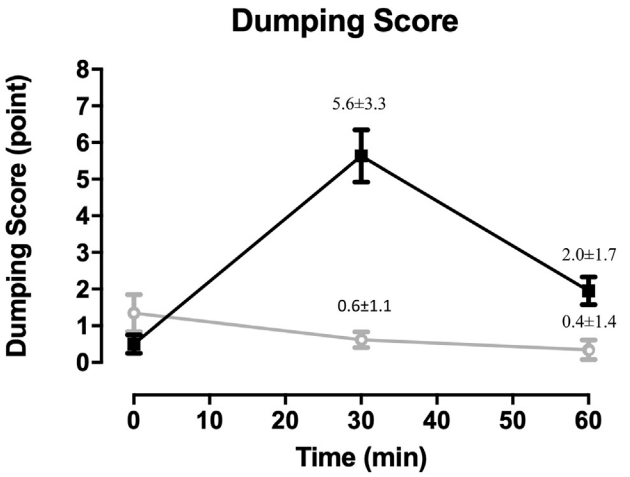

Fig. 2. Comparison between patients at low and high suspicion of early dumping for sum score of early dumping. Calculated as the sum of the 8 dumping complaints using a 4-point Likert scale (0 = absent; 1 = mild; 2 = moderate; and 3 = severe). Means ± standard deviations are presented. Black squares indicate an increase of dumping syndrome complaints. Gray open circles indicate no increase of dumping syndrome complaints.

at baseline before the meal (time [t] = 0) and at 30-minute time intervals for up to 3.5 hours after ingestion. Simultaneously, the patients scored their perceived DS complaints at 0, 30, and 60 minutes and PBH complaints at 90, 120, 150, 180, and 210 minutes using the Arts et al. [3] questionnaire.

Satiety and hunger were assessed every 30 minutes from baseline by means of a 10-cm visual analogue scale with scores ranging from "not at all" to "greatest thinkable."

Statistical analysis

Data are presented as median (interquartile range [IQR]). Categorical variables are presented as numbers with corresponding percentages. Differences between groups were assessed with *t*-tests or Mann-Whitney U tests for continuous variables or chi-square or Fisher exact tests for categorical variables, depending on the normality of distribution. A histogram was used to check the normality of distribution (Supplementary Data). Correlations were assessed using Spearman's coefficient. A P value of $<.05$ was considered statistically relevant. All analyses were done in Statistical Package for the Social Sciences version 26 (SPSS. Inc.).

Results

Patient characteristics

Data from 47 patients were available. The characteristics are shown in Table 1. Both study groups have the characteristics of most bariatric populations, with a female preponderance and patients in their 40s at surgery.

Table 1
Baseline characteristics of patients with and without an increase of dumping syndrome complaints after an MMT

	Patients in MMT study (total, n = 47)	Increase of dumping syndrome complaints (n = 22)	No increase of dumping syndrome complaints (n = 25)	*P* value
Female	36 (72)	17 (77)	17 (68)	.478
Age at study, yr	47 [31;63]	48 [33;63]	43 [25;61]	.620
Time between last surgery and study, yr	3 [2;4]	4 [3;5]	4 [3;5]	.429
Weight at surgery, kg	137 [101;163]	128 [104;152]	145 [114;186]	.003
Weight at MMT, kg	94 [70;118]	88 [73;103]	102 [66;138]	.001
Weight loss, kg	41 [17;64]	41 [21;61]	41 [12;70]	.794
BMI at surgery, kg/m^2	45 [38;53]	44 [38;50]	45 [34;57]	.015
BMI at MMT, kg/m^2	31 [24;38]	30 [27;33]	33 [24;42]	.004
BMI loss, kg/m^2	14 [7;20]	14 [8;20]	14 [7;21]	.921
EWL at MMT, %	67 [41;93]	75[55;95]	64 [37;91]	.029

MMT = mixed meal test; BMI = body mass index; EWL = excess weight loss.

Weight loss was from surgery to last MMT. BMI was measured at last visit. BMI loss was from surgery to last MMT. EWL was measured from surgery to MMT. Data are shown as numbers (percentages) or medians [interquartile ranges] where appropriate. Dumping syndrome complaints were defined as an increase of complaints after the meal. Supplemental data will be made available upon request to the corresponding author.

There was no difference in time between surgery and the MMT (median, 4 yr; IQR, 3–5 yr; $P = .429$). The median body mass index (BMI) loss after surgery was similar in both groups (14 kg/m^2; $P = .921$). The BMI at the time of the MMT, however, was different, with a lower value in the DS+ group (median, 30 kg/m^2; IQR, 27–33 kg/m^2) compared to the DS- group (median, 33 kg/m^2; IQR, 24–42 kg/m^2; $P = .004$; Table 1).

MMT

Out of a total 47 patients, 22 (47%) had an increase in DS complaints (DS+) 30 minutes after the meal, whereas 25 patients (DS-) showed no increase. The absolute DS scores at 30 minutes were 5.6 ± 3.3 for the DS+ group versus .6 ± 1.1 for the DS- group; at 60 minutes the scores were 2.0 ± 1.7 versus .4 ± 1.4, respectively (Fig. 2).

More patients in the DS+ group (13/22; 59%) than in the DS- group (9/25; 36%) had a plasma glucose nadir <3.3 mmol/L during the MMT ($P = .113$). As shown in Fig. 3A, the DS+ group had an overall lower glucose during the test until 210 minutes, and the difference reached significance at 90 and 120 minutes. At 90 minutes, the difference had an absolute value of 1.3 mmol/L. No differences were observed in insulin concentrations (Fig. 3B). Despite low blood sugar values in over half of the DS+ group, the PBH questionnaire score at 90 minutes was mainly 0 for both the DS+ (71%) and DS- (76%) groups ($P = .468$).

Higher active GLP-1 levels (Fig. 3C) were found at both early (t = 30 minutes) and late (t = 90 minutes) time points after the meal in the DS+ group. Results were similar for peptide YY (PYY; Fig. 3D) values, albeit at somewhat later time points (t = 60, 90, 150, and 180 minutes).

The satiety score (Fig. 3E) in the DS+ group was significantly higher compared to that of the DS- group and followed a pattern as seen in PYY. No differences were found in the hunger scores between the groups (Fig. 3F).

Associations between GLP-1 and PYY and perceived complaints

Active GLP-1 at 30 and 60 minutes showed positive correlations with total DS scores (r = .429 and .436, respectively) and DS symptoms of dizziness (r = .363 and .469, respectively), abdominal pain (r = .343 and .496, respectively), and nausea (r = .462 at 30 minutes; Table 2). PYY was also related to DS complaints (r = .304 at 30 min and .472 at 60 min), especially abdominal pain (r = .458 at 60 min) and nausea (r = .394 at 30 min).

At the time points after 2 hours, GLP-1 was inversely related to hunger (r = −.355 to −.515) and positively related to insulin. PYY was also positively correlated with insulin at these intervals. Throughout all corresponding time intervals, GLP-1 and PYY were most strongly correlated with each other (Table 2).

Discussion

With the aim of investigating a possible common etiology of DS and PBH, we performed a post hoc analysis of a meal test. Patients with post-meal DS in our definition had lower mean post-meal glucose values, which were significant at 90 and 120 minutes, characteristic time points of PBH. More patients in the DS+ group had a hypoglycemic event; however, this difference did not reach significance. Additionally, GLP-1 and PYY levels were higher in the DS+ group both during the first hour, when dumping complaints are expected, and after 1 hour, when PBH usually occurs. GLP-1, a key player in PBH, was also strongly associated with early dumping symptoms. Similar findings were observed for PYY, another L-cell hormone. These findings strengthen the hypothesis that there is a common etiology for DS and PBH. Both DS and PBH are possibly part of the DS disease spectrum, in which GLP-1 and PYY seem to play a key role.

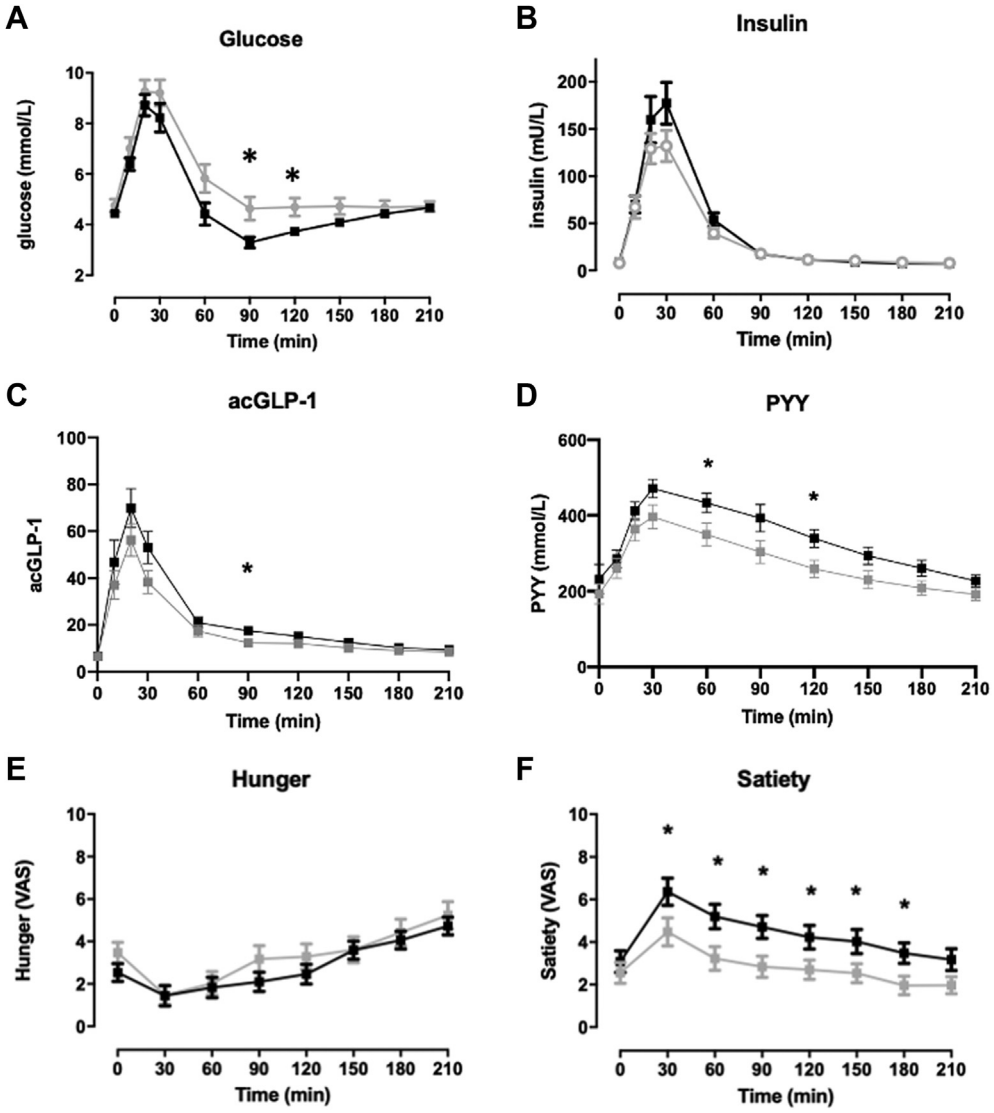

Fig. 3. Comparison between patients at low and high suspicion of early dumping for (A) glucose, (B) insulin, (C) GLP-1, and (D) PYY. Measurements of (E) hunger and (F) satiety after a mixed meal test. Black squares indicate an increase of dumping syndrome complaints. Gray open circles indicate no increase of dumping syndrome complaints. *$P < .05$; †$P < .01$; and ‡$P < .001$. GLP-1 = glucagon-like peptide-1; PYY = peptide YY.

In support of these results, Øhrstrøm et al. [13] also found increases in heart rates and hemoconcentration and norepinephrine levels, all suggesting early dumping, during an MMT in 11 women with documented PBH. The increasing heart rate was associated with rises in glucose, insulin, and GLP-1 levels in the first hour of the MMT [13]. Correlations with the glucose nadir after 1 hour were not studied. Treatment with acarbose and pasireotide, both known to ameliorate PBH, resulted in a decrease in the early heart rate response and norepinephrine levels. Contrary to the findings in our study, their patients had symptomatic postprandial hypoglycemia. The PBH symptom score in our study was low even in the presence of low glucose values, supporting the hypothesis of hypoglycemia unawareness, as mentioned in previous literature [11]. Studies with somatostatin analogs showed beneficial effects for both DS and PBH [6]. This does not provide sufficient evidence of a common etiology, as somatostatin analogs are known to inhibit multiple different hormone pathways. An apparently more specific intervention related to PBH is acarbose, an alfa glucosidase inhibitor that delays glucose absorption. While this intervention was repeatedly found to prevent hypoglycemia in PBH patients, it also appeared to reduce DS complaints effectively [12].

While the combined pathophysiology of DS and PBH remains to be elucidated further, a general picture has

Table 2
Correlations between active GLP-1 and PYY with perceived complaints at several time intervals after an MMT

	Time, min	Total DS score	Hunger*	Dizziness	Palpitations	Abdominal pain	Nausea	Insulin	PYY
GLP-1	0	.021	–.375†	–.017	–.137	.033	.085	.329†	.321†
	30	.429‡	–.354†	.363†	.266	.343†	.462‡	.248	.505§
	60	.436‡	–.330†	.469‡	.245	.496‡	.292	.171	.697§
	90		–.379†					.033	.503§
	120		–.459‡		.419‡			.439‡	.631§
	150		–.355					.308†	.629§
	180		–.500‡		.079			.311†	.587§
	210		–.515‡					.313†	.467§
PYY	0	−.153	–.188	–1111	–.135	–.109	–.109	.284	
	30	.304†	–.274	.284	.018	.215	.394‡	.162	
	60	.472§	–.267	.345†	.126	.458‡	.294	.202	
	90		–.219					.210	
	120		–.215		.375†			.417‡	
	150		–.123					.360†	
	180		–.149		–.137			.327†	
	210		–.173					.354†	

GLP-1 = Glucagon-like peptide-1; PYY = peptide YY; MMT = mixed meal text; DS = dumping syndrome.

Data are presented as correlation coefficients (r). Note that the following symptoms of DS showed no significance: perspiration, flushes, diarrhea, bloating. Also, no associations were found with glucose.

* Hunger was scored on a visual analogue scale.

† $P < .05$.

‡ $P < .01$.

§ $P < .001$.

emerged. Large populations of L-cells in the small and large intestine are exposed to nutrients by the altered flow of food after gastric bypass surgery. In addition, after RYGB, increased numbers of L-cells are found in the perianastomic jejunum [15]. Direct contact of L-cells with glucose as their main stimulus results in exaggerated secretion of GLP-1 and PYY [16]. In the early post-meal period, both hormones cause mainly nausea and abdominal pain, but also dizziness and suppression of hunger [5]. These symptoms resemble the well-known side effects of treatment with GLP-1 analogs [17]. PBH, however, occurs mainly in the setting of decreased insulin resistance and increased beta cell activity [11]. These circumstances are more likely to be met after significant weight loss [18]. This takes time after surgery, explaining the differences in time of onset between DS and PBH. It would be interesting to see whether DS, like PBH, could be effectively treated with the GLP-1 antagonist Exendin (9-39). Many questions of course remain, including the key questions of why some individuals develop DS and PBH and others do not and why disease severity can fluctuate remarkably over time. These questions remain to be answered, but the etiology is probably multifactorial, with an interplay of changes in hormones, the microbiome, and different surgery techniques, and potentially also a regulating role for bile acids [19].

Several limitations in our study need to be mentioned. First is the lack of use of a validated questionnaire for DS and PBH because no validated questionnaire exists [7,20]. The questionnaire from Arts et al. [3] provides a quantitative assessment of symptom severity. No cutoff score has been established in the literature to define DS [7]. By scoring symptoms at different postprandial time intervals, a distinction can be made between those who do and do not have DS symptoms.

Second, the study groups did not have comparable BMIs at the time of either surgery or the MMT. A lower BMI is associated with more insulin sensitivity and could therefore contribute to the development of lower glucose values in the DS+ group [11]. Third, another limiting factor is the retrospective format of this study. Future research should focus on the influences of GLP-1 and PYY on DS and PBH in bariatric surgery patients in a prospective setting. Finally, our studied patients were asymptomatic and therefore not representative of patients who present with severe symptomatic neuroglycopenic episodes, although these patients comprise only a small proportion of postbariatric patients. The results of our study can therefore not be extrapolated to these patients.

Conclusion

The MMT revealed that patients with more DS complaints have lower postprandial glucose concentrations at time points characteristic for PBH. Additionally, we showed that the gut hormones GLP-1 and PYY are associated with both DS and PBH. Therefore, these results support the hypothesis that both DS and PBH share a common etiology.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.soard.2021.05.020.

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