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Original article

Prevalence and pathophysiology of early dumping in patients after primary Roux-en-Y gastric bypass during a mixed-meal tolerance test ☆

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Abstract

Background: Early dumping is a poorly defined and incompletely understood complication after Roux-en-Y gastric (RYGB).

Objective: We performed a mixed-meal tolerance test in patients after RYGB to address the prevalence of early dumping and to gain further insight into its pathophysiology.

Setting: The study was conducted in a regional hospital in the northern part of the Netherlands.

Methods: From a random sample of patients who underwent primary RYGB between 2008 and 2011, 46 patients completed the mixed-meal tolerance test. The dumping severity score for early dumping was assessed every 30 minutes. A sum score at 30 or 60 minutes of ≥5 and an incremental score of ≥3 points were defined as indicating a high suspicion of early dumping. Blood samples were collected at baseline, every 10 minutes during the first half hour, and at 60 minutes after the start.

Results: The prevalence of a high suspicion of early dumping was 26%. No differences were seen for absolute hematocrit value, inactive glucagon-like peptide-1, and vasoactive intestinal peptide between patients with or without early dumping. Patients at high suspicion of early dumping had higher levels of active glucagon-like peptide-1 and peptide YY.

Conclusion: The prevalence of complaints at high suspicion of early dumping in a random population of patients after RYGB is 26% in response to a mixed-meal tolerance test. Postprandial increases in both glucagon-like peptide-1 and peptide YY are associated with symptoms of early dumping, suggesting gut L-cell overactivity in this syndrome. (Surg Obes Relat Dis 2019;15:73–82.) © 2018 Published by Elsevier Inc. on behalf of American Society for Bariatric Surgery.

Keywords: Early dumping; Gastric bypass; Gastrointestinal hormones; Prevalence; Pathophysiology; Incretins

Morbid obesity is a growing healthcare problem in the world; consequently, effective weight loss strategies are needed. Weight loss surgery is the most effective way to achieve sustained weight loss, resolve co-morbidity, and improve survival [1]. Currently, one of the most frequently performed operations is the laparoscopic Roux-en-Y gastric bypass (RYGB). This procedure is effective, but it is known to have several complications. One of these, early dumping, is poorly defined and incompletely understood. Early dumping represents a constellation of abdom-

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inal symptoms, including abdominal cramps, bloating, and diarrhea, which start within minutes after a meal and last for up to 1 hour. Early dumping is also accompanied by autonomic responses such as sweating, palpitations, drowsiness, and orthostatic symptoms.

The prevalence of early dumping after gastric surgery has been estimated at 12% to 42% [2–4]. The first shortcoming of these estimates is that there is no available gold standard to measure early dumping [5]. Second, none of the studies used a meal-induced provocation in a random patient cohort, which would probably lead to a better estimate of the prevalence of early dumping syndrome.

Several concurrent phenomena can contribute to the development of early dumping [6]. Due to the RYGB, the pylorus and the first part of the jejunum are bypassed, causing rapid delivery of undigested food to the small bowel. One theory suggests that these hyperosmolar nutrients cause a shift of fluid from the intravascular compartment (i.e., plasma) to the intestinal lumen, resulting in a reduction in plasma volume, tachycardia, and hypotension [7]. The triggers for these symptoms are not known. Another theory postulates that the increased release of multiple gastrointestinal hormones, including vasoactive agents (e.g., neurotensin and vasoactive intestinal peptide [VIP]) and incretins (e.g., glucose-dependent insulinotropic peptide and glucagon-like polypeptide 1 [GLP-1]), as well as glucose modulators (e.g., insulin and glucagon), are involved in the onset of early dumping [8–11]. Enhanced release of these hormones may induce uncoordinated gastrointestinal motility, inhibit secretion, and elicit hemodynamic effects [8–11]. However, these studies were mainly performed in the prebariatric era with small groups of (preselected) patients and using an oral glucose-tolerance test, which is less reliable than a mixed-meal tolerance test (MMTT) in inducing a physiologic stimulus [12]. To address these methodologic issues in prevalence estimations of early dumping and to gain further insight in its pathophysiology, we performed MMTTs in a random sample of patients after gastric bypass surgery.

Methods

Study population

This study was conducted between February 2014 and March 2015. Patients aged 18 to 75 years who underwent primary RYGB between 2008 and 2011 in our center were eligible for this study. The technique of the RYGB included an antecolic-antegastric Roux-en-Y reconstruction with 30- to 60-cm^3 gastric pouch, a biliopancreatic limb length of 80 cm, and an alimentary limb length of 150 cm [13]. We try to prevent dissecting the branches of the vagal nerve by strict perigastric dissection as we enter the lesser sac to create the pouch.

Patients with diabetes at the time of the study or who had undergone a revisional procedure were excluded.

We estimated that we needed between 50 and 70 patients to participate in our study to have enough patients with early dumping, assuming a prevalence of 18% [13]. A participation rate of 50% was expected; therefore, a random sample of 140 patients was created from the entire cohort (n = 550 by means of the random sample function in SPSS [SPSS, Inc., Armonk, NY, U.S.A.]). After initial invitation by telephone, those willing to participate received additional study information. After at least 1 week of consideration, the patients were scheduled for MMTT after their informed written consent was obtained. A total of 51 patients participated. After the test we excluded 5 more patients because of a prior revisional operation (1 patient), withdrawal during the test (1 patient), and because of abdominal complaints before the start of the MMTT (3 patients) [3]. Therefore, in total 46 patients were analyzed. The selection process, including reasons for exclusion, is shown in Fig. 1.

Records for individual patients were completed by data review. The study protocol was approved by the hospital's medical ethical review board (RTPO 976 number 41604.099.12).

Study protocol

All scheduled patients underwent the MMTT in the morning after an overnight fast of at least 8 hours. Anthropometric measures were obtained before the test meal. Via a peripheral intravenous cannula, blood samples were obtained before the meal (t = 0) and again at 10, 20, 30, and 60 minutes after the meal. Additionally, heart rate and blood pressure were measured. Perceived symptoms (documented by disease-specific questionnaires) were filled out by the patients before the meal and again at 30 and 60 minutes after the meal.

A 200-mL liquid nutrition supplement (Ensure Plus, Hoofddorp, the Netherlands; Abbott) containing 300 kcal, 12.5 g protein, 40.4 g carbohydrate (of which 13.8 g sugar), 9.84 g fat, and 154.9 g water was used as a mixed meal. The patients were asked to finish the meal within 10 minutes.

Questionnaires and definition of early dumping

Symptoms of early dumping were assessed according to the dumping severity score (DSS) using a 4-point Likert scale as developed by Arts et al. [14]. Each patient was asked to grade the intensity (0 = absent; 1 = mild; 2 = moderate; and 3 = severe, i.e., interfering with daily activities) of 8 early-dumping symptoms.

Due to the explorative nature of this study, the group was divided into 2 subgroups based on the sum score of symptoms at 30 or 60 minutes, with all complaints weighted equally (Table 1). Patients with a sum score of $\leq$4 and incremental score of $\leq$2 points compared with baseline were

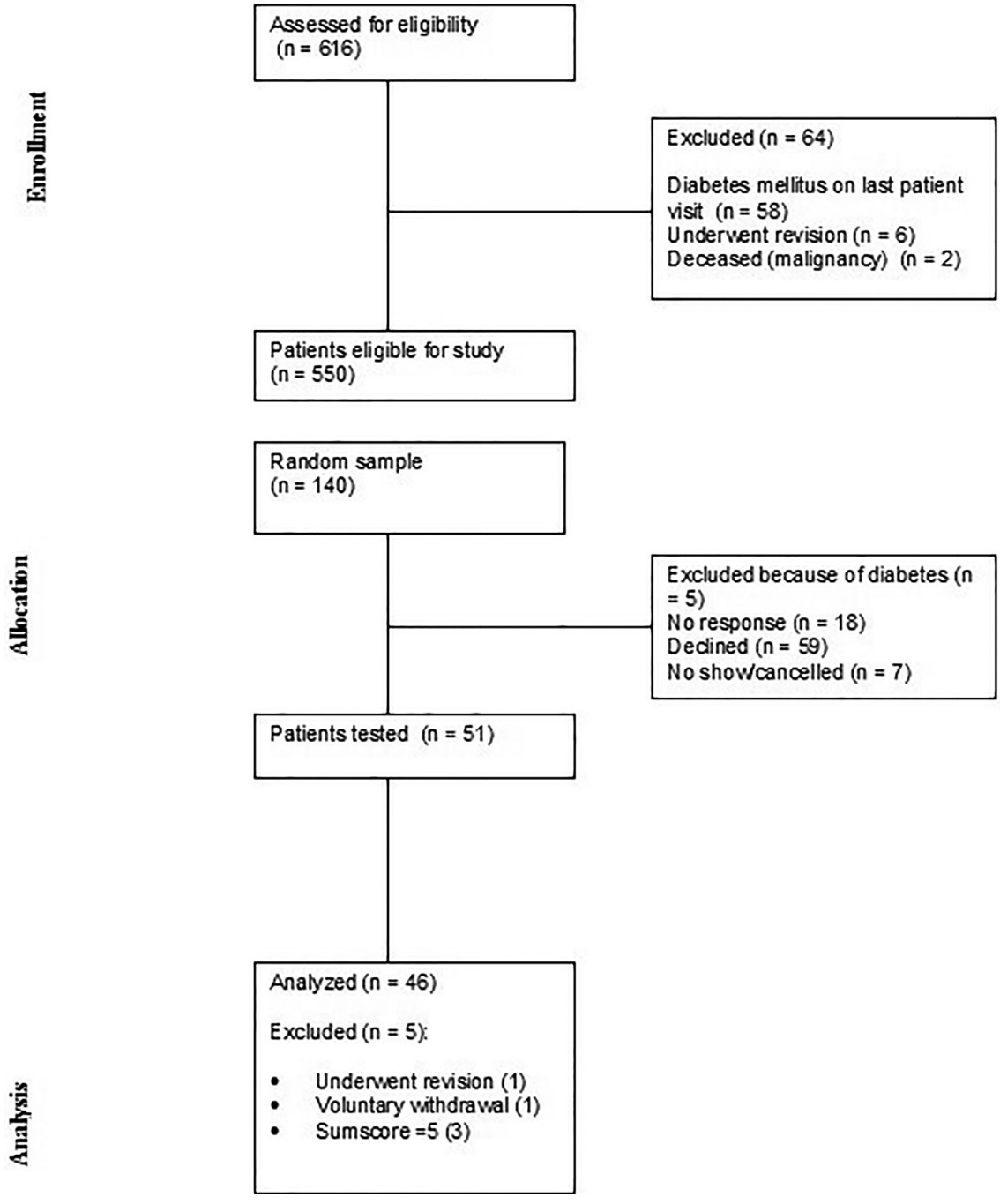

Fig. 1. Flow diagram showing the selection process according to Consolidated Standards of Reporting Trials (CONSORT) statement.

Table 1
Early dumping sum score during the mixed-meal tolerance test in the low- and high-suspicion group of early dumping.

	Low suspicion of early dumping n = 34	High suspicion of early dumping n = 12	*P* value
Early dumping sum score (t = 0 min)	0 [0; 0]	0 [0; .75]	.627
Early dumping sum score (t = 30 min)	1 [0; 2]	6.5 [0; 9.75]	<.001
Early dumping sum score (t = 60 min)	0 [0; 0]	3 [2; 4]	<.001

Data are median [interquartile ranges].

defined as at low suspicion of early dumping. Patients with a sum score at 30 or 60 minutes of ≥5 and an incremental score of ≥3 points were defined as at high suspicion of early dumping.

Patients with a baseline sum score >5 (n = 3) were excluded from analysis as they were considered to have abdominal complaints in the fasting state that would interfere with interpretation of postprandial symptoms.

Blood analyses

For hematocrit analysis, blood was collected in spray-coated ethylenediaminetetraacetic acid (EDTA) tubes; for glucose and insulin analysis, lithium-heparin tubes with a gel separator were used. For the measurement of peptide YY (PYY), VIP, active GLP-1, and inactive GLP-1, blood was collected in precooled tubes containing 15% aprotinin to which 50-μL dipeptidyl peptidase 4 inhibitor (DPP4-010; Merck Millipore, the Netherlands) was added by injection through the cap directly before blood withdrawal without influencing the integrity of the preexisting vacuum in the tube [15].

The initial product GLP-1 (1–37) is susceptible to amidation and proteolytic cleavage, which gives rise to the 2 truncated and equipotent biologically active forms, GLP-1 (7–36) amide and GLP-1 (7–37). This proteolytic activation is the result of dipeptidyl peptidase 4. All samples were centrifuged at 4°C and analyzed immediately or stored at −80°C until analyzed.

Hematology analysis was done using the Abbott Cell-Dyne Sapphire (Abbott, Abbott Park, IL). Hemoglobin was measured spectrophotometrically using a Cell-Dyne Sapphire CN-free hemoglobin (HGB) reagent. The hematocrit was calculated by multiplying the mean of all measured red cell volumes by impedance analysis and the total red cell count (also based on the impedance analysis).

The glucose (hexokinase reaction) and insulin analyses (sandwich principle assay) were performed on a Roche analyzer (Sandhofer Strasse 116, D-68305; Roche Diagnostics GmbH, Mannheim, Germany).

The concentrations of the active GLP-1, VIP, inactive GLP-1, and PYY were determined by using commercial enzyme-linked immunosorbent assay kits on a 2-plate enzyme-linked immunosorbent assay processing system (DS2; DYNEX Technologies, Chantilly, VA), as per the manufacturer's instructions. The following commercial enzyme-linked immunosorbent assay kits were used for the active form and inactive form of GLP-1: IBL International (Hamburg, Germany) (code JP27784 and code JP27788); for human VIP: RayBiotech (Norcross, GA) (cat. # EIA-VIP); and for human PYY: Millipore Corporation (Billerica, MA) (cat. # EZHPYYT66 K). For the active and inactive form of GLP-1 and VIP, low- and high-level internal quality controls (QCs) were prepared by selecting and pooling plasma containing 15% aprotinin and dipeptidyl peptidase 4 inhibitor. Low and high QCs for human PYY were provided by the manufacturer. The interassay variations of the low-level internal QC and the high-level internal QC were 57.0% and 43.7% for active GLP-1; 7.4% and 15.7% for inactive GLP-1; 62.0% and 54.1% for human VIP; and 12.1% and 17.2% for human PYY, respectively. Considering these variations, only within-subject changes from baseline were used for analysis.

Statistical analysis

Data are presented as mean ± standard deviation, median and interquartile ranges, and frequencies where appropriate. Relative within-subject changes from baseline were assessed by the formula (Δ/baseline) × 100.

The *t* test was used for calculating differences for normally distributed data; the Mann-Whitney *U* test for data that were not normally distributed was used; for categorical data a χ^2 test or a Fisher exact test (with expected cell counts <5) was used. Results were considered significant at $P < .05$. Graphs were created in GraphPad Prism (GraphPad Software Inc., La Jolla, CA) using data calculated in SPSS version 23. For graphic representation, mean ± standard error of the mean is shown.

Results

Data of 46 patients were available for analysis: 34 women and 12 men with a median age of 47 years (39–54). BMI was 46.1 kg/m^2 (42.0; 48.5) before RYGB and 31.2 kg/m^2 (28.6; 35.0) after surgery, resulting in an excess weight loss of 68.1% (54.9; 79.4) and a total weight loss of 33.1% (23.6; 37.7). Time between operation and MMTT was 46 months (39; 54 mo).

The study population (n = 46) was representative of the entire surgical cohort (n = 550) and of the random sample (n = 140) in terms of age, sex, co-morbidities before surgery, preoperative weight, and postoperative weight at the time of the study (data not shown).

Table 2 shows the difference in patient characteristics between the patients with high and low suspicion for early dumping.

Prevalence of early dumping based on symptom scores

The prevalence of a high suspicion of early dumping was 26% (12/46). Fig. 2A presents the DSS in our predefined groups with low and high suspicion of early dumping. The patients with high suspicion of early dumping peaked at 30 minutes followed by a decline without returning to baseline values at 60 minutes.

Baseline characteristics of the 2 groups showed no differences in demographic characteristics, prevalence of co-morbidities, and percentages of excess and total weight loss.

Table 2
Comparison of patient characteristics between patients at low and high suspicion of early dumping.

	Low suspicion of early dumping n = 34	High suspicion of early dumping n = 12	*P* value
Age, y	46 [39; 53]	52 [41; 58]	.145
Female (%)	25 (74)	9 (75)	1.000
Time between surgery and study, mo	46 [39; 56]	47 [42; 54]	.954
Weight and weight loss			
Weight at surgery, kg	139 [127; 155]	131 [118; 141]	.100
BMI at surgery	46 [42; 51]	46 [40; 48]	.159
Weight at MMTT, kg	93 [85; 113]	92 [76; 97]	.086
BMI at MMTT	32 [29; 37]	30 [27; 33]	.159
EWL at MMTT (%)	67 [50; 78]	73 [61; 88]	.321
TWL at MMTT (%)	31 [24; 38]	32 [23; 39]	.700
Co-morbidities preoperative			
Type 2 diabetes	8 (23.5)	6 (50)	.091
Hypertension	14 (41.2)	6 (50.0)	.422
Dyslipidemia	4 (11.8)	4 (33.3)	.108
Co-morbidities postoperative			
Type 2 diabetes*	0	0	
Hypertension	7 (20.6)	2 (16.7)	.568
Dyslipidemia	3 (8.8)	0 (0)	.394

BMI = body mass index; MMTT = mixed-meal tolerance test; EWL = excess weight loss; TWL = total weight loss.
Data are median [interquartile ranges], or numbers and frequencies (percentages).
*Exclusion criteria.

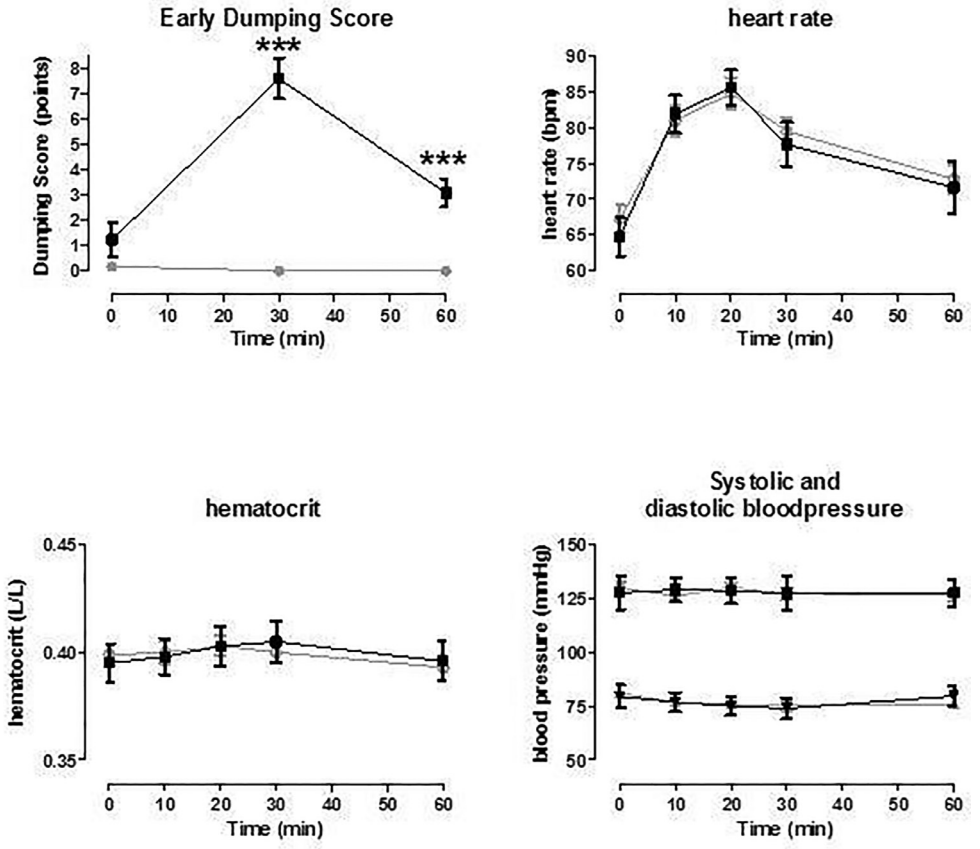

Fig. 2. Comparison between patients at low and high suspicion of early dumping for the sum score of early dumping (A), heart rate (B), hematocrit (C), and blood pressure (D). Black line: high suspicion for early dumping. Gray line: low suspicion for early dumping. ***$P < .001$.

Table 3
Comparison of early dumping symptoms between the group at low and high suspicion for early dumping at 30 and 60 minutes after ingestion of the test meal.

	Low suspicion for early dumping n = 34	High suspicion for early dumping n = 12	*P* value
At 30 min			
Transpiration	1 (2.9)	5 (41.7)	**.002**
Flushes	2 (5.8)	2 (16.7)	.220
Dizziness	4 (11.8)	9 (75)	**<.001**
Palpitations	4 (11.8)	6 (50)	**.004**
Abdominal pain	3 (8.8)	6 (50)	**.003**
Diarrhea	0	4 (33.3)	**.006**
Bloating	11 (33.3)	10 (83.3)	**.002**
Nausea	8 (24.3)	11 (91.7)	**<.001**
At 60 min*			
Transpiration	1 (2.9)	1 (9.1)	4.33
Flushes	2 (5.9)	0	.567
Dizziness	1 (2.9)	7 (63.6)	**<.001**
Palpitations	0	1 (9.1)	.244
Abdominal pain	0	3 (27.3)	**.012**
Diarrhea	2 (5.8)	1 (9.1)	.595
Bloating	4 (11.8)	6 (55.5)	**.004**
Nausea	1 (2.9)	5 (45.5)	**.004**

Data are numbers and frequencies (percentages).
Bold numbers are statiscal significant $P < 0.05$.
*One patient did not fill in the questionnaire at 60 min.

A significant difference between the sum score of low and high suspicion of early dumping was present in all subscales of the DSS at 30 minutes except for flushing (Table 3). At 60 minutes, there were significant differences in dizziness and gastrointestinal symptoms nausea, bloating, and abdominal pain (Table 3).

No differences were seen between the low and high suspicion of early dumping groups in the systolic and diastolic blood pressure and pulse rates at all time points (Figs. 2B, 2C). No differences were found between the groups in the absolute hematocrit value at all time points (Fig. 2D). However, the relative hematocrit at 30 minutes differed significantly between patients with low or high suspicion of early dumping (32% versus 2.56% $P = .039$). This difference is higher than the analysis variance.

Significant differences were seen in the postprandial response of active GLP-1 and PYY at 20, 30, and 60 minutes (Figs. 3A, 3C), whereas no differences in inactive GLP-1 and VIP were found between the 2 groups (Figs. 3B, 3D). No differences were seen between the groups in glucose or insulin concentrations (Figs. 4A, 4B).

Discussion

This study showed that 26% of the patients who had undergone a primary RYGB after a midterm follow-up were suspected of early dumping based on symptom scores. Compared with patients with low suspicion of early dumping, these patients had a slightly increased hematocrit at 30 minutes but no differences in blood pressure or pulse rate. Furthermore, this study showed a difference in levels of active GLP-1 and PYY between patients with low and high suspicion of early dumping, suggesting that gut L-cells are involved in the pathophysiology of the syndrome.

Early dumping is seen as a sum of symptoms in most studies. The most widely used is the Sigstad score [16], but the weighing of the symptoms and signs of this score is somewhat unclear and no distinction is made between early and late dumping (postprandial hypoglycemia). Therefore, Arts et al. [14] developed the DSS for the bariatric population; patients rate the severity of 8 specific symptoms of early dumping on a 4-point Likert scale [17]. This self-reporting DSS was used in the present study because of the possibility of grading the severity of symptoms and differentiating between early and late dumping. It has previously been used as a self-reporting symptom measure in a provocation setting in a bariatric population [17].

Our findings support the conclusion that early dumping is still present in patients almost 4 years after RYGB, with a prevalence of 26%. In an earlier study of our group, we showed that moderate-to-severe symptoms (i.e., at least 2 abdominal and 1 autonomic) result in poor quality of life, highlighting the clinical relevance of this syndrome [13]. The lower prevalence in the present study compared with studies describing higher prevalence can be explained by differences in syndrome definition, the use of a random sample as opposed to a preselected sample, the use of a MMTT instead of an OGTT, RYGB versus gastrectomy, and the longer postoperative period [6,12,18,19].

Pulse rate increment and hematocrit increment has often been used to diagnose early dumping in accordance with the fluid shift theory [5,7,14,19]. In our study, the pulse

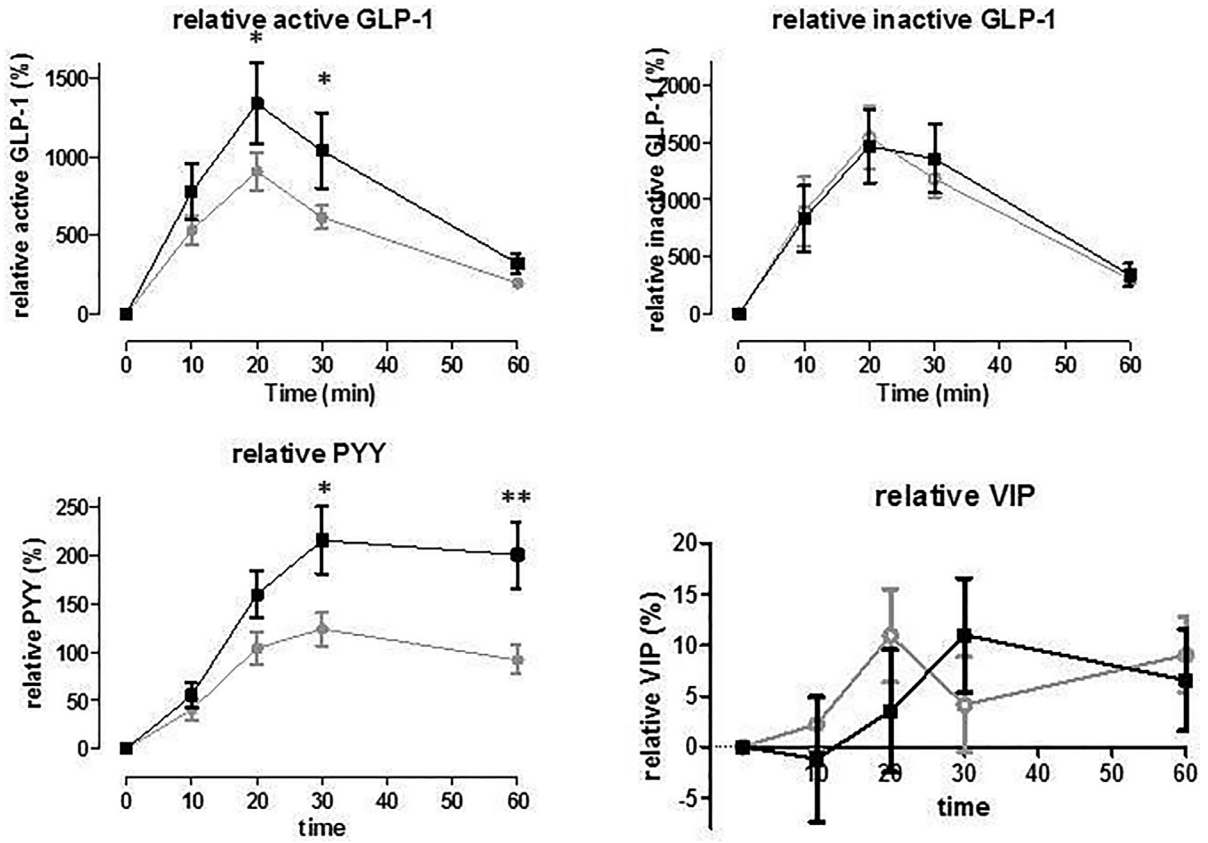

Fig. 3. Comparison between patients at low and high suspicion of early dumping for the relative active glucagon-like peptide-1 (A), inactive glucagon-like peptide-1 (B), peptide YY (panel C), and vasoactive intestinal peptide (panel D). $^{*}P < .05$ $^{**}P < .01$.

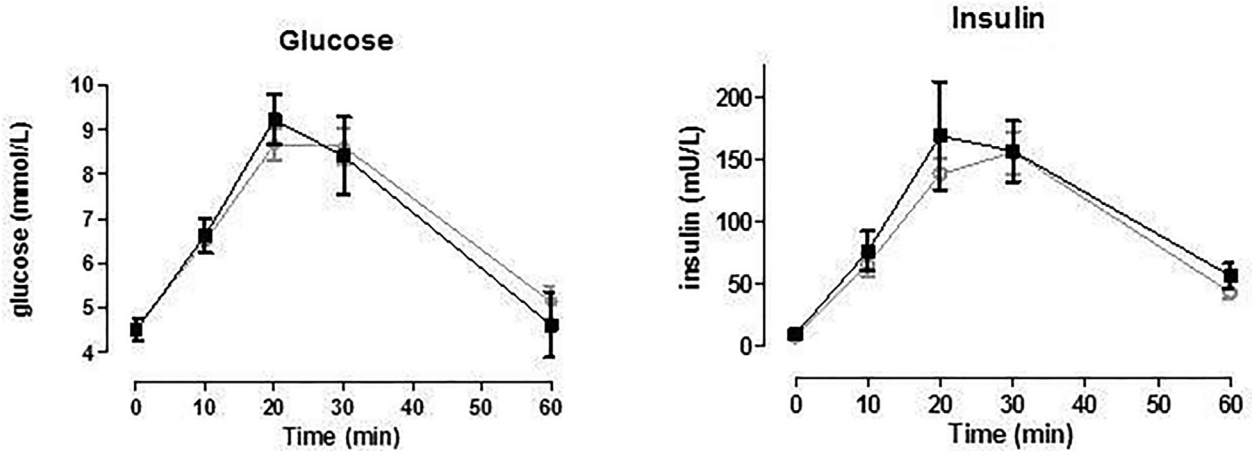

Fig. 4. Comparison between patients at low and high suspicion of early dumping for glucose (panel A) and insulin (panel B).

rate was not different between patients with low or high suspicion of early dumping. A difference in hematocrit of 3% is thought to be an objective measure of early dumping. However, in our study we only saw a difference of 2.6% between the 2 groups. Furthermore, whereas many studies have found significant differences in the postprandial heart rate increment, this was not the case in our study.

Reasons for the difference in our study compared with the literature are the use of a random sample versus a selected population of patients with symptoms and the use of a formula without predefined cut-off points instead of a questionnaire [18,20,21]. The question is whether this small difference in heart rate and hematocrit is clinically relevant or sufficient to support the fluid shift theory. A

review by Vecht et al. [20] has already questioned this supposed relationship. The hypovolemia that has been described during early dumping is often estimated to be quite small (300–700 mL) and could be considered tolerable; it is also present in nonoperated patients and in patients after gastrectomy without complaints, which is in line with our findings.

Another theory behind early dumping is based on the influence of gut hormones. Studies comparing patients with symptoms of dumping to asymptomatic patients support the theory that these hormones are related to the pathogenesis of early dumping [7]. Our study supports and extends this theory by finding increased concentrations of the L-cell hormones GLP-1 and PYY in patients with high suspicion of early dumping.

GLP-1 has multiple effects on several pathways, causing various symptoms, such as influence of the area postrema (causing nausea); stimulation of nitric oxide production (causing tachycardia and hypotension); vasodilatory effect on mesenteric, coronary, and brachial arteries (causing hypotension); and influence on insulin secretion (causing vasodilation and normalization of heart rates after 50–60 min) [22–25]. In support of this theory, treatment with somatostatin-analogues, known to diminish GLP-1 release from L-cells, has been successful in reducing early dumping complaints [14,26].

PYY is known to cause vasoconstriction, increase blood pressure, decrease intestinal motility, and stimulate absorption of nutrients [27–31]. PYY is also shown to decrease VIP-induced secretory diarrhea and inhibit intestinal chloride excretion [32]. As these effects contradict those seen in the immediate reaction of early dumping, it has been suggested as a negative feedback mediator. The effect of PYY would occur after the first phase of signs and symptoms (peak is at 30 min), and it would be higher in the group with most complaints [21,33]. In the present study, we found the concentrations of PYY to be significantly higher in the group with suggestive dumping than in the group with low suspicion. The peak was reached at 30 minutes, later than that of GLP-1, with subsiding levels of hormones thereafter and decreased symptom scores at 60 minutes. GLP-1, which is also released by the L-cells, is known to exert an inhibitory effect on PYY release and may therefore cause the delayed reaction of the PYY response seen in this study without reducing the level of the PYY release, explaining the later occurring peak in PYY compared with the GLP-1 [34]. The anatomy change after RYGB is known to cause an increased density in GLP-1– and PYY-producing L-cells in the perianastomotic jejunum, suggesting an increased direct stimulatory effect [35]. Furthermore, PYY levels are also known to increase as a biological adaptation in gastrointestinal diseases where higher amounts of undigested nutrients are present in the intestines and where VIP levels are raised [32,36,37].

VIP is known to cause a cascade of postprandial reactions upon direct and indirect pathways: a strong vasodilator, it reverses normal intestinal absorption and causes secretory diarrhea, stimulates gastrointestinal transit, relaxes vascular and nonvascular smooth muscle cells, increases heart rate, decreases diastolic blood pressure, and causes symptoms similar to those seen in early dumping [36,38,39]. We had expected to see a higher concentration of VIP in the group high suspicion for early dumping, but we could not confirm this hypothesis in our study.

Some limitations of the study must be mentioned. First, for various reasons, most unrelated to dumping, only 46 patients of the 140 patients in the random sample were tested. The demographic characteristics of the tested patients were not different from the total group of operated patients, but there is still a possibility of selection bias.

Second, we did not use a validated questionnaire for early dumping. After the start of our study (in 2013), Laurenius et al. [2] validated the dumping symptom rating scale, a questionnaire with a 7-point Likert scale. The questions addressing complaints are the same in the dumping symptom rating scale as they are in the DSS. One of the conclusions of Laurenius et al. [2] was that the 7-point Likert scale should be changed to a 4-point Likert scale, as used in the DSS. Also, there is no definition of early dumping in the dumping symptom rating scale; this questionnaire is mainly made for screening in the outpatient clinic to select patients with severe complaints in 1 of the symptoms.

Third, the test meal for an MMTT is not standardized, which is a general shortcoming of meal tests. Although difficult, standardization should be recommended to compare studies in future research.

Conclusion

In conclusion, we found that 26% of the patients who underwent a primary RYGB after a midterm follow-up were highly suspected of early dumping. The gut hormones GLP-1 and PYY are increased in these patients and are therefore implicated in the pathophysiology of early dumping.

Disclosures

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

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.soard.2018.10.004.

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