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Original article

Is testing for postprandial hyperinsulinemic hypoglycemia after gastric bypass necessary?

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SUMMARY

Introduction: Postprandial hyperinsulinemic hypoglycemia (pHH) is an increasingly reported complication after Roux-en-Y gastric bypass (RYGB). As pHH can cause life-threatening emergencies if occurring without warning symptoms, challenge testing may detect patients at risk. The study objective was to determine the frequency of occurrence of pHH with or without symptoms of hypoglycemia after RYGB.
Methods: We undertook an observational cohort study of consecutive, unselected patients approximately one year after uncomplicated RYGB. To simulate normal habits, all patients received a standardized carbohydrate-rich solid mixed meal. Plasma glucose and insulin were measured at 30, 60, 90, 120, and 150 min thereafter. Symptoms were classified as autonomous or neuroglycopenic. Patients with hypoglycemia (plasma glucose <3.0 mmol/L [55 mg/dL]), were tested a second time with a protein-rich solid mixed meal.
Results: 113 patients were included. Total weight loss at the first follow-up check (14 ± 0.4 months) was 33.97 ± 9.3%. After the carbohydrate-rich meal, glucose dropped to <3.0 mmol/L in 13.2% (n = 15) of patients vs no drop to <3.0 mmol/L after a protein-rich meal. The pHH occurred in 11.5% (n = 13) of patients. Asymptomatic patients (5.3%, n = 6) carried an increased risk (p = 0.008) for pHH. One patient needed emergency treatment after sudden loss of consciousness after the carbohydrate-rich meal.
Conclusions: The occurrence of pHH was quite high in our study population with 11.5% thereof 5.3% asymptomatic. We therefore suggest that detection of these patients warrants a screening of patients after RYGB. At-risk patients should than be adequately advised to avoid carbohydrate-rich meals in order to optimize risk management.

1. Introduction

Bariatric surgery is one of the most efficient and durable treatment for severe obesity [1,2]. Because of the growing number of affected patients, utilization of bariatric surgery is increasing worldwide [3]. However, severe obesity is currently incurable, and because patients remain at risk for relapse, the ideal operation would provide lifelong effectiveness with minimal risk. Regardless of the specific bariatric procedure selected, the anatomy and function of the gastrointestinal and humoral systems are changed. The alterations are minimal with adjustable gastric banding (AGB), as the esophagus is mainly affected, and most pronounced following the biliopancreatic diversion. Standard Roux-en-Y gastric bypass (RYGB) holds an intermediate position with respect to alterations and risk-to-benefit ratio.

RYGB is safe and has been performed for decades. Most long-term sequelae are well known and require a lifelong patient follow-up [1]. One of these is postprandial hyperinsulinemic hypoglycemia (pHH). It is generally considered a rare complication affecting ≤1.0% of patients [4–8]. However, pHH can occur with life-threatening neuroglycopenic symptoms (i.e., seizures, disorientation, impairment of vision, eventually loss of consciousness) or without any premonitory symptoms [9–11]. Surgical teams with thousands of patient years under surveillance will eventually be challenged to treat affected patients and prevent accidents or even late deaths related to surgery.

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To date, there is no generally recommended diagnostic procedure to detect pHH [12,13]. Ideally, continuous glucose monitoring (CGM) could be undertaken for every patient, but it is not practical for various reasons, especially cost. Furthermore, its accuracy is debated [14]. Unfortunately, pHH symptoms are not only misleading and in some patients even totally absent, but also there is no validated questionnaire available [14,15].

In our center, we had experience with successful surgical treatment of a marked number of patients with hypoglycemia following RYGB that were not mendable by adding restriction to the gastric pouch [16]. Also, we suspected that the cause of accidents of several patients was pHH. Thus, we decided to screen our patients for pHH by means of a solid mixed meal challenge, which emulated normal eating habits closely with consideration for the expected restriction induced by RYGB. Further, we wanted to study the frequency of occurrence of symptom-free pHH—the most dangerous manifestation of this complication. As carbohydrate-rich solid mixed meals provoke pHH more readily than low-carbohydrate meals, we did both tests to explore the differences in pHH patient symptoms and occurrence rates.

2. Material and methods

We undertook an observational cohort study of consecutive, unselected patients at the time of the first of the five mandatory annual check-ups, 12 months following uncomplicated standard laparoscopic RYGB. The study was conducted at the European Center of Excellence for Bariatric and Metabolic Surgery in Bern, Switzerland, from April 1, 2015, to July 31, 2016.

Patients who fulfilled the following inclusion criteria were able to participate: Those who had undergone RYGB surgery one year previously; were operated on by the same surgeon (RS); had a negative hypoglycemic agent history; had no diagnosis of insulinomas and nesidioblastomas; were ≥18 years old; and were willing to provide oral and written consent. Patients were excluded it they suffered complications following RYGB and required a further surgical intervention in which the anatomy was changed, especially in the region of the gastric pouch.

2.1. Data collection

In order to simulate normal habits, all patients received a standardized solid mixed meal (2 slices of toast with 20 g marmalade, 10 g butter, and unsweetened tea or coffee before the solid food); energy total 201 kcal (834 kJ), carbohydrates 34 g (49.0%), fat 8 g (32.0%), and protein 3.8 g (6.0%) [17]. The challenge tests were performed in our own laboratory in the morning after an overnight fast. Blood samples were drawn from a venous cannula simultaneously with capillary blood tests every 30 min (−5 to +10 min for logistic reasons) until 150 min after the standardized meal. Capillary glucose tests were analyzed in our laboratory. Glucose and insulin in venous blood samples were measured with spectrophotometry or electro-chemiluminescence immunoassay, respectively (Cobas® 8000 modular analyzer, Roche Diagnostics International Ltd, Rotkreuz, Switzerland). In cases with falling glucose or persistent hypoglycemia in capillary tests, further 30-min steps were performed until stable conditions were achieved. Patients with pHH underwent a second solid mixed meal test 1–2 weeks later, but this time with a low-carbohydrate solid mixed meal consisting of almost pure protein (100 g cottage cheese or 150 g low fat quark; energy total 195 kcal [815 kJ], carbohydrates 9 g [18.0%], fat 5 g [22.0%], and protein 26.9 g [60.0%]). Blood sampling was performed as aforementioned, but only up until 120 min. Both provocative test meals were nearly isocaloric.

The criteria described in the American Society for Metabolic and Bariatric Surgery (ASMBS) position statement paper were used as definition of pHH: (1) symptoms occurring >1 year after surgery, (2) normal fasting glucose and insulin levels, (3) correlation of symptoms with hypoglycemia, followed by (4) spontaneous resolution of hypoglycemia and a positive provocative test [12]. Glucose values <3.0 mmol/L (55 mg/dL) was and insulin values >18 pmol/L were the cut-off values used in this study [18]. Symptoms of hypoglycemia were documented with every blood sample and recorded either as autonomous (e.g., sweating, tremor, hunger, palpitation, fatigue) or neuroglycopenic (e.g., fainting, dizziness, vision impairment, confusion, cognitive impairment) [19]. Weight loss was documented as total percentage weight loss % [TWL].

2.2. Ethics approval

This study was conducted in accordance with the ethics guidelines of the 1957 Declaration of Helsinki. Ethics approval for the study was obtained from the local ethics committee (Ethics Board Canton of Bern, Switzerland: Kantonale Ethikkommission Bern KEK Study No. 2016-02090). Each patient provided written informed consent.

2.3. Statistical analysis

Statistical analysis was performed with IBM SPSS Statistics for Windows software, version 21.0 (IBM Corp., released 2012). Some data were assessed using descriptive statistics. Data were expressed as mean ± standard deviation or range for parametric values. Binomial testing was used to calculate the likelihood of asymptomatic pHH after the standard solid mixed meal. The p-values <0.05 were considered to be statistically significant. The statistics were calculated by the Department of Mathematics and Statistics of the University of Bern.

3. Results

A total of 113 consecutive non-selected patients were included in the study. Patients' characteristics are presented in Table 1. Mean pre-operative body mass index (BMI, kg/m^2) was 43.1 ± 5.8 female/male ratio was 84:29. TWL following RYGB intervention was 41.5 ± 13.8 (33.7 ± 7.5%). Ninety-seven patients (85.8%) received a primary RYGB, and 16 patients (14.2%) a secondary RYGB with simultaneous removal of an AGB. Sixty-three cases (55.8%) were banded bypasses (6.5 cm silastic ring). Limb lengths were 80–100 cm biliary and 100–150 cm alimentary. Pouches were

Table 1
Patients characteristics.

Patients characteristics	
Total participants, n	113
Caucasians, n (%)	113 (100)
Sex, [male/female], n (%)	29 (26)/84 (74)
Age [years], mean ± SD	42 ± 12.5
Body weight pre-operative [kg], mean ± SD	122.7 ± 24.9
BMI pre-operative [kg/m^2], mean ± SD	43.1 ± 5.8
Body weight at testing time point [kg], mean ± SD	81.1 ± 18.2
BMI at testing time point [kg/m^2], mean ± SD	28.7 ± 4.9
Total body weight loss [%], mean ± SD	33.9 ± 9.3
Operation	
- Primary RYBP, n (%)	97 (85.8)
- Secondary RYBP with AGB removal, n (%)	16 (14.2)
- Banded bypass, n (%)	63 (55.8)
Time since operation [months], mean ± SD	14.2 ± 0.4

RYBP: Roux-en-Y gastric bypass, AGB: adjustable gastric band, SD: standard deviation.

small along the lesser curvature and had an estimated volume of 20–30 cc.

Tests could be performed as planned in 109 of 113 patients (96.5%). Four patients withdrew for various reasons (e.g., difficulties in blood sampling). The results are presented in Table 2.

After the standardized solid mixed meal, 15 patients (13.2%) were hypoglycemic in 23 blood samples [Figs. 1 and 2]. One patient needed glucose to reach normal blood levels after 120 and 180 min. In all other patients, blood glucose raised to normal without any help. Insulin was >18 pmol/L in 21 samples, respectively 13 patients (11.5%).

One patient fainted and lost consciousness without warning symptoms at 80 min after the standardized carbohydrate-rich solid mixed meal. The patient's last measured glucose value (20 min prior) was 3.2 mmol/L. She had to undergo emergency treatment and hospitalization. Because of the emergency situation, no further glucose test was performed.

The protein-rich meal test was performed in 13 patients (86.7%): two patients withdrew for private reasons. None of the patients had a glucose level of <3.0 mmol/L after the protein-rich solid mixed meal. All remained normoglycemic [Fig. 3].

Twenty-five of 94 (26.6%) normoglycemic patients reported autonomous symptoms, and four, neuroglycopenic symptoms. Further, four patients reported symptoms of both. Among the hypoglycemic patients (n = 15), nine displayed symptoms (60%), six of which had autonomous symptoms. In three patients (20%), autonomous symptoms were also present along with neuroglycopenic symptoms. Six patients (40%) remained asymptomatic during the test, which means that 5.3% of all patients have an asymptomatic pHH. After the protein-rich meal, two patients (15.4%) reported autonomous symptoms.

Table 2
Results of the provocative meal tests.

Solid mixed meal challenge	Carbohydrate-rich	Protein-rich
Patients, n (%)	113 (100)	13 (100)
Plasma values		
Glucose		
- At base line [mmol/L], mean ± SD	4.9 ± 0.6	4.6 ± 0.2
- After 30 min [mmol/L], mean ± SD	8.0 ± 1.9	4.5 ± 0.6
- After 60 min [mmol/L], mean ± SD	5.6 ± 2.0	4.2 ± 0.5
- After 90 min [mmol/L], mean ± SD	4.5 ± 1.5	4.4 ± 0.2
- After 120 min [mmol/L], mean ± SD	4.2 ± 1.0	4.6 ± 0.2
- After 150 min [mmol/L], mean ± SD	4.6 ± 0.7	4.4 ± 0.2
Insulin		
- At base line [pmol/L], mean ± SD	46.3 ± 28.2	43.3 ± 21.6
- After 30 min [pmol/L], mean ± SD	515.8 ± 344.2	286.1 ± 291.8
- After 60 min [pmol/L], mean ± SD	198.8 ± 217.8	85.7 ± 53.3
- After 90 min [pmol/L], mean ± SD	83.5 ± 117.1	45.6 ± 24.5
- After 120 min [pmol/L], mean ± SD	48.5 ± 41.8	33.5 ± 14.5
- After 150 min [pmol/L], mean ± SD	34.2 ± 26.4	26.7 ± 7.3
Symptoms		
Neuroglycopenic symptoms		
- Normoglycemic patients, n (%)	4 (4.3)	N/A
- Onset [min], mean ± SD	48.0 ± 36.0	N/A
- Hypoglycemic patients, n (%)	0 (0.0)	0
- Onset [min], mean ± SD	N/A	N/A
Autonomous symptoms		
- Normoglycemic patients, n (%)	25 (26.9)	N/A
- Onset [min], mean ± SD	52.8 ± 40.7	N/A
- Hypoglycemic patients, n (%)	6 (40.0)	2 (15.3)
- Onset [min], mean ± SD	48.0 ± 36.0	45 ± 15
Both symptoms		
- Normoglycemic patients, n (%)	4 (4.3)	N/A
- Onset [min], mean ± SD	50.0 ± 28.3	N/A
- Hypoglycemic patients, n (%)	3 (20.0)	0 (0.0)
- Onset [min], mean ± SD	37.5 ± 22.5	N/A
No symptoms		
- Normoglycemic patients, n (%)	60 (64.5)	N/A
- Hypoglycemic patients, n (%)	6 (40.0)	10

min: minute, SD: standard deviation.

A likelihood of more than 10.0% for asymptomatic pHH was significant (p = 0.008, binominal test). The incidence of pHH was 0.353 in 46 patients without a band, and 0.269 in 63 patients who had undergone banded RYGB, and were thus less affected by pHH. Significance was not tested because of the non-randomized allocation.

4. Discussion

The purpose of this study was to evaluate the frequency of occurrence of pHH with and without symptoms of hypoglycemia in a sample of our large bariatric outpatient clinic covering 15,000 patient years following RYGB. This issue became urgent because of an unneglectable number of patients who developed presumptive pHH without any symptoms or with neuroglycopenia as a single symptom after RYGB. Most of the reported episodes, including seizures with and without accidents, or epileptic episodes treated in other hospitals often without timed glucose measurements, were assumed but not proven to be caused by pHH. We also suspected pHH to be the underlying cause of accidents suffered by patients either at work, at home, or while in traffic. Again, proof was impossible to establish in these cases because of the lack of timely workup. We did have one patient who, on being found unconscious at home by his wife, was able to have his blood glucose measured by her immediately; it was 1.6 mmol/L (28.8 mg/dL).

Diagnostic thresholds for measurement of hypoglycemia have not been uniformly applied [20]. The American Diabetes Association defined hypoglycemia as any low plasma glucose concentration that puts patients at risk for harm [21]. Whipple's triad is often cited diagnostically as well, which includes hypoglycemia of <3.0 mmol/L (55 mg/dL), the presence of symptoms, and amelioration by correction of low glucose or the spontaneous raise to normal values [12].

The definition of the ASMBS we based on, states (1) symptoms occurring >1 year after surgery, (2) normal fasting glucose and insulin levels, (3) correlation of symptoms with hypoglycemia, followed by (4) spontaneous resolution of hypoglycemia and a positive provocative test [12]. The limitation of these definitions, however, is presence of the symptoms, which may be weak or even totally absent either primarily or by acquisition through hypoglycemia tolerance. Autonomous symptoms can occur when the nadir of the former is reached, and neuroglycopenia with the latter. Most current literature considers pHH a rare complication occurring with a frequency of ≤1.0–2.0% [9]. However there are others who have found the incidence of pHH substantially higher, even up to ≥50.0% [22,23]. Underreporting of this complication should be assumed at its expected time of occurrence, around 1–2 years after surgery, but pHH can also occur beyond 5 years, although it is mainly not recognized and/or reported. In fact, a solid mixed meal tolerance test at one year (such as that used in the current study, resulting in a measured pHH frequency of occurrence of 11.5%, and 5.3% asymptomatic) may underestimate the future frequency of pHH occurrence [24,25].

In our series, 25 patients expressed typical autonomous symptoms for pHH even above the 3.0 mmol/L (55 mg/dL) threshold due to the rapid drop in blood glucose [26]. These patients' chronic fatigue (and that of other patients not reported in this study) even without severe hypoglycemic episodes suggests that our finding of 1.0% is likely not fully representative of the actual pHH incidence.

This means that the true prevalence of pHH in the broad postoperative RYGB population is as unknown as its significance. In the Swedish Obese Subject (SOS) study group, Marsk et al. found only 0.25% experienced pHH in 5040 patients that led to hospitalization [6]. However, diagnostic and detection methods differ. The oral glucose tolerance test (OGTT) is no longer recommended because of

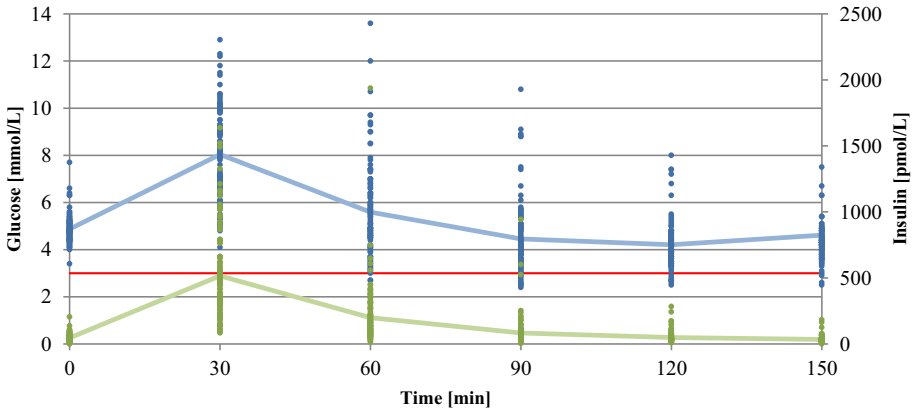

Fig. 1. Plasma-glucose and insulin distribution after the carbohydrate-rich provocative meal in the whole study population.

poor accuracy, and because of the uncertain accuracy of CGM in the hypoglycemic range [20]. Itariu et al. found a high pHH incidence using CGM in 51 patients post RYGB [27]. They showed a 75.0% rate of hypoglycemic episodes with <3.05 mmol/L (54.9 mg/dL) and an astonishing 38.0% of nocturnal hypoglycemia. The same group of patients was tested with a liquid mixed meal tolerance test, and hypoglycemia was found in 29.0%. Although the liquid mixed meal tolerance test is less accurate, this outcome was still far higher than previously reported. The difference between CGM and challenge tests points to the likelihood of false negative results with a far higher true incidence of pHH. In addition, CGM also measures hypoglycemia not related to elevated insulin, e.g. nocturnal episodes, which are perhaps caused by bypass-imposed caloric restriction.

We found 11.5% of patients with pHH, a rate not directly comparable, perhaps because we were using a solid meal challenge test. The solid mixed meals have been evaluated by Bunt et al. and by Shankar et al. in glycemic and hormonal responses in diabetes patients after RYGB but not specific for hypoglycemic testing [28,29].

We wanted to stay as close as possible with allowances made for the bypass-induced restriction of our patients and did use solid mixed meals. We choose carbohydrate-rich and protein-rich solid mixed meals as provocative tests in order to see possible difference, as the carbohydrate load is mainly responsible for the hypoglycemia and the total energy content of the meal has a small effect on the drop in blood sugar level.

Patients who are unaware of pHH are at special risk for emergency situations. In our study, the probability of more than 10.0% of "silent" hypoglycemic episodes was significant. In addition, sensitivity of alarming symptoms was only 23.1%. We suggest that detection of these patients is a priority that warrants a screening of all patients after RYGB [30,31]. Roslin et al., in their editorial comment to Itariu et al.'s findings, emphasized the importance and profound impact of pHH after RYGB [32]. Patients with pHH, especially those with severe episodes must not only be treated, but educated on how to prevent life-threatening situations. The fact that loss of consciousness can occur suddenly is worrisome, as occurred in one of our patients whose last measurement only 20 min prior to the life-threatening event showed only mild hypoglycemia. For this unique case, postural or reflex hypotension was excluded, we didn't have any positive signs for a vasovagal syncope, the patient didn't develop bradycardia nor hypotension, blood pressure was 113/75 mmHg and heart rate was 100 bpm. Loss of consciousness episode could be resolved after an infusion of glucose 20%. A CGM over one week performed later confirmed the appearance of pHH also in this patient.

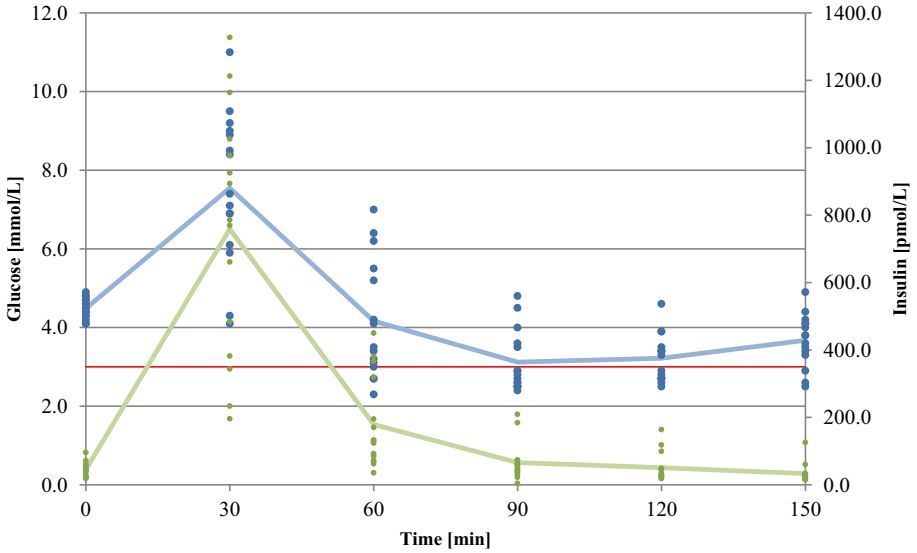

Fig. 2. Plasma-glucose and insulin distribution after the carbohydrate-rich provocative meal in hypoglycemic patients.

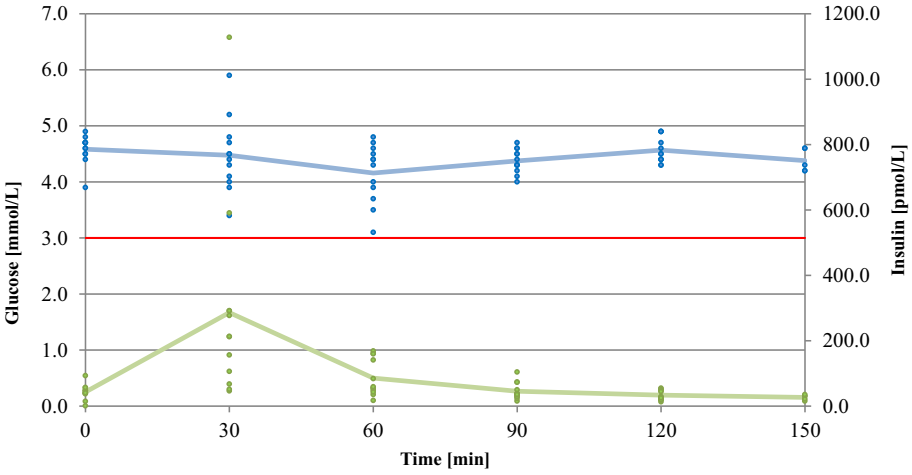

Fig. 3. Plasma-glucose and insulin distribution after the protein-rich provocative meal.

After a meal, impaired driving or poor concentration during other tasks cannot be predicted in these patients. Patients at risk must be detected before neuroglycopenia exposes them to life-threatening situations. If considered from another point of view, only one patient in our study fainted, resulting in an emergency situation. Had she been driving a vehicle, she would have without doubt caused an accident because there was not the slightest warning symptom. Looked at in isolation, pHH in this series caused emergency hospitalizations in <1.0%. This reflects other reports on patients who had to be hospitalized for hypoglycemic emergencies [6].

It is generally accepted that the rapid passage of food through the pouch into the intestine is the trigger for the GLP-1-mediated rapid increase of insulin and subsequent sharp decline in blood glucose [19]. We have shown that restoration of restriction after RYGB slows the passage of food and can improve pHH [16]. In this study, frequency of occurrence of pHH was lower in banded bypass patients (0.269 vs 0.353); however, this could be due to selection bias in the observational study set up. Nevertheless, presence or absence of restriction (as generally occurs in unbanded bypass over the years) appears to be important in development of pHH [33]. This is also suggested because pHH only rarely becomes an issue during the first postoperative year, after which restriction commonly begins to lessen. With these considerations, and because Roslin et al. found less pronounced pHH, we chose a solid food test for our study methodology [1].

Because of the common presence of mild symptoms after RYGB, the key objective is to diagnose patients at risk for sudden loss of consciousness or epileptic seizures, which can occur without warning. Hypoglycemia unawareness can develop in patients with frequent pHH. There is no agreed strong criteria for diagnosis for pHH after RYGB, nor for plasma glucose level which should be used [12,13]. This makes comparison of reports difficult. The appropriate method, time point(s), and frequency of testing remain open questions requiring further investigation.

Our study has limitations. Since none of our patients suffered from diabetes mellitus nor from insulinomas, which represent the main purpose for measuring C-peptide plasma value, we analyzed plasma-glucose and insulin as proposed by the ASMBS, as there is currently no strong consensus or guidelines on how to diagnose pHH after RYGB procedure [12,13]. Second, it is an uncontrolled observational study and patients were not tested before the operation. Further, the heterogeneous and not randomized patient group limits predictive statistical analysis; however, as a consecutive series of patients, our study represents an ideal cohort for practical purposes, and selection bias is avoided.

5. Conclusions

When tested for, the frequency of occurrence of pHH after RYGB is higher than generally reported in the literature and in some affected patients can impose life-threatening risks. The occurrence rate of pHH was quite high in our sample with 11.2%, thereof 5.3% asymptomatic. We therefore, suggest that detection of these patients warrants a screening of all patients after RYGB. Testing with solid mixed meals consents to stay close to the allowances made for the bypass-induced restrictions. At-risk patients should be adequately advised to avoid carbohydrate-rich meals in order to optimize risk management.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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