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Hypoglycemia Following Bariatric Surgery: Our Thirty-One Year Experience

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Abstract

Purpose—Identify the cumulative incidence of post-bariatric surgery hypoglycemia (PBSH), describe its symptomatology, and characterize treatment patterns at a large academic institution.

Materials and Methods—All patients who underwent bariatric surgery at a single institution from 1985–2015 were identified using a clinical database, administrative billing data identified patients who were treated for hypoglycemia, and chart reviews were performed to make a diagnosis of PBSH based on Whipple’s triad. PBSH cases were reviewed including patient diabetes history, symptomatology, and treatment measures. Univariate analyses were performed to identify correlations based on symptomatology, laboratory values, and treatments utilized.

Results—Ninety (2.6%) of 3,487 patients were diagnosed with PBSH with preoperative median age of 43 years, mean BMI of 50.0 kg/m², and median glycated hemoglobin of 6.0%. Median time-to-first hypoglycemic event was 40.6 months. No factors were identified which predict symptom severity or resolution. The 24 (27%) patients who received pharmacotherapy to treat hypoglycemia were younger, had lower nadir blood glucose levels, and more frequent symptoms. Sixty-nine (79%) cases eventually resolved.

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Ethical Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent Statement: For this type of study, formal consent is not required.

Conclusions—PBSH onset and severity are highly variable. Successful management of these patients can prove difficult and should include dietary therapy, the selective use of pharmacotherapy and surgery, and the use of a multidisciplinary team including bariatric surgeons and endocrinologists.

Keywords

post bariatric surgery hypoglycemia; post gastric bypass hypoglycemia; hyperinsulinemic hypoglycemia; PBSH; PBGH

Introduction

Obesity is a major epidemic in the United States, affecting nearly two fifths of the population [1]. Given the magnitude of this problem, it's not surprising that approximately 200,000 bariatric procedures are performed annually [2]. Bariatric surgery has been shown to be the best treatment option for achieving long-term weight loss and improvement in obesity-related comorbid diseases such as hyperlipidemia, type 2 diabetes (T2D), and cardiovascular disease [3, 4, 5, 6]. Many short- and long-term complications of bariatric surgery have been well described including marginal ulcer, stenosis, internal hernia, and dumping syndrome [7, 8, 9, 10]. Post-bariatric surgery hypoglycemia (PBSH), however, has not been as well characterized due to its late onset and rarity [11, 12].

PBSH is diagnosed by the presence of Whipple's triad including symptoms of hypoglycemia, low plasma glucose at the time of symptoms, and relief of symptoms when plasma glucose is raised to normal. It is most commonly post-prandial and usually develops one to several years following bariatric surgery [11]. A 2015 survey-based study found that PBSH may affect up to one third of patients while a nationwide Swedish cohort study showed that only 0.2% of patients undergoing roux-en-Y gastric bypass (RYGB) required hospitalization for PBSH [12, 13]. Early investigators suggested pancreatic nesidioblastosis with resultant hyperinsulinemia as the underlying cause, but further work has shown that PBSH is the result of a multifaceted alteration in glucose homeostasis [11, 14]. Recent studies have identified several risk factors for the development of PBSH such as lower preoperative glycated hemoglobin (A1C) and body mass index (BMI) as well as greater postoperative weight loss [15, 16].

Though recent research has shed some light on PBSH, more knowledge about the natural history of the disease would allow providers to better inform and care for patients. The aims of this study were to identify the cumulative incidence of PBSH, describe its symptomatology, and characterize treatment patterns at a large academic institution.

Materials and Methods

Patients

All patients who underwent bariatric surgery at a large University Health System from January 1, 1985 through December 31, 2015 were identified using clinical database approved by the University Institutional Review Board for Health Sciences Research. This database includes each patient's name, age, sex, preoperative weight and comorbidities,

postoperative complications, postoperative comorbidities, and annual postoperative weights from follow-up appointments. To identify patients who potentially had PBSH, we queried our Clinical Data Repository (CDR) for hypoglycemia-related ICD-9 codes (251.0-hypoglycemic coma; 251.1-other specified hypoglycemia; 251.2-hypoglycemia, unspecified) in the bariatric surgery population.

Definitions

The electronic medical record was accessed and retrospective chart review was performed for all patients who had undergone bariatric surgery and had a diagnosis of hypoglycemia in the CDR. Patients were identified as having PBSH if physician notes and blood glucose laboratory values documented the presence of Whipple's triad, excluding those occurring in the setting of acutely decreased oral intake and improper dosing of T2D medications.

Time-to-first hypoglycemic event was defined as the time in months between surgery and first mention of hypoglycemia in a physician's note. Anti-diabetic medications both preoperatively and at the time of the first hypoglycemic event were categorized as oral medications only, insulin only, both, or none. Autonomic symptoms including irritability, anxiety, nausea, chills, headache, weakness, fatigue, shakiness, palpitations, diaphoresis, and lightheadedness were categorized as mild-to-moderate. Neuroglycopenic symptoms including visual changes, altered mental status, syncope, and seizure were categorized as severe. Episode frequency was classified as daily, weekly, monthly, or less than monthly. Nadir blood glucose was categorized as 0–9 mg/dl, 10–19 mg/dl, 20–29 mg/dl, etc. A patient was considered to be treated with an anti-PBSH medication if they were prescribed one or more of the following: acarbose, verapamil, diazoxide, octreotide, exenatide, or liraglutide. PBSH was considered resolved if a physician's note documented resolution or significant improvement or there were no further mentions of hypoglycemia in clinic notes despite regular follow-up. PBSH was considered unresolved if the most recent clinic note states that the PBSH is not improving or that the patient is still significantly symptomatic. Phone survey was performed for PBSH patients lost to follow-up to determine resolution status.

Statistics

Statistical analyses were performed using χ^2 for categorical variables and either t-test or Mann-Whitney U-test for continuous variables, as appropriate. A *p* value of <0.05 was used for statistical significance. SAS version 9.4 (SAS Company, Cary NC) was used for analyses.

Results

Among 3,487 patients who underwent bariatric surgery at our academic medical center over the 31-year study period, 140 were treated for hypoglycemia. A total of 90 (2.6%) were diagnosed with PBSH following chart review. The remainder had hypoglycemia due to dumping syndrome or improper diabetes medication dosing with or without acutely decreased oral intake. Eighty-eight patients (98%) underwent RYGB and two (2%) underwent sleeve gastrectomy (SG). At the time of surgery, median age was 43 years (IQR 37–51) and median BMI was 50.0 kg/m² (IQR 43.0–54.0). Median preoperative A1C was

6.0% (IQR 5.6–8.3). While only 22 (24%) patients were prescribed T2D medications preoperatively, even fewer (19%) were on T2D medications at the time of their first hypoglycemic event. The median time-to-first hypoglycemic event was 40.6 (IQR 13.3–77.4) months.

All PBSH patients were initially treated with dietary modifications for prevention of future episodes and glucose pills for symptomatic relief. Twenty-four (27%) patients required pharmacologic treatment. In general, patients who received dietary-only therapy were treated in our multidisciplinary surgery clinic which includes dietitians, and those who underwent pharmacologic treatment were seen by endocrinologists. Three (3%) patients underwent invasive therapies for PSBH. Two had gastrostomy tube placement with feeds into the gastric remnant. Of these two, one had resolution of symptoms and subsequently underwent conversion of RYGB to SG with complete PBSH resolution despite a decrease in BMI from 43.6 kg/m² to 38.5 kg/m² over the following year. One additional patient with frequent, severe PBSH episodes despite trials of multiple medications also underwent conversion of RYGB to SG and has had no hypoglycemic episodes in the two months since her surgery. Eleven of the 14 patients lost to clinical follow-up were able to be reached by telephone to have their resolution status determined, resulting in a 97% follow-up rate. Overall, 65 (75%) patients eventually had resolution of their PBSH.

There were no statistical differences between those who experienced severe symptoms and those who had only mild-to-moderate symptoms, including nadir blood glucose levels, as detailed in Table 1. Nadir blood glucose was not associated with preoperative A1C, or T2D medications either preoperatively or at the time of first event. Patients with a nadir blood glucose <40 mg/dl presented later than those with a higher nadir blood glucose (23.5 months vs 48.2 months, $p=0.049$).

The differences in characteristics between the 24 patients who were treated pharmacologically versus the 66 who only required dietary modification are displayed in Table 2. Younger patients (38.6±8.5 years vs 44.1±10.4 years, $p=0.01$) and those with a lower nadir blood glucose (35.0±11.8 mg/dl vs 44.5±14.8 mg/dl, $p=0.01$) were more likely to be started on medications. Though only patients with at least weekly symptoms were treated pharmacologically (39% vs 0%, $p=0.001$), the severity of symptoms did not correlate with the likelihood of being prescribed PBSH medications.

Of the 65 patients whose PBSH resolved, 55 (80%) resolved without pharmacologic treatment and only 14 (58%) patients who required medications eventually resolved. The differences between patients with resolution and those without are listed in Table 3. Of note, neither age, nor preoperative A1C, nor timing of onset correlates with the likelihood of resolution. Preoperative BMI did not affect the natural history of PBSH or its treatment.

Discussion

The present study aimed to describe the epidemiology and symptomatology of PBSH and to identify treatment patterns at a large academic institution. Through the use of clinical databases and chart review, we identified the patients in our cohort who developed PBSH

and characterized their disease and treatments. To our knowledge, this is the largest series of PBSH to date.

We found a 2.6% cumulative incidence of PBSH in patients who underwent bariatric surgery at our institution. The fact that incidences ranging from less than 1% to greater than one third of patients have been reported is in large part due to studies using different definitions [12, 13, 16]. This highlights a major issue at play. In order to be better able to treat our patients, we need a consensus definition for the diagnosis of PBSH and consensus guidelines for its workup and management. Lee et al. reported an incidence of PBSH of 13.1% at 5 years, which is substantially higher than the current findings [16]. Over 60% of their patients were diagnosed only by the presence of any postoperative blood glucose between 40 and 60 mg/dl or any postoperative diagnosis of hypoglycemia. Fifty patients (36% of patients with hypoglycemia in our cohort) were excluded from our definition when chart review revealed either acutely decreased oral intake, improper dosing of T2D medications, and/or symptoms consistent with dumping syndrome. In a 20-year Swedish nationwide study, Marsk et al. reported that 0.2% of bariatric surgery patients required hospitalization for hypoglycemia with a median follow-up time of 32.4 months [12]. Lee et al. found a 0.7% incidence of severe PBSH at five years [16]. In the current study, the incidence of severe symptoms was similar at 0.9% with a mean time-to-first hypoglycemic event of 67 months. When differences between our and others' definitions are taken into account, our reported incidences are in line with prior studies and likely represent patients with hypoglycemia attributable to their surgery. Interestingly, we also found that patients with lower blood glucose levels tend to present later. Recent studies suggest that bariatric surgery can lead to an attenuated counter-regulatory hormone response to hypoglycemia and that there are many bariatric surgery patients with asymptomatic hypoglycemia [14, 17]. It is possible that these patients have some level of hypoglycemic unawareness so only developed symptoms at more extreme levels of hypoglycemia, and therefore had delayed presentation of PBSH.

As the pathophysiology and natural history of PBSH are incompletely understood, there are no widely-accepted guidelines for its management. Rariy et al. recently published a review with a proposed treatment algorithm [18]. In short, they recommend starting with dietary interventions with the addition of acarbose if neuroglycopenic symptoms are present. For continued symptoms, they recommend octreotide followed by a calcium channel blocker or diazoxide. Our institution takes a pragmatic approach to the diagnosis and treatment of PBSH. We check serum glucose, insulin, c-peptide, and a sulfonylurea screen at the time of hypoglycemia. We then begin treatment unless atypical symptoms are present, such as fasting or overnight hypoglycemia, which would instead prompt a more thorough evaluation including cross-sectional imaging and a mixed-meal tolerance test. Throughout the entire 31-year study period, the presence of neuroglycopenia was not associated with an increased likelihood of being started on pharmacotherapy. Over the past few years, however, our endocrinologists have been more aggressive with prescribing PBSH medications in patients with neuroglycopenic symptoms such as vision changes, syncope, and seizures as these carry a risk for substantial risk of severe injury and death. Importantly, neuroglycopenic symptoms did not correlate with preoperative BMI or A1C, timing of PBSH onset, nadir blood glucose levels, or frequency of episodes. Given that there are no trials comparing the various pharmacologic agents for PBSH, prescribing at our institution is based on cost and

side effect profiles. Accordingly, 88% of patients received acarbose as their first-line medication. If symptoms persist, we recommend a trial of each agent before moving to more invasive therapies. A recent review by Mala found that pancreatic resection was the most common surgical treatment for PBSH with 34/51 (67%) patients experiencing resolution [19]. Reversal of RYGB was the second most common procedure with 13/17 (76%) cases resolving, five of which included a concomitant SG to reduce weight gain. Only three patients at our center required surgery: one had placement of a gastric tube with subsequent removal due to continued symptoms while the other two underwent conversion from RYGB to SG and have done well since.

The strengths of our study include the use of a large validated clinical database with long-term follow-up, prospectively collected for the past 31 years and the use of extensive chart review. By reviewing individual charts, patients diagnosed with hypoglycemia who did not have PBSH were excluded. In addition, detailed information was obtained for those patients with PBSH regarding their disease and treatment courses. This study has multiple limitations including its retrospective nature. Patients who may have been evaluated for PBSH outside of our institution would not have been captured which may lead to underestimating the true incidence. Patients who underwent surgery in the last three years have had a shorter follow-up time than the median time of onset which could also lead to an underestimation. Fourteen patients included in the PBSH group were on insulin or a sulfonylurea at the time of hypoglycemia. Though we attempted to exclude all cases of medication-induced hypoglycemia, some of these may not have been true PBSH which may overestimate the incidence of PBSH.

Conclusion

PBSH onset and severity are highly variable. Given the natural history of PBSH, physicians caring for bariatric surgery patients should be aware that patients who present later tend to have lower blood glucose nadirs and that no factors associated with severity or resolution could be identified. As successful management of these patients can prove difficult, there is the need for a consensus definition of PBSH to facilitate further research and to direct guidelines for its diagnosis and treatment.

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Table 1

Patient Characteristics by Symptom Severity

Variable	Severe (n=32)	Mild-Moderate (n=58)	p-value
Age (Years)	43.1 ± 11.8	42.3 ± 9.2	0.72
Sex (Female)	30 (93.8%)	48 (83.4%)	0.11
Preoperative BMI (kg/m ²)	48.9 ± 7.0	51.1 ± 11.0	0.25
No Preoperative Diabetes Treatment	26 (81.3%)	42 (71.2%)	0.60
Preoperative Insulin	7 (21.9%)	9 (15.3%)	0.43
Preoperative A1C (%)	7.1 ± 2.1	6.9 ± 1.7	0.75
Time-to-First Hypoglycemia (Months)	67.2 ± 69.1	53.7 ± 50.1	0.72
Nadir blood glucose <40 mg/dl	22 (39.3%)	34 (60.7%)	0.29
Insulin at Hypoglycemia	4 (12.5%)	8 (13.6%)	0.89
Resolution of Symptoms	21 (65.6%)	47 (79.4%)	0.11

BMI, body mass index; A1C, glycated hemoglobin

Table 2

Patient Characteristics by Treatment Regimen

Variable	Dietary and Pharmacotherapy (n=24)	Dietary Alone (n=66)	p-value
Age	38.6 ± 8.5	44.0 ± 10.4	0.02
Sex (Female)	22 (91.7%)	56 (84.8%)	0.62
Preoperative BMI (kg/m ²)	49.5 ± 7.6	50.7 ± 10.5	0.61
No Preoperative Diabetes Treatment	17 (70.8%)	51 (77.3%)	0.17
Preoperative Insulin	4 (16.7%)	12 (18.2%)	0.89
Preoperative A1C (%)	6.5 ± 1.6	7.2 ± 2.0	0.29
Time-to-First Hypoglycemia (Months)	38.7 ± 32.0	65.5 ± 62.9	0.01
Severe Symptoms	9 (37.5%)	23 (34.8%)	0.78
Nadir blood glucose <40 mg/dl	19 (79.2%)	37 (56.1%)	0.04
Insulin at Hypoglycemia	2 (8.3%)	10 (15.2%)	0.41
Resolution of Symptoms	14 (58.3%)	51 (77.3%)	0.03

BMI, body mass index; A1C, glycated hemoglobin

Table 3

Patient Characteristics by Resolution

Variable	Resolved (n=65)	Not Resolved (n=22)	p-value
Age	43.2 ± 10.5	42.3 ± 9.0	0.72
Sex (Female)	55 (84.6%)	20 (90.9%)	0.46
Preoperative BMI (kg/m ²)	51.0 ± 9.8	49.1 ± 6.9	0.40
No Preoperative Diabetes Treatment	49 (75.4%)	17 (77.3%)	0.77
Preoperative Insulin	11 (16.9%)	4 (18.2%)	0.89
Preoperative A1C (%)	7.0 ± 1.9	6.7 ± 1.9	0.63
Time-to-First Hypoglycemia (Months)	58.4 ± 59.1	55.2 ± 57.1	0.82
Nadir blood glucose <40 mg/dl	37 (56.9%)	14 (68.7%)	0.34

BMI, body mass index; A1C, glycated hemoglobin