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BRIEF COMMUNICATION

Hypoglycemia after Roux-en-Y Gastric Bypass: The BOLD Experience

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Background

Obesity is a global epidemic associated with higher mortality and increased incidence of type 2 diabetes, hypertension, and obstructive sleep apnea [1]. Although dietary and lifestyle interventions can achieve modest weight loss, they are difficult to sustain over the long-term [2]. Patients are increasingly turning to bariatric surgery to achieve greater weight loss and increase remission of type 2 diabetes, hypertension, and obstructive sleep apnea. Roux-en-y gastric bypass (RYGB) is one of the most commonly performed bariatric procedures due to its safety (mortality ~0.5 %), efficacy in weight loss (~60 % excess weight lost), and disease remission (77 % for type 2 diabetes, 62 % for hypertension, 86 % for obstructive sleep apnea) [3].

However, these impressive postoperative outcomes are tempered by the development of metabolic, nutritional, and cosmetic complications. Hypoglycemia after RYGB is a troublesome metabolic complication that typically develops 6 months or more after RYGB and usually occurs after a meal. An estimated 671,959 bariatric procedures were performed in the USA between 2003 and 2008 [4]. In 2008 alone, an estimated 344,221 bariatric procedures were performed in the world and 124,838 in the USA, respectively [4, 5]. Since RYGB is one of the most commonly performed bariatric procedures in the world, it is essential for patients to be aware of the true risk for post-RYGB hypoglycemia prior to surgery [4, 5].

Two independent studies by Marsk and Kellog estimated the incidence of post-RYGB hypoglycemia to be 0.2 % and 0.36 % in 5,040 and 3,082 subjects, respectively [6, 7]. Although the low incidence of hypoglycemia reported in these studies is reassuring, there were some methodological limitations in both studies. The Marsk study included only Swedish subjects which limits its applicability to the more ethnically diverse US population [6]. The Kellog study was from a single center which increases the odds for institutional bias [7]. A large prospective outcomes database of US patients

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undergoing bariatric surgery would overcome the methodological limitations of the Marsk and Kellog studies and provide a better estimate of the incidence of post-RYGB hypoglycemia.

The Bariatric Outcomes Longitudinal Database (BOLD) administered by the Surgical Review Corporation (SRC) contains prospective data on US patients who have undergone bariatric surgery. BOLD (NCT01002352) is registered on www.clintrials.gov and has a stated aim "to assess the mid- and long-term outcomes of bariatric surgeries and to analyze the relationship between these outcomes and …patient demographics and co-morbidities". We obtained written permission from the SRC to analyze data on 275,618 patients within BOLD who had undergone Roux-en-y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), or sleeve gastrectomy (SG), respectively.

Our primary study objective was to characterize the incidence of hypoglycemia after Roux-en-y gastric bypass and to determine if any pre- or postoperative factors predicted a higher risk for post-RYGB hypoglycemia. Our secondary study objective was to characterize incidence of hypoglycemia after LAGB and SG as these two procedures are the two most commonly performed bariatric procedures after RYGB.

Methods

BOLD Database

A BOLD data access request was submitted and approved by the SRC for access to the BOLD data on patients undergoing RYGB, LAGB, and SG, respectively. All procedures were performed by Bariatric Surgery Centers of Excellence or Fellows of the American Society for Metabolic and Bariatric Surgery. Our institutional review board (IRB) reviewed our study and deemed it exempt from IRB oversight because the BOLD data lacked patient identifiers.

Subjects

All patients undergoing RYGB, LAGB, and SG were included in the BOLD dataset. Hypoglycemia was self-reported by the patients and listed as an adverse event in BOLD. Incidence of hypoglycemia was calculated as the total number of self-reported cases of hypoglycemia postoperatively after each particular bariatric procedure (i.e. RYGB, LAGB, and SG) divided by the total number of the specific bariatric procedure performed. Age, gender, ethnicity, living status (i.e. alive or dead), weight in kilograms, and BMI pre- and post- procedure were assessed for statistical association with hypoglycemia only in the RYGB patients.

Incidence of hypoglycemia was also calculated for a subgroup of hypoglycemic patients in BOLD who were on no diabetic medicines or insulin prior to bariatric surgery. Demographic variables (age, gender, ethnicity, living status, and pre- and post-procedure weight) were assessed for statistical association with hypoglycemia in only the RYGB patients,

Statistical Analysis

The number of patients self-reporting hypoglycemia after LAGB and SG patients was reported as summary statistics on the recommendation of our statistician (A.I.) due to low event numbers. Statistical analysis was only conducted on self-reported hypoglycemia after RYGB. A Fisher exact test was used to examine the statistical association between hypoglycemia and race (i.e. Caucasian, African-American), gender (i.e. male, female), and living status (i.e. living or dead). An independent samples t test was used to determine if a statistical association existed between hypoglycemia and age. An independent samples Mann-Whitney test was used to determine if a statistical association existed between hypoglycemia and pre- and postoperative weight.

Results

RYGB was the most commonly performed procedure (145,582 cases) followed by LAGB (100,106 cases) with sleeve gastrectomy (29,930 cases) a distant third (Table 1). The incidence of self-reported hypoglycemia post-procedure was 0.1 % for RYGB, 0.01 % for LAGB, and 0.02 % for SG, respectively (Table 1). There was no statistically significant association between post-RYGB hypoglycemia and age (p=0.087), Caucasian (p=0.6106) or African-American (p=0.8646) race, gender (p=0.789), and living status (p=0.2322) (Table 2). Furthermore, there was no statistically significant association between post-RYGB hypoglycemia and preoperative BMI (p=0.858) or weight (p=0.825) or post-operative BMI (0.387) or weight (p=0.511), respectively (Table 2).

Table 1 Incidence of hypoglycemia after bariatric surgery

	Hypoglycemia (none reported)	Hypoglycemia (reported)	Incidence (%)
Roux-en-Y gastric bypass	145,500	82	0.1
Laparoscopic adjustable gastric banding	100,091	15	0.01
Sleeve gastrectomy	29,923	7	0.02
Total	275,514	104	–

Table 2 Statistical association of hypoglycemia with weight loss and demographic variables

	Statistical test	*P* value	Statistical significance
Weight (kg) before RYGB	Mann-Whitney	0.825	NS
Weight (kg) after RYGB	Mann-Whitney	0.511	NS
BMI before RYGB	Mann-Whitney	0.858	NS
BMI after RYGB	Mann-Whitney	0.387	NS
Age	Independent samples *t* test	0.087	NS
Gender	Fisher's exact test	0.789	NS
Caucasian race	Fisher's exact test	0.6106	NS
African-American race	Fisher's exact test	0.8646	NS
Living status	Fisher's exact test	0.2322	NS

When patients on diabetic medications and/or insulin prior to bariatric surgery were excluded, the incidence of hypoglycemia after bariatric surgery was much lower (Table 3). RYGB had an incidence of 0.02 %, sleeve gastrectomy 0.01 % and gastric banding 0 %.

There was also no statistically significant association between hypoglycemia and age, gender, race, living status, or weight loss (Table 4). With regards to glucose metabolism, 73 % of the patients in this cohort had normal glucose metabolism pre-RYGB (17 % elevated fasting glucose, 10 % DM 2) and this percentage increased to 90 % after RYGB.

Conclusion

We found a 0.1 % incidence of post-RYGB hypoglycemia in 145,582 patients within the BOLD database. However, when we excluded patients on diabetic medicines and/or insulin prior to RYGB, the incidence was even lower at 0.02 %. This is reassuring considering that RYGB is one of the most commonly performed bariatric procedures in the world. Our calculated incidence is lower than the 0.2 % and 0.36 % incidences reported by Marks and Kellogg, respectively which may be due in part to a larger sample size [6, 7].

Table 3 Incidence of hypoglycemia after bariatric surgery in patients on no diabetic medicines or insulin prior to RYGB

	Hypoglycemia (none reported)	Hypoglycemia (reported)	Incidence (%)
Roux-en-Y gastric bypass	145,500	30	0.02
Laparoscopic adjustable gastric banding	100,091	1	0
Sleeve gastrectomy	29,923	3	0.01
Total	275,514	34	–

A majority of patients experiencing hypoglycemia post-RYGB did not have abnormal glucose metabolism before RYGB (73 %). We found no statistically significant association between hypoglycemia and age, gender, Caucasian or African-American race, and weight loss in all post-RYGB patients reporting hypoglycemia including the subgroup of patients who were on no diabetic medicines or insulin prior to RYGB. Our results indicate that neither demographic characteristics (i.e. age, gender, race, living status) nor degree of pre- and post-operative weight confers an increased risk for post-RYGB hypoglycemia.

The strengths of this study are the very large cohort of Roux-en-Y patients (145,582) used in the analysis, the predominantly US patient population, and the prospective nature of the data collection. The primary weakness of this study is that hypoglycemia was self-reported and was not verified by blood glucose monitoring and we also could not determine what medications patients were on post-RYGB. Symptoms of nervousness, tachycardia, and lightheadedness are nonspecific and can be due to hypoglycemic or other medical conditions like anxiety, depression, or panic attacks. Therefore, we cannot exclude the possibility of under or over reporting of hypoglycemia due to absence of objective blood glucose monitoring data. A systemic approach to measuring venous blood glucose levels in post-RYGB patients is the only accurate way of determining the true incidence of post-RYGB hypoglycemia.

Hypoglycemia after Roux-en-y gastric bypass is a metabolic complication first described in 2005 and subsequently confirmed by others [8–11]. The initial reports described patients with severe postprandial hypoglycemia refractory to diet and medical therapy who underwent extensive pancreatic resection (i.e. Whipple surgery) for concern of nesidioblastosis [8–11]. The postsurgical specimens were felt to show evidence of nesidioblastosis but others have disputed these conclusions because the controls group had pancreatic

Table 4 Statistical association of hypoglycemia with weight loss and demographic variables in patients on no diabetic medicines or insulin prior to RYGB

	Statistical test	*P* value	Statistical significance
Weight (kg) before RYGB	Mann-Whitney	0.632	NS
Weight (kg) after RYGB	Mann-Whitney	0.632	NS
BMI before RYGB	Mann-Whitney	0.923	NS
BMI after RYGB	Mann-Whitney	0.924	NS
Age	Independent samples *t* test	0.122	NS
Gender	Fisher's exact test	0.2445	NS
Caucasian race	Fisher's exact test	0.119	NS
African-American race	Fisher's exact test	1.00	NS
Living status	Fisher's exact test	1.00	NS

cancer [8, 9]. Butler and colleagues found no evidence of nesidioblastosis in pancreatic specimens taken from six patients with post-RYGB hypoglycemia when compared to pancreatic specimens of lean and obese controls [12]. Another study by Goldfine and colleagues suggested a role for excessive glucagon-like-petide-1 (GLP-1) release after meals in the etiology of post-RYGB hypoglycemia [13]. However, a more recent study by Salehi et al in which a GLP-1 antagonist was infused continuously showed no difference in insulin secretion rates between euglycemic and hypoglycemic post-RYGB patients [14]. Therefore, there appear to be additional unknown mechanism(s) involved in post-RYGB hypoglycemia.

The severity and frequency of post-RYGB hypoglycemia spans a continuum but an adverse impact on quality of life is uniformly felt by all patients suffering from this complication. Dietary counseling consisting of a lower carbohydrate diet is initially offered to patients [7, 15]. For those patients failing diet, anecdotal reports of improvements with diazoxide, octreotide, acarbose, and calcium-channel blockers have been reported (16–19). For those failing medical therapy, placement of a gastric band on the newly created stomach pouch has been effective in some cases [16]. However, performing a Whipple's procedures for post-RYGB hypoglycemia has been largely abandoned even by the initial proponents of this procedure due to its invasiveness and variable effectiveness.

The results from this and other studies suggest that the vast majority of patients undergoing RYGB will be spared from experiencing post-RYGB hypoglycemia. However, for those unfortunate individuals who have to deal with hypoglycemia, it can be an extremely frustrating and difficult experience for both the patient and provider. More studies are needed to systematically measure venous or serum blood glucose before and after RYGB to truly characterize the incidence of hypoglycemia. More research is also needed to better understand the mechanism(s) underlying post-RYGB hypoglycemia. A better understanding of this complication could lead to more effective clinical treatments and could also inform us of the key mechanism(s) responsible for RYGB's glucose lowering effect.

Author Contributions H.S. wrote the manuscript, W.H.C. contributed to the discussion, J.R.P. contributed to the discussion, A.I. researched and statistically analyzed the data, A.J.D. contributed to the discussion, W.J.P. contributed to the discussion, M.S.D. wrote the manuscript, researched the data, and reviewed/edited the manuscript.

Conflict of Interest All authors have no conflicts of interest to disclose.

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