Original article

Glycemic variability and hypoglycemia before and after Roux-en-Y Gastric Bypass and Sleeve Gastrectomy – A cohort study of females without diabetes

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Abstract

Background: Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) lead to lower fasting glucose concentrations, but might cause higher glycemic variability (GV) and increased risk of hypoglycemia. However, it has been sparsely studied in patients without preoperative diabetes under normal living conditions.

Objectives: To study 24-hour interstitial glucose (IG) concentrations, GV, the occurrence of hypoglycemia and dietary intake before and after laparoscopic RYGB and SG in females without diabetes.

Setting: Outpatient bariatric units at a community and a university hospital.

Methods: Continuous glucose monitoring and open-ended food recording over 4 days in 4 study periods: at baseline, during the preoperative low-energy diet (LED) regimen, and at 6 and 12 months postoperatively.

Results: Of 47 patients included at baseline, 83%, 81%, and 79% completed the remaining 3 study periods. The mean 24-hour IG concentration was similar during the preoperative LED regimen and after surgery and significantly lower compared to baseline in both surgical groups. GV was significantly increased 6 and 12 months after surgery compared to baseline. The self-reported carbohydrate intake was positively associated with GV after surgery. IG concentrations below 3.9 mmol/L were observed in 14/25 (56%) of RYGB- and 9/12 (75%) of SG-treated patients 12 months after surgery. About 70% of patients with low IG concentrations also reported hypoglycemic symptoms.

Conclusions: The lower IG concentration in combination with the higher GV after surgery, might create a lower margin to hypoglycemia. This could help explain the increased occurrence of
Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG), the 2 most common metabolic and bariatric procedures, result in vast metabolic changes with lower fasting blood glucose concentrations and frequent remission of Type 2 diabetes mellitus [1]. However, glucometabolic alterations might also lead to higher postprandial glycemic variability (GV), which may be the result of high glucose peaks, low nadirs, or a combination; increasing the risk of hypoglycemia [2]. In a meta-analysis, the mean prevalence of hypoglycemia, assessed with continuous glucose monitoring 1–8.9 years postoperatively, was 56.1% and 42.2% for RYGB- and SG-treated patients, respectively. Time since surgery was positively associated with the prevalence [3]. Hypoglycemia can impair quality of life and cause life-threatening accidents [4,5]. Moreover, the amount and quality of carbohydrates consumed have been indicated as the most important factors for glycemic response in subjects with an intact digestive system [6], and despite a lowered self-reported intake of carbohydrates after RYGB, carbohydrates seemed to have a larger impact on GV postoperatively [7].

Longitudinal studies on GV, hypoglycemia and its association with dietary intake before and after RYGB and SG are sparse. Therefore, our primary aim was to investigate 24-hour interstitial glucose (IG) concentrations, GV, and the occurrence of hypoglycemia under normal living conditions before and after RYGB and SG, in a cohort of female patients without diabetes. Our secondary aim was to examine whether macronutrient intake was associated with GV.

Materials and methods

This was a prospective, longitudinal, observational study of female patients with a body mass index (BMI) of ≥35 kg/m², accepted for laparoscopic RYGB or SG. Exclusion criteria and our operative techniques have been described previously [8–11]. The participants were recruited during routine medical assessments and gave written informed consent. The study was approved by the Uppsala Regional Ethics Committee (Dnr.2016/068) and conducted in accordance with the Declaration of Helsinki [12].

We performed CGM, open-ended food-recording and pedometer readings over 4 days at 4 study periods: 10 weeks (baseline) and 1 week before surgery (low-energy diet, LED regimen), then at 6 and 12 months postoperatively (Supplemental Fig. 1). Body weight (BW) and height were measured at the start of each study period.

Diet

Except during the LED regimen, patients continued with their usual diet. No calorie goal was recommended postoperatively, but patients were advised to have a daily intake of ≥60 grams of protein [13]. Postoperatively, supplements were prescribed in accordance with guidelines [14]. During the 4 study periods, patients reported their dietary intake in a paper-based, open-ended food record, and step counts were registered as previously described [9].

Continuous glucose monitoring

The Minimed IPRO-2 CGM system (Medtronic, Northridge, CA, USA) was used to measure glucose concentrations in the extracellular interstitial fluid continuously for 4 days in each study period, but only data for the last 3 days were analyzed, according to recommendations [15]. Diurnal (24 hour) mean IG concentrations were calculated, as well as the mean amplitude of glycemic excursions (MAGE), which is a common measure of GV [16]. Cut-off level for high MAGE was 2.8 mmol/L and for low glucose concentrations <3 mmol/L and 3.0 to <3.9 mmol/L [4,17]. A hypoglycemic episode was defined as at least 3 consecutive CGM readings at low glucose concentrations [18].

Edinburgh Hypoglycemia Scale

Twelve months postoperatively, patients were asked to complete a translated version of the Edinburgh Hypoglycemia Scale, rating each of the 18 symptoms from 1 (none) to 7 (very severe) (Supplemental Fig. 2). Symptoms rated as moderate trouble or worse [4–7] indicated hypoglycemia [19].

Statistics

We used a linear mixed-effect model with study period (baseline, LED regimen, 6 and 12 months postoperatively), surgical technique, and their interactions as fixed effects; a random intercept for patients, and a compound symmetric correlation structure. Based on this model, marginal means were computed for 24-hour IG concentrations and MAGE per surgical group and study period. We compared RYGB and SG per study period and changes over time within each surgical group. In our secondary analysis, we examined possible associations between risk factors and MAGE after surgery, adjusting for test period (6 and 12 months postoperatively) and surgical technique. Hence, 5
theoretically motivated models were chosen, i.e., a reference model and 4 different models including: 1) step counts, protein, fat, carbohydrates and fiber in g/kg BW, 2) carbohydrates and fiber, 3) fiber, and 4) carbohydrates. The model including carbohydrates was selected based on the Bayesian Information Criteria (BIC) and Akaike’s Information Criterion (AIC). Lastly, we dichotomized data according to cut-off levels for low IG concentrations and the Edinburgh Hypoglycemic Scale to calculate the percentage of patients having hypoglycemic episodes and hypoglycemic symptoms. Normality was checked using Q–Q plots, and the level of significance was two-sided ($P < .05$) for all analyses. We used IBM SPSS Statistics for Windows version 26.0 (IBM Corp, Armonk, NY, USA) and lme package v3.1-149 in R v 4.0.3.

Results

Baseline data and body weight changes

Of the 47 included patients, 83%, 81%, and 79% completed the remaining 3 study periods (Supplemental Fig. 1). The median age before surgery was 37 [17] years with no difference between the 2 groups. At baseline, BMI was significantly higher in patients undergoing RYGB rather than SG, 45.3 ± 5.7 versus 39.5 ± 4.5 kg/m², $P = .001$, respectively. However, at 12 months postoperatively BMI did not differ between groups, 31.2 ± 6.6 versus 27.9 ± 3.5 kg/m², $P = .107$, (Supplemental Table 1).

Interstitial glucose concentrations and GV

The mean 24-hour IG concentration was similar for both RYGB and SG within each study period, except being significantly lower in SG at 6 months (Supplemental Table 2A). Compared to baseline, the mean 24-hour IG concentrations were lower in both groups during the preoperative LED regimen, as well as at 6 and 12 months (Fig. 1A, Supplemental Table 2A and B).

MAGE increased continuously in both groups from baseline to 12 months postoperatively (Fig. 1B, Supplemental Table 2A and B). However, RYGB had a more pronounced increase than SG, reaching a significant difference between groups at 6 months (Supplemental Table 2A). Furthermore, when applying the suggested normative cut-off level for MAGE, 18/25 (72%) RYGB and 6/12 (50%) SG had MAGE $\geq 2.8$ mmol/L at 12 months, $P = .189$ (RYGB versus SG).

Hypoglycemic episodes detected by CGM

The CGM data showed an increasing prevalence of hypoglycemic episodes over time in both groups, 56% of RYGB and 75% of SG having glucose concentrations below 3.9 mmol/L at 12 months (Fig. 2).

Hypoglycemic symptoms

The Edinburgh Hypoglycemia Scale was completed by 34 patients (RYGB N = 23, SG N = 11) at 12 months (Supplemental Fig. 3A and B). The number of patients rating at least one symptom as moderate or worse was similar after RYGB and SG, 17/23 (74%) versus 8/11 (73%) respectively, $P = .888$. About 70% of patients with IG concentrations $< 3.9$ mmol/L at 12 months reported moderate to severe hypoglycemic symptoms with no differences between groups, 10/14 (71%) versus 6/9 (67%) of RYGB and SG respectively, $P = .809$.

![Fig. 1. Estimated marginal means and 95% CI based on linear mixed model for 24-hour interstitial glucose concentrations in RYGB and SG patients for each of the 4 study periods. (A) Compared to baseline, the mean 24-hour interstitial glucose concentrations were significantly lower during the LED regimen and at 6 and 12 months after surgery for RYGB and SG. At 12 months, no differences were seen between the 2 procedures. (B) A continuous increase was observed in both groups from baseline to the final follow-up 12 months after surgery. RYGB had a more pronounced increase, reaching a significant difference between the groups at 6 months after surgery. Baseline is 10 weeks before surgery. LED regimen is 1 week before surgery. MAGE = Mean Amplitude of Glycemic Excursions; RYGB = Roux-en-Y Gastric Bypass; SG = Sleeve Gastrectomy; LED = Low-Energy Diet.]
Diurnal glucose curves and dietary intake

As visualized in Figure 3A and B, the fluctuations in individual 24-hour glucose curves were higher 12 months postoperatively compared to baseline, but with similar carbohydrate intake patterns (Supplemental Fig. 4A and B). However, the self-reported total daily carbohydrate intake 12 months after surgery was significantly reduced in RYGB compared to baseline, $147.4 \pm 53.3$ versus $199.9 \pm 67.1$, $P < .001$, while a trend was seen in SG, $158.1 \pm 68.6$ versus $187.0 \pm 76.1$, $P = .066$. At the same time, carbohydrate intake estimated in g/kg BW increased at 12 months compared to baseline in both groups (RYGB $P = .015$, SG $P = .033$) (Supplemental Table 3). Similar patterns were observed for energy intake and the other macronutrients, namely, lower total reported intakes at 12 months, but higher intakes when assessed in g/kg BW. The self-reported total energy and carbohydrate intake was similar between groups within each study period, except for energy intake at baseline being significantly higher in RYGB. The number of daily steps were similar during the entire study period, with no difference between groups (Supplemental Table 3).

Factors affecting glycemic variability after surgery

Of the 5 models compared in our secondary mixed model analysis, both AIC and BIC favored the model that included carbohydrate as the main risk factor. According to this model, carbohydrate intake was positively associated with MAGE, with 1 g/kg BW of carbohydrates corresponding to a mean increase in MAGE of $0.37$ mmol/L (95%CI $0.176-0.564$, $P = .0003$) (Fig. 4).

Discussion

In this study, performed in female patients without diabetes under real-life circumstances, GV increased at 6 and 12 months postoperatively. This contrasted with the mean 24h IG concentration, which maintained similar levels postoperatively as during the preoperative LED regimen, all being lower than baseline. Moreover, the self-reported dietary carbohydrate intake was positively associated with GV in the postoperative situation. Finally, we found an increased proportion of patients having hypoglycemic episodes after surgery with similar prevalence in RYGB and SG.

At baseline, our MAGE levels were similar to those previously reported in healthy controls [17], and at 12 months, they resembled previous reports in RYGB- and SG-treated patients without preoperative diabetes [20,21]. RYGB showed a higher MAGE than SG 6 months postoperatively, with 72% of RYGB and 50% of SG having MAGE above the suggested cut-off level of 2.8 mmol/L at 12 months. Previous studies reported higher or similar glucose peaks and nadirs in RYGB- compared to SG-treated patients after a mixed meal test consisting of liquid nutritional supplements or mixed everyday food ingredients [22,23]. The postprandial glucose alterations after RYGB, and to a lower extent
after SG, might be explained by a swift passage of nutrients into the small intestine and with a rapid absorption. The subsequent quick clearance of glucose from the circulation, likely caused by an exaggerated plasma concentration of insulin and glucagon-like-peptide-1, increased insulin sensitivity, and a blunted counter-regulatory response to low glucose concentrations, might contribute to postprandial hypoglycemia [23–25].

A glucose concentration of 3.9 mmol/L is suggested as a threshold for neuroendocrine response to falling glucose concentrations in people without diabetes [4]. Female gender and lack of diabetes increase the risk of hypoglycemia after bariatric surgery [24]. This might explain the higher prevalence of hypoglycemia in the current study compared to a recent meta-analysis [3]. Surprisingly, we found high proportions of patients with IG concentrations below 3.9 mmol/L at 6 months after surgery, implying that hypoglycemia appears earlier than previously suggested [24]. Postoperative hypoglycemia might be the result of increased GV in combination with lower mean glucose concentration, thus creating a reduced margin to low glucose concentrations. Unfortunately, we only measured hypoglycemic symptoms 12 months postoperatively, but at that time, about 70% of patients reported moderate to severe hypoglycemic symptoms. However, these numbers should be taken with some caution since there might be an overlap regarding symptoms of early dumping syndrome [24].

The self-reported total energy and carbohydrate intakes at baseline in our study were comparable to those observed in previous studies, as were the reduced intakes at 12 months [26,27]. The higher postoperative GV, in spite of a lower self-reported total daily carbohydrate intake, and the positive association between carbohydrate intake in g/kg BW and GV, are in line with previous observations after RYGB, which report that dietary carbohydrates cause a more pronounced glucose increase and more rapid glucose disposal, thus increasing the susceptibility for hypoglycemia [7]. Furthermore, patients with postprandial hypoglycemia reported a higher intake of complex and simple carbohydrates at one and 2 years after surgery, compared to patients without hypoglycemia [28]. The higher consumption of carbohydrates might be caused by decreased adherence to dietary recommendations or attempts to reverse hypoglycemic symptoms. The cause-effect relationship is difficult to determine. Interestingly, when compared to a conventionally recommended diet, a carbohydrate-reduced, high-protein diet...
resulted in lower peak and higher nadir glucose concentrations in RYGB patients with hypoglycemia, but with no difference in the time to peak [29]. Because of the accelerated emptying of the gastric pouch after RYGB [23], previous understanding of how macronutrient composition and carbohydrate quality affect the digestion and absorption, and consequently GV and hypoglycemia, require further exploration.

Our study has some limitations. IG concentrations from CGM might overestimate the glucose values compared to plasma glucose concentrations, particularly at low levels [30], which could indicate an even higher percentage of patients with hypoglycemic IG concentrations in our study. Another limitation is the well-known risk of underreporting dietary intake described by other authors [26], and although we assume that comparisons of food intake over time and between surgical techniques were valid, we cannot exclude the risk of bias when examining correlations between carbohydrate intake and GV.

The strengths of our study include the longitudinal approach, from 10 weeks before surgery and up to 12 months postoperatively, allowing patients to be their own controls and thereby eliminating differences between patients. Furthermore, the inclusion of female patients without diabetes, differs from many of the previous studies examining patients with diabetes, or mixed patient groups. Finally, the CGM method allows the study of patients under normal living conditions and the protocol included parallel registration of physical activity and dietary intake.

Conclusion

After RYGB and SG, the mean interstitial glucose concentration remained at the lower level observed during the preoperative LED regimen. However, glycemic variability increased after surgery and the self-reported carbohydrate intake was positively associated with the glycemic excursions. Episodes of hypoglycemia increased after both surgical procedures. The combination of a lower mean interstitial glucose concentration and higher glycemic variability might have created a lower margin to hypoglycemia.

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.2023.07.008.

References

Comment on: Glycemic variability and hypoglycemia before and after Roux-en-Y gastric bypass and sleeve gastrectomy—a cohort study of females without diabetes

Wearable devices and monitoring all sorts of personal biologic data from temperature to heart rate to blood oxygen saturation have become increasingly common, especially with the focus of monitoring data for health and fitness purposes. From the metabolic surgeon’s perspective, continuous glucose monitoring has also become increasingly prevalent—even in our patients without diabetes. While post–bariatric surgery hypoglycemia has been a long-standing complication of surgical weight loss, clinically significant hypoglycemia appears to affect a small portion of surgical patients. Regardless, better understanding of how metabolic surgery affects glycemic variability is important for improving the care of all patients, and these wearable tools are helping to highlight this subject area. Prior studies have demonstrated significant glycemic variability in both animals [1] and humans [2,3] after metabolic/bariatric surgery, but many questions remain, including how glycemic variability affects behavioral and food choices as well as its clinical significance and the mechanisms driving this variability [4].