

Continuous Glucose Monitoring After Gastric Bypass to Evaluate the Glucose Variability After a Low-Carbohydrate Diet and to Determine Hypoglycemia

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Published online: 12 January 2016
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Abstract

Background Roux-en-Y gastric bypass (RYGB) alters glucose metabolism and can cause postprandial hypoglycemia. Continuous glucose monitoring (CGM) has been proposed as an evaluation tool in hypoglycemic RYGB individuals. The objective of this study is to investigate the use of CGM in clinical decision-making including diagnosing hypoglycemia and evaluating treatment effects. Furthermore, we aim to assess its accuracy in RYGB-operated individuals.

Methods Thirteen RYGB individuals with symptomatic hypoglycemia and 13 asymptomatic RYGB individuals underwent CGM for 5 days. During this period, a mixed-meal test with concomitant plasma glucose (PG) measurements was performed. Furthermore, the RYGB individuals followed a low-carbohydrate diet (LCD) for 1 day and maintained their ordinary diet (OD) for the rest of the period.

Results LCD reduced the CGM-determined glycemic variability of the mean interstitial fluid glucose (IFG) significantly

compared to OD ($p < 0.0001$). Receiver operating characteristic analysis confirmed that low blood glucose index (e.g., the frequency and amplitude of hypoglycemic events) is the most reliable parameter related to the development of symptomatic hypoglycemia, with a sensitivity of 0.91 (confidence interval [CI] 0.59; 1.00) and a specificity of 0.77 (CI 0.46; 0.95). However, CGM, measuring the IFG in the subcutaneous adipose tissue, overestimated the *minimum* glucose levels by 1.1 ± 0.9 mmol/l compared with PG.

Conclusions CGM was a good method for demonstrating increased glycemic variability among RYGB individuals and for displaying dietary effects on reducing this glycemic variability, including hypoglycemic events. In RYGB individuals, CGM-measured IFG overestimated the real glucose value by about 1 mmol/l in the hypoglycemic range. This should be taken into consideration if CGM is used to diagnose hypoglycemia after RYGB.

Keywords Roux-en-Y gastric bypass · Continuous glucose monitoring · Hypoglycemia measurement · Low-carbohydrate diet · Glucose variability · Method comparison

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Introduction

Roux-en-Y gastric bypass surgery (RYGB) has favorable effects on weight loss and obesity-related morbidity, but concern has been raised over its long-term side effects [1]. Symptomatic hypoglycemia is one of these side effects characterized by either autonomic symptoms including palpitation, tremor, and sweating or neuroglycopenic symptoms including weakness, cognitive failure, and confusion after meal ingestion [2].

RYGB results in rapid delivery and uptake of nutrition, including carbohydrates to the small intestine, and, thereby,

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an increased postprandial response of insulin and incretin hormones, such as glucagon-like peptide-1 (GLP-1). This may contribute to the enhanced risk of hypoglycemia [3, 4]. However, studies of RYGB individuals disagree on the difference in these postprandial responses between subjects with or without hypoglycemic symptoms, and both RYGB groups have similar improvement in insulin sensitivity [4–6].

Since it can be difficult to diagnose post-RYGB hypoglycemia, it has been proposed to use continuous glucose monitoring (CGM) in this evaluation [7, 8]. Especially during hypoglycemia, the correlation between interstitial fluid glucose (IFG), measured by CGM in the subcutaneous adipose tissue, and plasma glucose (PG) may depend on specific subject characteristics including age, insulin sensitivity, and diabetes status [9]. In younger, healthy, or type 1 diabetic subjects, most studies have found IFG to drop earlier to PG due to the push-pull phenomenon [10–13], characterized by an insulin-induced uptake of IFG by adipocytes that is not fully compensated for by the increased delivery of glucose from the circulation. Conversely, studies in elderly, healthy subjects [14] and studies in elderly, type 2 diabetic patients [9] found IFG to be significantly higher than PG at different levels of hypoglycemia. To our knowledge, the *accuracy* of CGM technology in determining hypoglycemia in RYGB individuals has not been evaluated.

We aim to describe the glycemic variability among RYGB individuals with and without hypoglycemic symptoms compared to nonoperated individuals, including an assessment of using CGM to distinguish between the asymptomatic and the symptomatic group. Moreover, we aim to evaluate the effect of a dietary carbohydrate content reduction on these measurements. Finally, we aim to assess the accuracy of CGM in the RYGB individuals.

Participants and Methods

Study Participants

The RYGB individuals (13 with hypoglycemic symptoms and 13 without hypoglycemic symptoms) were operated at least 1 year before inclusion. They were recruited from the Department of Endocrinology of Aarhus University Hospital or at Viborg Hospital, Denmark, and age, height, weight, and body mass index (BMI; calculated as kg/m^2) were assessed at inclusion. A control group ($n=7$) of age- and BMI-matched, nonoperated individuals was also recruited.

Continuous Glucose Monitoring

The CGM sensor (iPro2™, Medtronic Minimed, Northridge, CA, USA) was inserted into the upper abdominal area

according to the manufacturer's directions, recording the IFG every 5 min for 5 days. All individuals measured the capillary blood glucose four times a day for CGM calibration, including before and after a mixed-meal test (MMT), and kept a journal of meal composition and times. Furthermore, they made a registration in the journal if they experienced hypoglycemia-like symptoms. They were asked to maintain real-life circumstances during the CGM period except for 2 days: (1) low-carbohydrate diet (LCD) day at home and (2) an MMT performed in the laboratory.

The sensor did not display the current glucose concentration measured, but stored the data for retrospective analysis using CareLink® iPro2. Valid data were defined as minimum of three calibrations in 24 h, the mean absolute difference percentage below 28 (blood glucose level 5.6 mmol/l or above) or below 18 (blood glucose levels below 5.6 mmol/l) and a correlation of above 0.79.

CGM data during the 16-h daytime (from 6:00 a.m. until midnight) on the LCD day was compared to the same daytime interval at a prespecified day of ordinary diet (OD). The glucose variability was estimated as the standard deviation (SD) measuring the dispersion from the mean IFG and as the mean amplitude of glycemic excursions (MAGE) measuring the mean height of those glycemic excursions greater than 1 SD. The low blood glucose index (LBGI) and high blood glucose index (HBGI) accounted for the frequency and the amplitude of hypoglycemic and hyperglycemic events, respectively [15–17]. All CGM data were analyzed using the EasyGV® algorithms (www.easygv.co.uk).

We used receiver operating characteristic (ROC) curves to calculate the sensitivity and specificity of each test to classify RYGB individuals as with or without hypoglycemic symptoms based on the data from the 5-day CGM period.

The LCD

An individual diet assessment was used to construct an isocaloric LCD plan. It contained six small meals with a maximum of 10 g carbohydrates per meal (i.e., 60 g carbohydrates daily) primarily originating from complex carbohydrates such as grains and fibers and avoiding simple carbohydrates such as fruit, milk, and honey. Individuals were instructed to follow specific eating techniques, e.g., chewing the food thoroughly, eating slowly, and separating solids and liquids. The diet assessment revealed a carbohydrate intake of approximately 120 g on their ordinary diet days.

The MMT

After 10-h overnight fast, the individuals consumed an MMT at the laboratory. The test meal (Fresenius energy drink; 200 ml; 300 kcal; 50 % carbohydrate, 15 % protein, and 35 % fat) was consumed within 20 min. Blood samples were

collected at 0, 10, 20, 30, 45, 60, 75, 120, 180, 240, and 300 min. CGM measurements of IFG were continued during the MMT. PG was analyzed by Gluco-quant (Roche Diagnostics, Rotkreuz, Switzerland). Blood was collected into EDTA tubes and immediately centrifuged (2000g) and stored at -80°C until insulin was analyzed using an enzyme-linked immunosorbent assay (DAKO, Cambridgeshire, UK). The rates of changes for both IFG and PG were calculated as the maximal ascending and descending slopes of the glucose profiles following the MMT. The trapezoidal method was used to calculate the mean area under the curve (AUC) for glucose and insulin [18].

Bland-Altman plots were used to evaluate the agreement between IFG and PG during MMT. The mean difference between the two methods is the estimated bias, and the SD of the differences measures the random fluctuation around this mean [19]. We compared the maximum IFG to the maximum PG and the minimum IFG to the minimum PG. These values were used independently of the timing after the start of the MMT.

Statistics

Normality was checked by Q-Q plots, and a logarithmic transformation was performed on nonnormally distributed data. Parametric data are presented as mean (SD) values. Lognormally distributed data are presented as median (95 % CI) values. Comparisons between groups were done using unpaired Student's *t* test or Wilcoxon-Mann-Whitney U test. Differences between LCD and OD were assessed by paired Student's *t* test. Sensitivity and specificity were assessed by ROC curve analysis. Data analysis was performed with Stata IC13 and Sigma Plot 12.5.

Results

Characteristics of the Participants

The RYGB individuals were comparable to the control individuals with respect to gender, age, and BMI at inclusion (Table 1). Before RYGB, two individuals had type 2 diabetes and one individual had gestational diabetes.

Glycemic Variability After LCD Compared to an OD

CGM data for the LCD day were available for 25 RYGB individuals (96 %) and for 6 control individuals (86 %) (Table 2). During an OD, RYGB individuals had significantly higher glycemic variability, expressed as SD and MAGE, than control individuals. The glycemic variability was equal between RYGB individuals with and without prior diabetes (data not shown). This variability was significantly reduced after 1 day with LCD in both RYGB and control individuals

compared to OD, which is illustrated in three representative individuals with hypoglycemia after RYGB (Fig. 1). The frequency and the amplitude of hypoglycemic events were comparable among RYGB and control individuals (1.9 [CI 1.4; 2.4] vs 1.8 [CI 1.0; 3.2]), but LCD reduced LBG1 significantly in both groups compared with OD. The frequency and the amplitude of hyperglycemic events were significantly higher among RYGB individuals than among control individuals (0.9 [CI 0.4; 1.7] vs 0.2 [CI 0.0; 0.8]) during OD, but LCD removed this difference in the HBGI between RYGB and control individuals.

Sensitivity and Specificity of CGM Parameters to Distinguishing RYGB Individuals With and Without Symptomatic Hypoglycemia

The ROC curve analysis confirmed LBG1 as the most reliable parameter related to the development of postprandial symptomatic hypoglycemia after RYGB, with a sensitivity of 0.91 (CI 0.59; 1.00) and a specificity of 0.77 (CI 0.46; 0.95). The AUC under the ROC curve for LBG1 was 0.85 (CI 0.70; 1.01); $p < 0.005$. Based on clinical experiences using CGM in patients susceptible to suffering from post-RYGB symptomatic hypoglycemia, we assumed a pretest probability of 0.60 % and found an optimal cutoff of >2.11 for LBG1. For SD and MAGE the AUC under the ROC curves were 0.55 (CI 0.30; 0.79) and 0.61 (CI 0.36; 0.86); $p > 0.20$.

Comparison Between PG and IFG During the MMT

Twenty RYGB individuals (77 %) and five control individuals (71 %) had valid CGM data, and their IFG and PG data are shown in Table 3 and in Fig. 2. The RYGB group had a significantly lower minimum PG than the control group (3.6 ± 0.7 vs 4.6 ± 0.4 mmol/l; $p = 0.01$), whereas we found no statistically significant difference in minimum IFG between RYGB and control individuals (4.7 ± 0.7 vs 5.0 ± 0.4 mmol/l; $p = 0.43$). RYGB individuals demonstrated a steeper increase followed by an even steeper decrement in both PG and IFG following the meal than control subjects ($p < 0.0001$). From the Bland-Altman plot (Fig. 3), the estimated difference between minimum IFG and minimum PG in RYGB subjects was 1.1 mmol/l (SD 0.9 mmol/l) ($p < 0.0001$). The estimated difference between maximum IFG and maximum PG was 0.5 mmol/l (SD 2.2 mmol/l), which was nonsignificant ($p = 0.29$).

Insulin Levels During MMT

Both maximum insulin levels and AUC of insulin were significantly higher in RYGB individuals than in control individuals ($p < 0.05$), and those individuals with symptomatic

Table 1 Baseline characteristics of the study subjects

	RYGB subjects (<i>n</i> = 26)	Control subjects (<i>n</i> = 7)	<i>p</i> value
Age (years)	43.3 ± 8.3	46.5 ± 6.8	0.36
Gender (M/F)	5/21	2/5	0.62
Preoperative BMI (kg/m ²)	49.8 ± 8.7	–	–
Postoperative duration (months)	42.5 ± 19.4	–	–
Weight loss (kg)	55.4 ± 21.3	–	–
BMI at evaluation (kg/m ²)	30.3 ± 5.1	29.2 ± 1.6	0.76
Diabetes prior to RYGB (Y/N)	3/22	–	–

Data presented as mean ± SD unless otherwise specified. The *p* value is for the comparison between the two groups using unpaired *t* test or Fischer's exact test

RYGB Roux-en-Y gastric bypass surgery; BMI Body Mass Index

hypoglycemia had significantly higher maximum insulin levels and AUC of insulin than those remaining asymptomatic (*p* < 0.05).

Discussion

Based on CGM, RYGB individuals demonstrated higher glycemic variability than control individuals during real-life circumstances. This finding is in corroboration with other studies [7, 8], and reflects the well-established increased postprandial glucose uptake and the exaggerated insulin and GLP-1 responses after RYGB [3, 4]. The impact of meal composition on the postprandial responses in RYGB individuals is sparsely examined, but carbohydrate-content reduction in a test meal has been shown to diminish postprandial hypoglycemia [20, 21]. We used CGM to demonstrate a marked reduction in glycemic variability in RYGB individuals following a LCD. Moreover, we asked the subjects to make a registration if they experienced hypoglycemia-like symptoms. Seven out of 26

RYGB individuals had symptoms along with an IFG measurement below 3.6 mmol/l once or more during the whole CGM period; none of these events were experienced during the low-carbohydrate diet.

CGM has primarily been evaluated in type 1 diabetic subjects, showing positive effects in achieving metabolic control, reducing glycemic variability, and limiting hypoglycemic and hyperglycemic episodes [22]. Previous studies evaluating the accuracy of CGM in detecting hypoglycemia has indicated that IFG corresponds to PG levels in younger and nonobese subjects with or without type 1 diabetes [11–13]. However, studies in insulin-resistant individuals such as type 2 diabetes patients, elderly individuals [9, 14], and obese subjects (present study) have indicated that IFG overestimates the glucose levels compared with PG in the hypoglycemic range.

Our study was designed to investigate the use of CGM in diagnosing postprandial hypoglycemia, so we focused on the agreement between minimum IFG, measured by CGM, and PG after MMT. Minimum IFG was 1.1 mmol/l higher than minimum PG. RYGB is known to improve both hepatic and

Table 2 Variation in interstitial fluid glucose during ordinary diet compared with a low-carbohydrate diet

	RYGB subjects (<i>n</i> = 25)		<i>p</i> value	Control subjects (<i>n</i> = 6)	
	OD	LCD		OD	LCD
Mean IFG (mmol/l)	5.6 ± 0.5	5.4 ± 0.5	0.08	5.3 ± 0.4	5.4 ± 0.3
SD (mmol/l)	1.0 (0.9; 1.2)*	0.6 (0.5; 0.7)	<0.0001	0.6 (0.4; 1.0)*	0.4 (0.2; 0.7)
MAGE (mmol/l)	2.7 (2.4; 3.1)*	1.5 (1.3; 1.9)	<0.0001	1.5 (1.0; 2.5)*	1.2 (0.6; 2.2)
LBGI	1.9 (1.4; 2.4)	1.3 (1.0; 1.8)	0.02	1.8 (1.0; 3.2)	1.0 (0.5; 2.0)
HBGI	0.9 (0.4; 1.7)*	0.3 (0.1; 0.5)	0.01	0.2 (0.0; 0.8)*	0.4 (0.1; 2.3)

IFG was measured by CGM. All subjects consumed an isocaloric diet: one day an OD and another day an LCD. The *p* value is given for the comparison between the two different days for RYGB individuals (paired Student's *t* test). SD, MAGE, LBGI, and HBGI are lognormally distributed data and presented as median and accompanied 95 % confidence interval after using the exponentiation to return the computation to the original scale. Normally distributed data are presented as mean ± SD

IFG interstitial fluid glucose, CGM continuous glucose monitoring, LCD low-carbohydrate diet, RYGB Roux-en-Y gastric bypass surgery, SD standard deviation, MAGE mean amplitude of glycemic excursions, LBGI low blood glucose index, HBGI high blood glucose index

**p* < 0.05 for the comparison between RYGB and control subjects during OD (unpaired Student's *t* test)

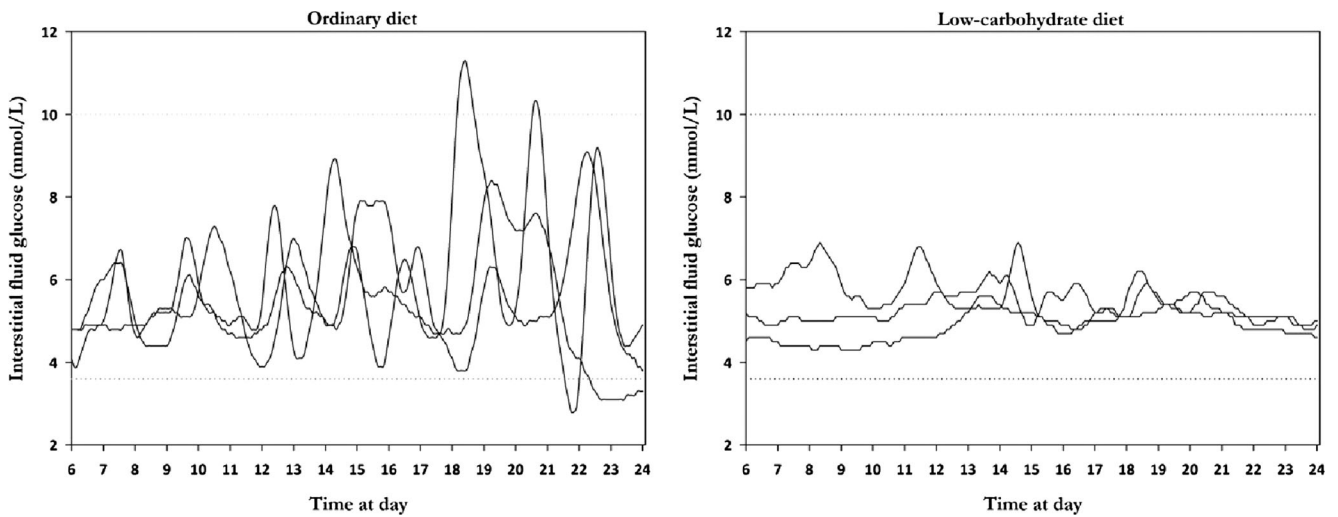


Fig. 1 Effects of low-carbohydrate diet on interstitial fluid glucose variability after Roux-en-Y gastric bypass. Interstitial fluid glucose was measured by CGM from 6:00 a.m. until midnight in three representative

subjects with symptomatic hypoglycemia after Roux-en-Y gastric bypass during an ordinary diet (a) and during a low-carbohydrate diet (b)

peripheral insulin resistance [3, 23–25], but despite this weight loss-dependent improvement in insulin sensitivity compared to baseline values 6–12 months after RYGB, insulin sensitivity still differs significantly from lean control subjects [26]. As seen in type 2 diabetics and elderly subjects [9], we suggest that the RYGB individuals may still be insulin resistant

in the subcutaneous adipose tissue, which may explain why CGM overestimated glucose levels in our RYGB individuals.

Most studies investigating the correlation between IFG and PG are based on clamp techniques allowing standardized glucose profiles to be obtained. These techniques enable a time delay calculation between fluctuations in PG and IFG; but

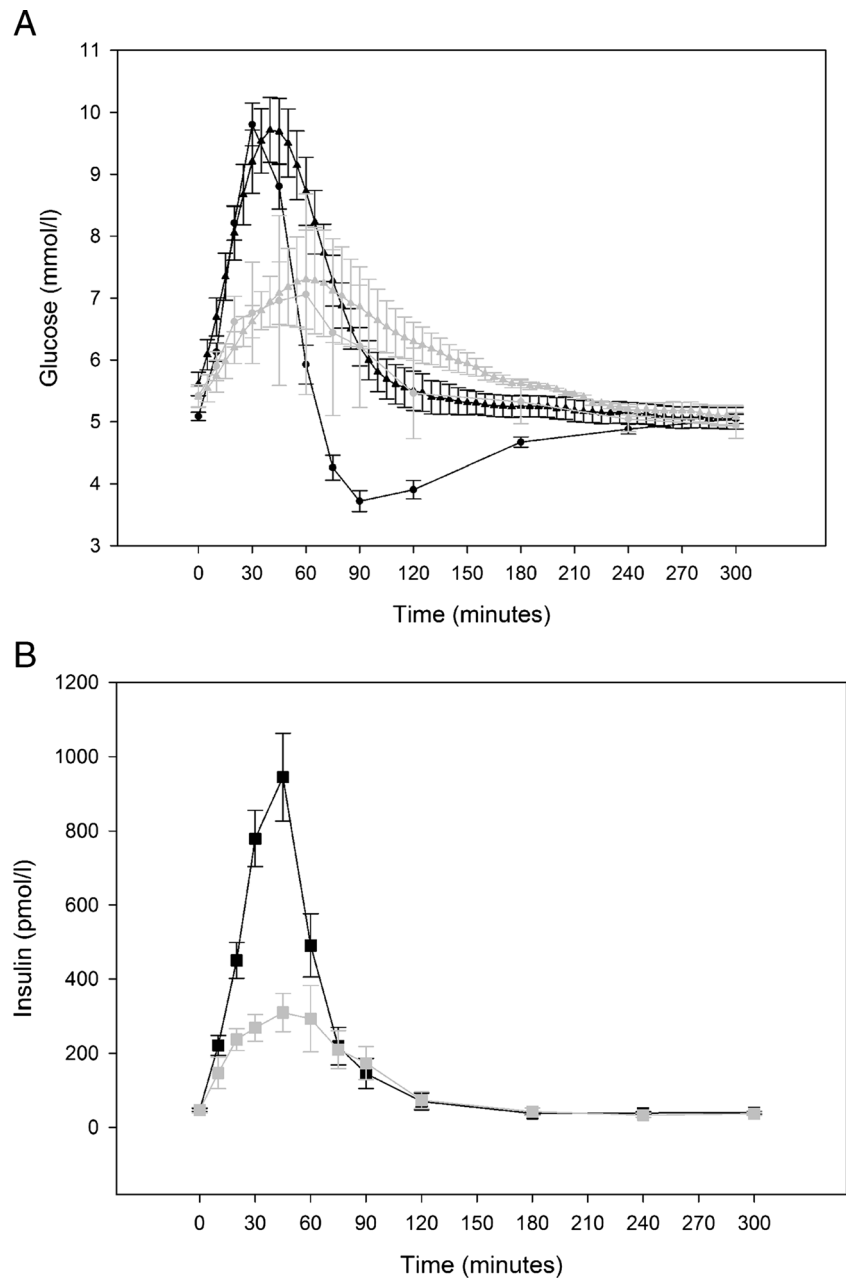
Table 3 Plasma glucose, interstitial fluid glucose, and insulin measurements during the mixed-meal test

	RYGB subjects (n = 20)	Control subjects (n = 5)	p value
Plasma glucose (PG)			
Fasting PG (mmol/l)	5.1 ± 0.3	5.4 ± 0.4	<0.05
Maximum PG (mmol/l)	10.1 ± 1.5	7.8 ± 3.1	0.07
Minimum PG (mmol/l)	3.6 ± 0.7	4.6 ± 0.4	0.01
AUC PG	1550 ± 147	1699 ± 350	0.31
Rates of PG increase (mmol/l/min)	0.16 ± 0.06	0.05 ± 0.02	<0.001
Rates of PG decrease (mmol/l/min)	-0.15 ± 0.11	-0.03 ± 0.02	0.02
Interstitial fluid glucose (IFG)			
Fasting IFG (mmol/l)	5.6 ± 0.8	5.4 ± 0.4	0.60
Maximum IFG (mmol/l)	10.6 ± 2.2	7.5 ± 1.7	<0.01
Minimum IFG (mmol/l)	4.7 ± 0.7	5.0 ± 0.4	0.43
AUC IFG	1800 ± 238	1791 ± 127	0.84
Rates of IFG increase (mmol/l/min)	0.12 ± 0.01	0.04 ± 0.003	0.0001
Rates of IFG decrease (mmol/l/min)	-0.09 ± 0.01	-0.02 ± 0.001	0.0001
Insulin			
Fasting insulin (pmol/l)	45.2 ± 17.8	50.1 ± 17.6	0.35
Maximum insulin (pmol/l)	887 (725; 1086)	388 (278; 541)	<0.0005
AUC insulin 0–300 min	48,483 (40,344; 58,263)	31,647 (23,632; 42,382)	0.03

Normally distributed data are shown as mean ± SD. Nonnormally distributed data are shown as mean with corresponding confidence intervals (CI). The statistical p value is showing the comparison between the two groups (unpaired t test or Wilcoxon-Mann-Whitney U test)

AUC area under the curve

Fig. 2 Glucose and insulin measurements during a 5-h mixed-meal test. **a** CGM-measured interstitial fluid glucose (triangles) for RYGB (black triangles) and control subjects (gray triangles) and plasma glucose (circles) for RYGB (black circles) and control subjects (gray circles). **b** Insulin (squares) for RYGB (black squares) and control subjects (gray squares). Data given by mean \pm SEM



they may not reflect rapid glucose fluctuation occurring in a clinical situation and completely bypass the effects of incretins, which, especially in RYGB individuals, probably play a major role for glucose homeostasis after a meal [3].

Our study was designed to determine whether CGM could be used to detect and manage postprandial hypoglycemia in RYGB individuals, so we did not focus on this time delay [27]. The MMT was carried out over 5 h, allowing a sufficient time to achieve equilibrium between PG and IFG, so we are rather convinced that our findings do not reflect the physiological lag (known to be 4–21 min) [18, 27]. In summary, we presume that

our findings are merely related to the insulin resistance of our study population and/or the “clinical situation” of the test than to methodological differences or technical issues in the CGM device.

In evaluating the use of CGM as a tool for diagnosing hypoglycemia in RYGB individuals, we used ROC curve analysis. The frequency and the amplitude of hypoglycemic events (i.e., LBG) showed a high accuracy for discriminating RYGB individuals with and without hypoglycemia. In agreement with the ROC curve analysis, we showed that the LBG was significantly higher among symptomatic individuals than among asymptomatic individuals (2.4 (1.6; 3.6) vs 1.5 (1.2; 2.0); $p < 0.05$).

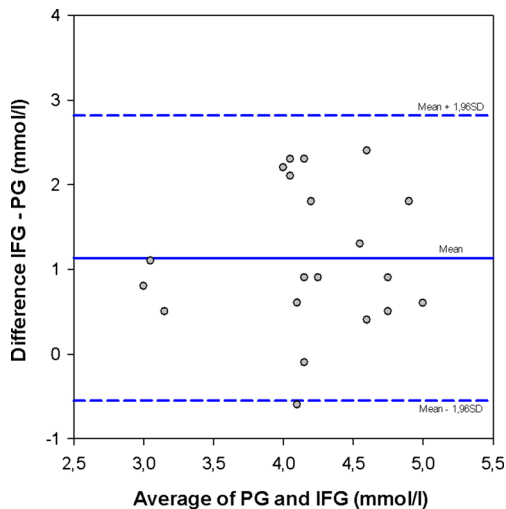


Fig. 3 Bland-Altman plot showing the mean difference between CGM-measured interstitial fluid glucose (*IFG*) and plasma glucose (*PG*) in RYGB subjects. The average minimum glucose ($(PG + IFG)/2$) is on the x axis, and the minimum glucose difference ($IFG - PG$) is on the y axis. The mean difference between *IFG* and *PG* is the estimated bias (solid line), and the mean difference ± 1.96 SD is the limit of agreement (dotted line)

Conclusion

CGM was a very good method for demonstrating increased glycemic variability among RYGB individuals and for displaying dietary effects on reducing this glycemic variability, including hypoglycemic events after RYGB. Despite overestimating the minimum *IFG* in a laboratory setting, we presume that CGM, with this difference taken into account, is a good method to help clinicians diagnose hypoglycemia in RYGB individuals.

Acknowledgments We thank Lenette Pedersen and Pia Hornbek for their very skillful technical assistance and Nurse Dorthe Møller for helping with the patients during the study. We thank Bayer HealthCare for supporting the delivery of Contour Next meters and test strips for the measurement of glucose.

Grant Information This study has primarily been supported by the Central Denmark Region, but the A.P. Møller Maersk Foundation and the Novo Nordisk Foundation have also supported this study.

Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was approved by the Regional Ethics Committee and registered in Clinicaltrials.gov (1-16-02-138-13).

Conflict of Interest The authors declare that they have no conflicts of interests.

Informed Consent Written informed consent was obtained from all participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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