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"Dual-remission" after Roux-en-Y gastric bypass surgery: Glycemic variability cannot always be improved in Chinese obese patients with type 2 diabetes

Haoyong Yu, M.D.[a], Jian Zhou, Ph.D.[a,b], Yuqian Bao, M.D.[a], Pin Zhang, Ph.D.[c], Wei Lu, M.D.[a], Weiping Jia, M.D., Ph.D.[a,*]

[a]*Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai Clinical Center of Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Key Clinical Center for Metabolic Disease, Shanghai, China*

[b]*Department of Endocrinology and Metabolism, Kashgar Prefecture Second People's Hospital, Kashgar, China*

[c]*Department of General Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China*

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Abstract

Background: Glycemic variability after Roux-en-Y Gastric Bypass (RYGB) has not been adequately examined in Chinese obese patients with type 2 diabetes (T2D).

Objective: We aimed to evaluate glucose variability after RYGB by continuous glucose monitoring (CGM) and then evaluate the remission rate based on the complete diabetes remission criteria combined with normal ranges of CGM for the Chinese population, which we defined as "dual-remission."

Setting: The study was done at our academic university-affiliated hospital.

Methods: Over a 3-day period, CGM was performed on 43 Chinese obese T2D patients combined with a mixed-meal test before and 1 year after RYGB. Mean amplitude of glucose excursions (MAGE), standard deviations (SD), and the time that patients' blood glucose levels were $\geq$7.0 mmol/L, $\geq$7.8 mmol/L, $\geq$11.1 mmol/L, and $\leq$3.9 mmol/L within 24 hours was analyzed. Multiple logistic regression analyses were used to identify predictors of "dual-remission."

Results: Complete diabetes remission was achieved in 27 patients (62.8%) 1 year after RYGB. However, MAGE didn't change in the group, and only 18.6% patients met "dual-remission." Compared with patients in the complete remission group, patients in the dual-remission group had a shorter duration of diabetes, younger age, lower glycated hemoglobin (HbA1c) level, and no insulin usage at baseline. Correlation analysis showed MAGE after RYGB was positively correlated with diabetes duration ($r = .43$, $P < .01$). Multiple logistic regressions indicated a shorter duration was associated with a higher possibility to achieve dual-remission after adjusting for age, gender, HbA1c, and insulin therapy.

Conclusion: Glucose variability can't be effectively improved in most Chinese obese diabetic patients after RYGB. Shorter diabetes duration was associated with higher possibility to achieve "dual-remission." (Surg Obes Relat Dis 2016;▮:00–00.) © 2016 Published by Elsevier Inc. on behalf of American Society for Metabolic and Bariatric Surgery.

Keywords: Bariatric surgery; Gastric bypass; Obesity; Diabetes; Continuous glucose monitoring; Glycemic variability

Introduction

The acute excursion of glucose around a mean value over a daily period of intermittent hyperglycemia, activating oxidative stress, might play an important role in cardiovascular

H.Y. and J.Z. contributed equally to this work.

*Correspondence: Weiping Jia, M.D., Ph.D., Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai Diabetes Institute, Shanghai Clinical Center of Diabetes, Yishan Road 600, Shanghai, China

E-mail: wpjia@sjtu.edu.cn

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disease in type 2 diabetes (T2D) [1]. It is strongly suggested that an effective antidiabetic strategy should be aimed at reducing the different components of dysglycemia, including glycated hemoglobin (HbA1C), fasting/postprandial glucose, and glucose variability. Metabolic surgery has been recommended as an effective treatment option for obese patients with T2D that do not achieve satisfactory control with lifestyle changes alone [2]. RYGB is the most commonly performed procedure for patients with obesity and T2D. The remission or improvement of diabetes is observed in >80% of the cases after RYGB [3]. While fasting plasma glucose is usually normalized in these patients, little is known about their glucose profiles throughout the day, particularly after meals.

Continuous glucose monitoring (CGM) provides much more glycemic information, including magnitude, duration, and frequency of blood glucose levels, which is used to better understand the properties of shifting blood glucose levels throughout the day. CGM is an effective and common method to reveal these rapid excursions in glucose levels that might be underestimated in real life. Mean amplitudes of glucose excursions (MAGE) and standard deviations (SD) [4] are sensitive to large excursions in blood glucose and have previously been proposed as components to assess glycemic control, along with HbA1C, postprandial glucose, and fasting plasma glucose. A prior study [5] has shown that glucose variability is exaggerated after gastric bypass, combining unusually high and early hyperglycemic peaks and rapid interstitial glucose decreases. However, in the Raffaele et al. study [6], biliopancreatic diversion was found to have an important role in the normalization of glycemic variability.

The current standard of diabetes remission after metabolic surgery only takes into account HbA1C and serum glucose levels. This standard does not seem very comprehensive, as the parameters on glycemic variability haven't been considered. In our previous study [7], we have established preliminary normal reference values for CGM parameters in a sample of healthy Chinese patients. These values have been widely used in clinic to aid diabetes management. Thus, we used CGM technology to compare the MAGE and SD both before and 1 year after RYGB to evaluate whether RYGB can effectively improve glucose variability after mixed-meal challenge in these patients. Then, we further evaluated diabetes remission rates according to the current complete diabetes remission standard [8] combined with the normal reference values for CGM parameters we have proposed, which we define as "dual-remission" in the present study. If a patient meets these 2 standards simultaneously, the patient achieves "dual-remission."

Methods

Patient population

This is a retrospective study. Between February 2011 and August 2012, a total of 43 obese individuals with T2D were enrolled in the study. Medical history, age, height, weight, BMI, and current medications were recorded before and after surgery. Glucose, C-peptide (both in fasting and 2 h postprandial states), and HbA1C levels were measured preoperatively and 1 month, 3 months, 6 months, and 12 months postoperatively. Any patient with a history of open abdominal surgery, a serious disease (such as heart or lung insufficiency) that was incompatible with surgery, an acute T2D complication, severe alcohol or drug dependency, a mental disorder, type 1 diabetes (T1D), secondary diabetes, or unstable psychiatric illness or who was a relatively high surgical risk (such as a patient with an active ulcer) was excluded.

Informed consent was obtained from all participants before the start of the study and the Ethics Committee of our institution approved the study, in accordance with the World Medical Association's Declaration of Helsinki.

Definitions of diabetes, obesity, diabetes remission, normal glycemic variability, and dual-remission

The diagnosis criteria of T2D was based on the 1999 World Health Organization criteria: fasting plasma glucose ≥7.0 mmol/L and/or 2 h plasma glucose ≥11.1 mmol/L. BMI was categorized using Working Group on Obesity in China (WGOC) standards: normal weight = 18.5 kg/m^2 ≤ BMI <24 kg/m^2; overweight = 24 kg/m^2 ≤ BMI <28 kg/m^2; obesity = BMI ≥28 kg/m^2 [9].

Standard I: Diabetes complete remission was defined as HbA1C level <6.0% and a fasting glucose concentration <5.6 mmol/L for 1 year or more without active pharmacologic intervention [8].

Standard II: Normal ranges of CGM for the Chinese population are a mean blood glucose (MBG) value <6.6 mmol/L, with the time spent in blood glucose (BG) levels ≥7.8 mmol/L <17% (4 hours) and the time spent in BG levels ≤3.9 mmol/L <12% (3 hours) [7].

Standard III: Dual-remission was defined to meet both standard I and standard II.

Surgical procedure

All obese patients with T2D underwent RYGB, performed laparoscopically by a single surgeon using a standardized technique as previously reported [10]. A 25 mL gastric pouch was divided from the distal remnant. The biliopancreatic and alimentary limbs were 100–120 cm in length.

CGM

CGM was recorded for 3 days on an inpatient basis (Medtronic MiniMed, Northridge, CA). As described in our previous publication [7], the CGM sensor was inserted into all patients by the same nurse on Day 0 between 8:00 a.m. and 9:00 a.m. in our hospital. The first CGM calibration by

finger-stick BG was performed 1 hour after initialization. If no abnormal CGMS situation was observed, the patients were discharged and continued with CGM for 3 consecutive days. Calibration was performed 4 times per day.

Mixed-meal test

All patients received dietary instructions according to uniform criteria as the CGMS was implemented. The total calorie intake from the 3 daily meals was 30 kcal/kg per day during CGM, with 50% carbohydrates, 15% proteins, and 35% fats. The amount of drinking water was not restricted. The calorie distribution between breakfast, lunch, and dinner was 20%, 40%, and 40%, respectively. There was a disciplinary time from 6:30 to 7:30 a.m. for breakfast, 11:30 a.m. to 12:30 p.m. for lunch, and 6:00 to 7:00 p.m. for dinner. Each meal had to be consumed within 30 minutes. Patients were required to follow the dietary instructions during the CGM.

Data analyses

At the end of each CGM recording period, CGM parameters were analyzed using CGMS software 3.0. For SD determination, the SD of a total of 288 values collected during a 24-hour CGM period for each study subject was calculated. MAGE was defined as the average of absolute values of the differences between adjacent peaks and nadirs for all differences >1 SD, which was described by Service et al. [11]. In addition, the mean blood glucose (MBG), minimal blood glucose (Min BG), maximum blood glucose (Max BG), and areas under the curve for blood glucose ≥ 7.0 mmol/L, ≥ 7.8 mmol/L, ≥ 11.1 mmol/L, and ≤ 3.9 mmol/L of blood glucose concentration within 24 hours were calculated.

Laboratory examinations

Plasma glucose concentrations were measured using the glucose oxidase method. HbA1C level was determined by high-performance liquid chromatography (Bio-Rad Inc., Hercules, CA, USA). All lipid profiles included serum total cholesterol (TC), serum triglyceride (TG), HDL-C, and LDL-C, assayed with a 7600-120 Hitachi automatic analyser (Hitachi, Tokyo, Japan). TC and TG were measured by enzyme assay (Roche Diagnostics GmbH, Mannheim, Germany). HDL-C and LDL-C concentrations were measured via the direct assay method (Sekisui Medical Co. Ltd., Tokyo, Japan). An electrochemiluminescence immunoassay (Roche Diagnostics GmbH) was used to measure fasting serum insulin (FINS) on a Cobase 411 analyzer, with intra- and interassay coefficients of variation of 1.7% and 2.5%, respectively. C-peptide (CP) was measured using radioimmunoassay (Linco Research, St Charles, MO, USA).

Statistical methods

All continuous variables were tested for normal distribution using the Kolmogorov–Smirnov normality test. Log-transformations were used to normalize skewed variables. Data are presented as means $\pm$ SD or median [interquartile range (IQR)]. Paired t test was used to compare variables before and after the study. Unpaired t test was used to compare variables between "dual-remission" group and "conventional complete remission" group. Spearman rank correlation analysis was utilized to measure the relationships between diabetes duration and MAGE. Multiple logistic regression analysis was performed to assess the independent predictive effects of the variables (age, gender, HbA1C and duration) on the dual remission of diabetes after surgery. P values $<.05$ (2-tailed tests) were considered to indicate statistical significance. Statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL, USA).

Results

There were 43 patients (24 female, 19 male) involved in the study. The patients were 50.0 $\pm$ 11.8 years old and the diabetes duration was 7.9 $\pm$ 4.9 years. According to Standard I, complete remission of T2D was achieved in 27 out of 43 (62.8%) patients 1 year after surgery. Table 1 shows the alterations of clinical characteristics in these patients at baseline and 1 year after RYGB. We observed that the BMI, systolic blood pressure (SBP), fasting blood glucose (FBG), postprandial blood glucose (PBG), HbA1C, fasting C-peptide, HOMA-IR, and blood lipid profiles were significantly decreased 1 year after RYGB compared to the baseline. The variables measured by the CGMS were examined at baseline and 1 year post-RYGB (Table 2). The Min BG and time in BG ≥ 7.0 mmol/L, 7.8 mmol/L, and 11.1 mmol/L were decreased, whereas time in BG ≤ 3.9 mmol/L was increased after 1 year. However, no changes were found in Max BG, MAGE, and SD 1 year after RYGB compared with the baseline.

According to the standard of "dual-remission," only 8 patients (18.6%) achieved the standard. Comparing the difference between the 2 groups, the dual-remission group had a younger age, shorter duration, lower HbA1C, and no insulin usage at baseline (Table 3). For both groups, we observed that the BMI, blood pressure (BP), FBG, PBG, HbA1C, fasting C-peptide, blood lipid profiles, and HOMA-IR were significantly decreased 1 year after RYGB compared to the baseline. At 1year after RYGB, we found FBG, PBG, HbA1C, and HOMA-IR decreased more significantly in the dual-remission group compared with the complete remission group.

Fig. 1 shows the CGM profiles in the complete remission group (A) and dual-remission group (B) before and 1 year after RYGB. Before RYGB, both groups have comparable

Table 1
Clinical characteristics in obese patients with T2D before and 1 year after RYGB (n = 43)

	Before RYGB	1 Year after RYGB	*P* value
BMI (kg/m^2)	31.3 ± 3.2	24.4 ± 2.2	.000
SBP (mm Hg)	132.9 ± 13.9	122.2 ± 12.1	.000
DBP (mm Hg)	83.8 ± 8.9	76.9 ± 7.7	.000
TC (mmol/L)	5.0 ± 1.0	4.1 ± .8	.000
TG (mmol/L)	2.5 ± 3.1	1.0 ± .4	.000
HDL-c (mmol/L)	1.0 ± .2	1.2 ± .3	.000
LDL-c (mmol/L)	2.9 ± .9	2.3 ± .6	.000
FPG (mmol/L)	8.6 ± 2.7	6.0 ± 1.4	.000
2 hPG (mmol/L)	13.5 ± 4.7	7.6 ± 3.3	.000
C-peptide (ng/mL)	2.6 ± 1.2	1.8 ± .5	.000
2 hC-peptide (ng/mL)	5.9 ± 3.7	5.7 ± 2.5	.663
HbA1C (%)	8.4 ± 2.0	6.2 ± 1.0	.000
HOMA-IR	5.6 (3.6, 9.4)	1.20 (.9, 2.0)	.000
OHA (n, %)	36 (83.7%)	6 (14.0%)	.000
Insulin therapy (n, %)	21 (48.8%)	1 (2.3%)	.000

Data represent means ± SD or median (centile 25, centile 75) or percentages.

BMI = Body mass index; DBP = Diastolic blood pressure; FPG = Fasting plasma glucose; HbA1C = glycated hemoglobin; HDL-c = High-density lipoprotein; HOMA-IR = Homeostasis model assessment–insulin resistance; 2 hPG = Plasma glucose 2 hours after meal; LDL-c = Low-density lipoprotein; OHA = Oral hypoglycemic agents; RYGB = Roux-en-Y gastric bypass; SBP = Systolic blood pressure; T2D = type 2 diabetes; TC = Total cholesterol; TG = Total triglycerides.

MAGE and SD levels. However, 1year after RYGB, MAGE in the dual-remission group tend to decrease and is significantly reduced compared with the complete remission group (Fig. 2). Correlation analysis shows diabetes duration was positively correlated with MAGE (Fig. 3). Multiple logistic regression models indicated that shorter duration was associated with higher possibility to achieve dual-remission of diabetes 1year after RYGB. The odd ratio was .70 (95% CI, .52–.93) after adjustment for age, gender, HbA1C, and insulin therapy.

Discussion

Glycemic variability has been identified as a predictor of cyclic hyperglycemia and hypoglycemia episodes and has been associated with microvascular and macrovascular complications. Several studies have highlighted the potential mechanisms of glucose variability in cardiovascular disease [12] and diabetic retinopathy [13]. Sustained glycemic control is crucial to the prevention and delay of diabetes-related cardiovascular diseases and diabetic chronic complications [14].

Although a lot of prior studies [15–17] have supported RYGB as an effective therapy in most morbidly obese patients with T2D, some studies suggest that mortality may be decreased by as much as 40% [18]. A recent published meta-analysis shows that T2D remission rate 1 year after RYGB ranged from 42% to 96% [19]. However, high glycemic variability assessed by CGMS seemed difficult to improve after RYGB [20]. In our study, according to standard I, which is commonly used in clinic, the overall 1-year remission rate was 62.8%, consistent with many prior studies. In support, CGM data shows that mean BG, min BG, time in BG $\geq$7.0 mmol/L, 7.8 mmol/L, and 11.1 mmol/L were decreased significantly 1 year after RYGB. However, MAGE, SD (which represents glycemic variability), and max BG fail to be improved. In addition, the time in BG $\leq$ 3.9 mmol/L increased significantly. These

Table 2
Variables measured by the continuous glucose monitoring system before and 1 year after RYGB (n = 43)

	Before RYGB	1 Year after RYGB	*P* value
MAGE (mmol/L)	5.4 ± 2.3	5.9 ± 2.4	.282
SD (mmol/L)	2.2 ± .9	2.2 ± .8	.664
Mean BG (mmol/L)	9.1 ± 1.8	7.3 ± 1.5	.000
Max BG (mmol/L)	14.6 ± 3.2	13.7 ± 3.4	.198
Min BG (mmol/L)	5.4 ± 1.7	4.3 ± 1.1	.004
Time in BG $\geq$7.0 mmol/L (min)	1040.7 ± 342.6	641.9 ± 335.4	.000
Time in BG $\geq$7.8 mmol/L (min)	862.6 ± 395.2	467.9 ± 283.9	.000
Time in BG $\geq$11.1 mmol/L (min)	322.2 ± 314.4	127.7 ± 138.7	.001
Time in BG $\leq$3.9 mmol/L (min)	.0 ± .0	39.7 ± 87.9	.010

Data represent means ± S.D

BG = Blood glucose; RYGB = Roux-en-Y gastric bypass; MAGE = Mean amplitude of glycemic excursion; SD = Standard deviations.

Table 3
Clinical characteristics between dual-remission group and complete remission group before and 1 year after RYGB.

	Dual-remission (Standard III)		Complete remission (Standard I)	
	Baseline	1 Year	Baseline	1 Year
N (F/M)	8 (4/4)		27 (14/13)	
Age (y)	39.3 ± 7.9		47.5 ± 11.4*	
Duration (y)	3.3 ± 3.3		6.0 ± 4.0*	
BMI (kg/m^2)	32.0 ± 4.0	23.7 ± 2.7†	31.6 ± 3.2	24.5 ± 2.3†
SBP (mm Hg)	133.0 ± 9.8	120.3 ± 6.5†	133.9 ± 12.5	122.4 ± 12.8‡
DBP (mm Hg)	84.4 ± 4.5	81.0 ± 6.7	85.0 ± 7.9	78.2 ± 7.6‡
TC (mmol/L)	4.4 ± .7	3.9 ± .6†	4.7 ± .8	4.0 ± .8†
TG (mmol/L)	1.9 ± .7	0.9 ± .5†	1.9 ± .9	.9 ± .4†
HDL-c (mmol/L)	1.0 ± .2	1.3 ± .2†	1.0 ± .2	1.2 ± .3‡
LDL-c (mmol/L)	2.5 ± .6	2.0 ± .4†	2.8 ± .7	2.3 ± .5†
FPG (mmol/L)	7.8 ± 2.8	4.7 ± .5†	8.3 ± 2.5	5.0 ± .5*‡
2 hPG (mmol/L)	12.9 ± 4.1	5.5 ± 1.5†	13.3 ± 4.8	6.5 ± 1.2*†
C-peptide(ng/mL)	3.4 ± 1.2	1.7 ± .4†	2.9 ± 1.2	1.9 ± .5‡
2 hC-peptide (ng/mL)	7.4 ± 3.6	6.1 ± 3.0	7.1 ± 4.0	6.2 ± 2.6
HbA1C (%)	7.1 ± 1.4	5.3 ± .3†	7.9 ± 1.6§	5.7 ± 0.3*‡
HOMA-IR	5.6 (4.0, 8.5)	0.9 (.8, 1.0)†	5.4 (2.4, 18.7)	1.2 (.8, 3.4)†
OHA (n, %)	8 (100%)	0†	24 (88.9%)	0†
Insulin therapy (n, %)	0	0	15 (55.6%)*	0†

Data represent means ± S.D. or median (centile 25, centile 75) or percentages.

BMI = Body mass index; DBP = Diastolic blood pressure; FPG = Fasting plasma glucose; HbA1C = glycated hemoglobin; HDL-c = High-density lipoprotein; HOMA-IR = Homeostasis model assessment–insulin resistance; 2 hPG = Plasma glucose 2 hours after meal; LDL-c = Low-density lipoprotein; OHA = Oral hypoglycemic agents; RYGB = Roux-en-Y gastric bypass; SBP = Systolic blood pressure; TC = Total cholesterol; TG = Total triglycerides.

Homeostasis model assessment: insulin resistance (HOMA-IR; mIU/mmol/L^2) = fasting insulin (mIU/L) × fasting glucose (mmol/L) / 22.5.

*P < .01 between group.

†$P < .01$ within group.

‡$P < .05$ within group.

§$P < .05$ between group.

results were consistent with those of the Helene Hanaire et al. [5] study. Taken together, though RYGB can lead to high remission rate in Chinese obese patients with T2D, it fails to improve glycemic variability after a mixed-meal challenge.

An important reason behind high glycemic variability after RYGB is dumping syndrome, which is one of the prominent features occurring in varying degrees in up to 70% of patients [21,22]. Due to the anatomic changes of RYGB, ingested nutrients can empty rapidly from the gastric pouch to reach the distal small intestine in greater quantities than normal, leading to postprandial hyperglycemia and increased release of gut hormones, including cholecystokinin (CCK), peptide YY (PYY), and the so-called "incretin hormones" – glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The presence of a large nutrient load in the intestine can also increase splanchnic blood flow and, in turn, lead to early or late dumping syndrome and increased glycemic excursion.

Currently, bariatric literature presents results in terms of rate of diabetes cure or remission, usually defined as the normalization of glucose levels and HbA1C in the absence of active antidiabetic therapy. Glycemic variability hasn't yet been included in diabetes remission criteria. Although an accurate assessment of glycemic fluctuation might be difficult clinically and highly costly, it should be taken into account when evaluating glucose homeostasis after metabolic surgery. Patients who are apparently cured of diabetes by standard criteria might still be exposed to significant glucose variability, which could cause future chronic complications of diabetes. In our previous multicenter study, we established normal reference values for CGM parameters in the Chinese population. This can be used to aid diabetes management. According to standard III, only 18.6% of patients achieve "dual-remission." To further explore the features of the dual-remission group, we compared the clinical parameters between these 2 groups at baseline. A younger age, shorter duration, lower HbA1C level, and no insulin usage were found in the dual-remission group. One year after RYGB, MAGE tends to reduce in dual-remission group and is significantly decreased compared with the complete remission group. Correlation analysis shows MAGE postoperative was positively correlated with diabetes duration. Furthermore, multiple logistic regression models indicated that shorter duration was an independent factor associated with a higher possibility to achieve dual-remission 1 year after RYGB. As described in previous studies [23], diabetes duration is the main prognostic factor for diabetes remission after metabolic surgery. Individuals with a greater glycemic excursion are presumably further along the progressive course of

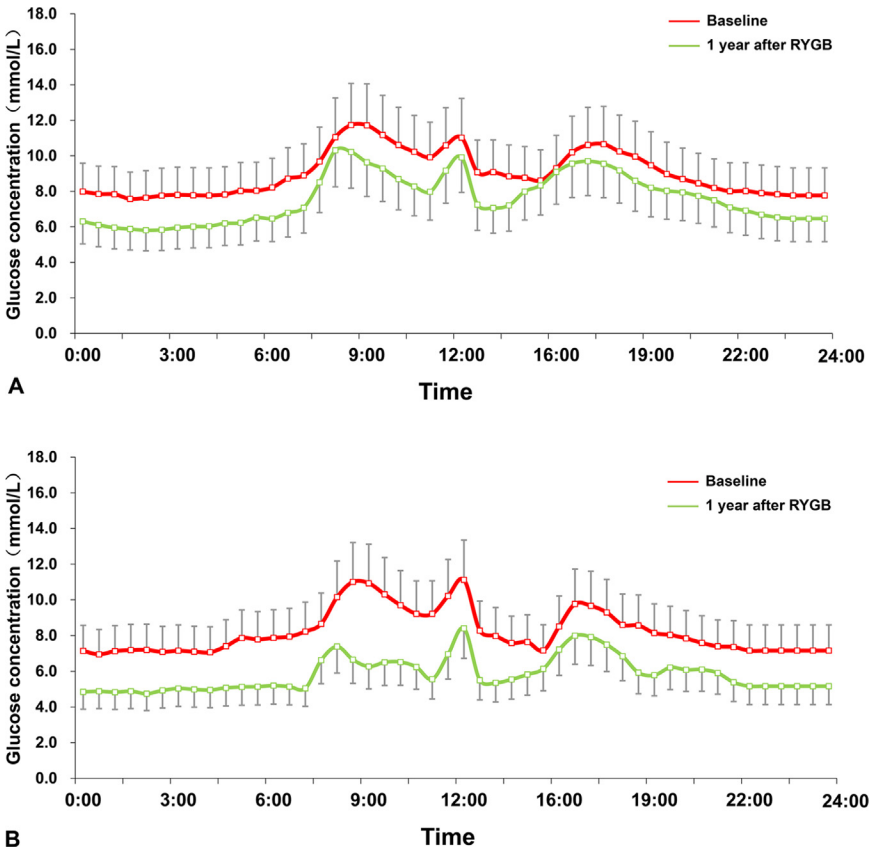

Fig. 1. Continuous glucose monitoring profile in the complete remission group (A) and dual-remission group (B) before and 1 year after RYGB. RYGB = Roux-en-Y gastric bypass.

beta-cell dysfunction that characterizes the natural history of T2D.

Since glycemic excursions remain a challenge even after RYGB, some intervention strategies are required to overcome it. Physical activity (PA) might be a simple and effective way to decrease glycemic excursions. Manohar et al. [24] reported that walking 3.5–4.0 miles during a 24-hour period at normal velocity (1.2 mph) has a significant impact on postprandial glucose excursions in healthy population and T1D patients.

In terms of diet management, caloric restriction [25] has been reported to effectively improve glycemic variability after RYGB. In routine practice, eating multiple small meals rather than 3 larger ones is an effective way to avoid postprandial hyperglycemia. The Valderas et al. [26] study indicated that oral administration of 100 mg of Acarbose (α-glucosidase inhibitor) 15 minutes before the meal can be helpful to avoid postprandial hypoglycaemia following RYGB by decreasing the hyperinsulinemic response. A recent study shows that treatment with sitagliptin,

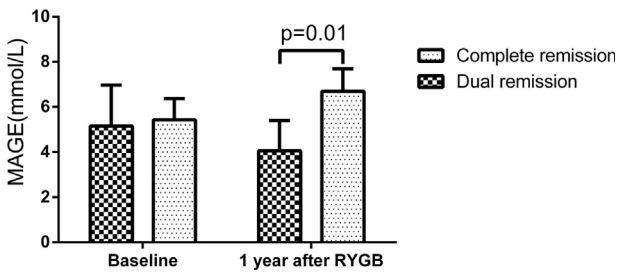

Fig. 2. MAGE in the complete remission group and dual-remission group before and 1 year after RYGB. MAGE = Mean amplitude of glucose excursion; RYGB = Roux-en-Y gastric bypass.

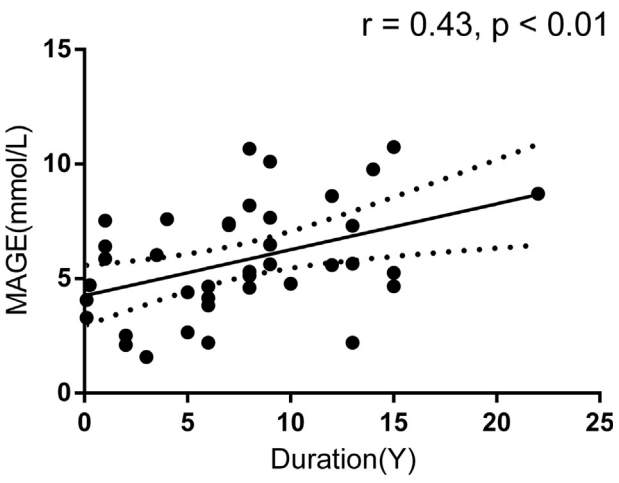

Fig. 3. Correlation analysis between diabetes duration and MAGE. MAGE = Mean amplitude of glucose excursion.

a dipeptidyl peptidase-4 inhibitor, can lead to significant reduction in glucose excursions [27].

The present study has several limitations, such as a relatively small population size and a limited follow-up duration. Therefore, the results should be regarded as preliminary. Secondly, we did not investigate the levels of incretin hormones before and after RYGB. Thus, the link between glycemic variability and the changes in incretin hormones remain unclear. In addition, it would be more accurate if the measurement of glucose variability was performed in free living conditions before and after the operation. The specific diet instruction and meals during the assessment might reduce the representation of the real life state.

Conclusion

In summary, our study suggested that although RYGB was an effective procedure to treat obese patients with T2D, further concern should be warranted on postoperative exaggerated glycemic variability in real life. HbA1C and glucose levels and parameters on glycemic variability could be involved in the evaluation on diabetes remission after metabolic surgery, even though the clinical importance of glucose variability is still under discussion. In the present study, we found that diabetes duration is the most important factor to predict dual-remission after the surgery. More lifestyle and pharmaceutical strategies following RYGB aimed at reducing glucose excursion and preventing post-prandial symptoms are required.

Disclosures

The authors declare that they have no conflict of interest.

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