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ORIGINAL CONTRIBUTIONS

Risk Factors for Relapse of Hyperglycemia after Laparoscopic Roux-en-Y Gastric Bypass in T2DM Obese Patients: a 5-Year Follow-Up of 24 Cases

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Abstract

Objectives To explore the risk factors for relapse of hyperglycemia in obese patients with type II diabetes mellitus (T2DM) who received laparoscopic Roux-en-Y gastric bypass (LRYGB) surgery.

Methods A retrospective analysis was performed on all obese patients with T2DM who underwent a LRYGB during the period 2011–2013. Demographics, preoperative body mass index (BMI), preoperative glycated hemoglobin A1c (HbA1c), adherence to lifestyle intervention, preoperative medication of insulin, and the time interval between surgery and diagnosis of T2DM were investigated and compared.

Results A total of 24 patients were included in our study. The median age was 45.5 years, the median BMI was 29.9 kg/m^2, and the median HbA1c was 7.9%. Out of 24 patients, 54.2% (13/24) experienced a relapse of hyperglycemia. The 1-year, 3-year, and 5-year relapse rates were 4.2%, 12.5%, and 50.0%, respectively. The preoperative HbA1c level, C-peptide (2 h) level, and C-peptide (3 h) level were identified as independent variables for the relapse of hyperglycemia (8.11 ± 0.48 vs 7.72 ± 0.37 kg/m^2, $p = 0.036$; 4.35 ± 1.46 vs 7.13 ± 4.10 ng/ml, $p = 0.032$; 3.76 ± 0.61 vs 5.99 ± 3.39 ng/ml, $p = 0.029$). Lifestyle intervention could reduce the hyperglycemia relapse rate (66.7 vs 41.7%) after LRYGB surgery.

Conclusions The preoperative HbA1c level and C-peptide level at surgery have an important significance in predicting the relapse of hyperglycemia after LRYGB surgery; lifestyle intervention is crucial for these patients.

Keywords Recurrence of T2DM · Obesity · LRYGB

Introduction

The growing pandemic of type 2 diabetes mellitus (T2DM) is a major health problem worldwide. People with diabetes have an increased risk of developing serious life-threatening health problems resulting in higher medical care costs, reduced quality of life, and increased mortality [1]. It is estimated that in 2017, there were 451 million (age 18–99 years) people with diabetes mellitus worldwide and that figure is expected to increase to 693 million by 2045 [2].

Obesity has a strong association with T2DM and cardiovascular risk factors. Even though both observational studies and randomized trials have shown that bariatric surgery results in a significant and durable weight loss, as well as remarkable improvement in T2DM, there are still many once "cured" patients suffering from a relapse of hyperglycemia [3–5]. To determine the risk factors for the relapse of hyperglycemia, we present the 5-year follow-up data of 24 once "completely cured" patients after laparoscopic Roux-en-Y gastric bypass, some of which ultimately had a relapse of hyperglycemia. Analyzed data included demographics, preoperative body mass index (BMI), preoperative glycated hemoglobin A1c (HbA1c), preoperative C-peptide level, preoperative medication of insulin, adherence to postoperative lifestyle intervention, and the time interval between surgery and diagnosis of T2DM.

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Methods

Study Design and Patients

Inclusion criteria were an age of 25–65 years, a BMI of 27.5 kg/m^2 or more, a history of type 2 diabetes lasting at least 3 years, preoperative HbA1c concentration of ≥ 7.0%, and the ability to understand and comply with the study protocol. Exclusion criteria were a history of type 1 diabetes, diabetes secondary to a specific disease, previous bariatric surgery, pregnancy, incomplete remission of diabetes within 6 months after surgery, other medical disorders requiring short-term hospital admission, and severe diabetes complications.

Demographics, preoperative BMI, preoperative HbA1c, preoperative usage of insulin, adherence to postoperative lifestyle intervention, and the time interval between surgery and diagnosis of T2DM were investigated and compared to explore the risk factors for relapse of hyperglycemia.

In this retrospective study, we looked at 24 obese patients with T2DM who underwent bariatric surgery from 2011 to 2013 at a single center and had a complete remission (FBG 5.6 mmol/L and HbA1c < 6.0% for at least 1 year without the use of oral hypoglycemic medication or insulin) according to the ADA criteria [6] within 6 months after LRYGB surgery. All patients were advised to receive standard management for diabetes in the department of endocrinology and have a regular postoperative follow-up every 3 months at our department; data including weight, height, waist, blood pressure, blood glucose, HbA1c, c-peptide level, and nutritional status was recorded.

Surgical Procedure

The surgical procedure is the standard Roux-en-Y procedure, which including the identification of the Treitz ligament, section of the omentum, and measurement of a 100-cm long, biliopancreatic limb. The gastric pouch was divided by consecutive applications of linear endostaplers (60 mm/3.5–4.2 mm) to create a 25- to 30-ml gastric pouch. Side to side gastrojejunal anastomosis was performed using linear endostaplers (60 mm/3.5–4.2 mm). An alimentary limb of 100 cm was accurately measured from that point. A jejunojejunal side to side anastomosis was performed with a linear endostapler (60/2.5 mm). Mesenteric space was closed with a nonabsorbable suture, and the jejunum between the two anastomoses was finally transected. The Petersen space was closed. Finally, a para-anastomotic Silastic drain was placed.

Statistical Analysis

Statistical analysis of the data was carried out using SPSS software version 22.0 and GraphPad Prism 5. Data were summarized as the median and interquartile range (IQR) for continuous variables and as count and frequency for categorical variables. Relapse-free survival (RFS) was defined as the time from surgery to the first postoperative onset of hyperglycemia (HbA1c concentration ≥ 7.0%). Follow-up was calculated using the reverse Kaplan–Meier method. Median survival was estimated using the Kaplan–Meier method, and the difference was tested using the log-rank test. Classified variable was accessed by performing the χ^2 test. Significance levels were assessed at p value < 0.05.

Ethics

The study protocol was approved by the institutional review board of the First Hospital Affiliated to Army Medical University. Written informed consent was obtained from all selected patients.

Results

The flow diagram shows the study selection process (Fig. 1), only 26.4% (24/91) patients got completely remission of diabetes within 6 months after surgery. A total of 24 patients with a median age of 45.5 years (IQR, 39.0–54.8) were included in the study, of which 17 (70.8%) were men and 7 (29.2%) were women (Table 1). All patients underwent primary LRYGB and none of them experienced complications during hospitalization. At the time of the surgery, the median BMI was 29.9 kg/m^2 (IQR, 27.8–32.1) and the median HbA1c was 7.9% (IQR, 7.6–8.3). The median interval between the surgery and diagnosis of T2DM was 75.0 months (IQR, 61.0–89.5). The median complete remission time after surgery was 4.5 months (IQR, 3.0–5.0).

The median follow-up period was 69.5 months (IQR, 62.3–74.0). Out of 24 patients, 13 (54.2%) experienced a relapse of hyperglycemia with a median relapse time of 52 (12–66) months. At the time of the 1-year, 3-year, and 5-year follow-

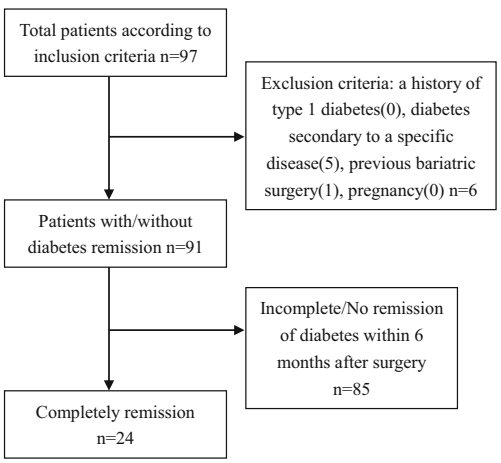

Fig. 1 Patient selection process

Table 1 Characteristics of 24 patients stratified by hyperglycemia relapse

Characteristics	Relapse ($n = 13$)	Nonrelapse ($n = 11$)	p value
Sex (n)			0.793
Male	9	8	
Female	4	3	
Age	46.15 ± 8.92	44.73 ± 12.17	0.751
Preoperative BMI	30.65 ± 2.11	28.86 ± 2.40	0.065
Preoperative HbA1c	8.11 ± 0.48	7.72 ± 0.37	*0.036*
Remission time	3.77 ± 1.59	4.45 ± 1.21	0.255
T2DM duration	74.62 ± 25.55	78.36 ± 18.33	0.681
C-peptide (pre)	2.32 ± 0.96	3.09 ± 0.87	0.053
C-peptide (1 h)	3.43 ± 0.64	5.03 ± 2.87	0.063
C-peptide (2 h)	4.35 ± 1.46	7.13 ± 4.10	*0.032*
C-peptide (3 h)	3.76 ± 0.61	5.99 ± 3.39	*0.029*
Use of insulin			0.413
Yes	8	4	
No	5	7	

BMI, body mass index; *HbA1c*, glycosylated hemoglobin; *T2DM*, type 2 diabetes mellitus; *C-peptide (pre)*, C-peptide level before C-peptide release tests; *C-peptide (1 h)*, C-peptide level after (1 h) C-peptide release tests

Italics emphasis means $p < 0.05$ (statistically significant)

up, the relapse rates were 4.2% (1/24), 12.5% (3/24), and 50.0% (12/24), respectively, of which one patient was diagnosed relapse of hyperglycemia at the 66th months after surgery (Fig. 2).

Among the evaluated risk factors, preoperative HbA1c level, C-peptide (2 h) level, and C-peptide (3 h) level were identified as independent variables for the relapse of hyperglycemia (8.11 ± 0.48 vs 7.72 ± 0.37 kg/m^2, $p = 0.036$; 4.35 ± 1.46 vs 7.13 ± 4.10 ng/ml, $p = 0.032$; 3.76 ± 0.61 vs 5.99 ± 3.39 ng/ml, $p = 0.029$). Patients with higher preoperative HbA1c levels and lower C-peptide (2 h and 3 h) levels were more likely to have a higher risk of hyperglycemia relapse. There was no significant difference in other characteristics between these two groups.

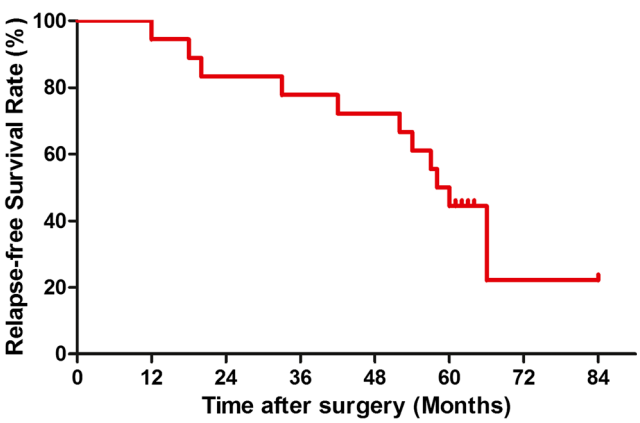

Fig. 2 The relapse of hyperglycemia after surgery

In addition, lifestyle intervention was likely to reduce the relapse rate of hyperglycemia after bariatric surgery; overall, five of the 12 (41.7%) patients who underwent lifestyle intervention and eight of the 12 (66.7%) patients who refused lifestyle intervention experienced hyperglycemia relapse during our follow-up.

Discussion

Many studies have shown that T2DM is closely associated with obesity, and bariatric surgery has been confirmed to be efficient in treating T2DM in morbidly obese patients [3, 7, 8]. In addition, bariatric surgery has been proven to be an option for obese individuals with uncontrolled obesity-induced T2DM [9, 10]. While in many centers, including our center, the reported complete remission rate is relatively low. Pournaras et al.[11] reported that only 40.6% (65/160) of the patients had a complete remission after gastric bypass. Aminian et al [4] reported that only 11% of the patients had complete remission after bariatric surgery and only 3% of the patients could be cured (continuous complete remission for ≥ 5 years). In our study, only 24 (26.4%) of 91 patients had complete remission. Most diabetes patients need continuous therapy on diabetes after surgery. Furthermore, even though plenty of studies have reported a remission of T2DM after bariatric surgery, many patients have still experienced disease recurrence over time [12, 13]. Mingrone et al. [3] carried out an open-label, single-center, randomized controlled trial which showed that approximately 53% of patients experienced a relapse of hyperglycemia after Roux-en-Y gastric bypass. Chikunguwo et al. [13] reported that 68 of 157 (43.3%) patients developed T2DM recurrence after Roux-en-Y gastric bypass. In our center, 13 of 24 (54.2%) patients developed hyperglycemia relapse within 6 years after Roux-en-Y gastric bypass. Based on these results, we hypothesized that there are some potential risk factors contributing to the relapse of hyperglycemia after bariatric surgery.

Obesity, especially central obesity, is closely associated with insulin resistance and the development of T2DM, which is also the reason bariatric surgery can reduce insulin resistance and be used for treating T2DM [14, 15]. BMI can quantify the degree of obesity, which is also the most important indication for bariatric surgery for the treatment of T2DM. BMI has been found to be associated with T2DM remission after bariatric surgery [16], yet BMI alone cannot adequately predict diabetes remission or relapse after surgery [3]. When we evaluated the role of BMI in predicting the relapse of hyperglycemia in our study, we found that although the mean preoperative BMI of the relapse arm was slightly higher than that of the nonrelapse arm (30.65 ± 2.11 vs 28.86 ± 2.40, $p = 0.065$), the difference showed no statistical significance.

Table 2 Relationship between hyperglycemia relapse rate and lifestyle intervention

Lifestyle intervention	Relapse (*n*)	Nonrelapse (*n*)	Relapse rate	χ^2	*P*
Yes	5	7	41.7%	1.51	0.219
No	8	4	66.7%		

The indication for metabolic surgery should be uncontrolled T2DM, which is represented by an elevated HbA1c. Although BMI was regarded as a criterion for the surgical indication for bariatric surgery due to its association with increasing mortality, the risk of T2DM is highly associated with an elevated HbA1c. Hall et al. [17] reported that patients with a baseline HbA1c > 10 had a 50% rate of remission compared to 77.3% for patients with an HbA1c of 6.5–7.9 after Roux-en-Y gastric bypass surgery, suggesting that better control of diabetes prior to surgery corresponds to a higher rate of remission. It was also reported that patients with complete resolution of diabetes had lower preoperative HbA1c levels and lower daily doses of metformin and insulin use [18]. All patients included in our study received the standard therapy for diabetes, hence the preoperative HbA1c level could partially reflect the therapeutic efficacy for diabetes and the β-cell function. From our study, we found that the relapse arm showed significantly higher (8.11 ± 0.48 vs 7.72 ± 0.37 kg/m^2, $p = 0.036$) preoperative HbA1c levels than that of the nonrelapse arm, suggesting that preoperative HbA1c level could be a predictor for a relapse of hyperglycemia after Roux-en-Y gastric bypass surgery.

The β-cell function and the islet cell mass have been demonstrated to be closely associated with the remission and relapse of T2DM after bariatric surgery [19, 20]. The C-peptide level is a direct measurement of insulin secretion and reflects the islet cell mass. Sjöström et al. [21] reported that baseline insulin was an independent predictive factor of cardiovascular disease reduction after bariatric surgery, indicating the importance of the C-peptide level in evaluating patients considering metabolic surgery. Furthermore, Aarts et al. [18] reported that 90% of T2DM patients with preoperative fasting C-peptide levels > 1.0 nmol/l achieved a postoperative HbA1c < 6.5% and 74% achieved complete resolution of their diabetes after Roux-en-Y gastric bypass. In our study, we found that preoperative fasting C-peptide levels (2 h and 3 h) correlated with the relapse of hyperglycemia after surgery, indicating that islet cell mass and β cell function could be predictors of the recurrence of hyperglycemia. In addition to the preoperative fasting C-peptide levels, we investigated the role of T2DM duration in predicting the relapse of hyperglycemia. The duration of T2DM reflects the natural course and deterioration of β cell function. A longer history of T2DM reflects a greater percentage of an irreversible β cell damage [22]. The duration of T2DM has been shown in previous studies to independently predict the success of metabolic surgery, which indicates that a shorter duration of T2DM corresponding to a higher rate of diabetes remission [17, 19]. While the T2DM duration was not statistically associated with relapse of hyperglycemia in our study, this may have been due to the relatively small sample size.

Lifestyle intervention is a classical and effective method for controlling T2DM, yet few studies have reported the relationship between lifestyle intervention and the relapse of hyperglycemia after bariatric surgery for obese patients with T2DM (Table 2). For obese patients, an integrated program that combines advice on diet, physical activity, and psychosocial concerns both before and after surgery is needed according to the Clinical Guidelines for the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults from the National Heart, Lung, and Blood Institute (NHLBI) [23]. Nonetheless, the correlation between lifestyle management and hyperglycemia relapse has still been undefined. Our study showed that lifestyle intervention after bariatric surgery was likely to reduce the possibility of relapse of hyperglycemia (41.7 vs 66.7%).

Our study had a few limitations. First, the relatively small size of the study samples might have weakened the statistical power of our study, although we found that only HbA1c and C-peptide level showed a statistical significance, the prognostic value of other factors for relapse of hyperglycemia still needs further study to clarify. Second, the predictive power was limited by the lack of data at every follow-up; we would need to record more data at every follow-up to make our results more receivable and convictive. Third, there were no unitive criteria for lifestyle intervention judgment in our study. The subjectivity of our judgment might weaken the reliability of the results. Even though we found that lifestyle intervention may correlate to hyperglycemia relapse, the unitive criteria need to be carried out in our further studies.

In conclusion, the preoperative HbA1c level and C-peptide level at surgery have important significance in predicting the relapse of hyperglycemia after LRYGB surgery. For patients having higher HbA1c and C-peptide levels, we need to pay more attention to postoperative follow-up and continuous therapy for diabetes, hence to increase the remission rate. In addition, we need to pay more attention to lifestyle intervention or even pharmaceutical therapy to patients after surgery, as they could be crucial for them.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Baena-Díez JM, Peñafiel J, Subirana I, Ramos R, Elosua R, Marín-Ibañez A, Guembe MJ, Rigo F, Tormo-Díaz MJ, Moreno-Iribas C, Cabré JJ, Segura A, García-Lareo M, Gómez de la Cámara A, Lapetra J, Quesada M, Marrugat J, Medrano MJ, Berjón J, Frontera G, Gavrila D, Barricarte A, Basora J, García JM, Pavone NC, Lora-Pablos D, Mayoral E, Franch J, Mata M, Castell C, Frances A, Grau M, FRESCO Investigators. Risk of cause-specific death in individuals with diabetes: a competing risks analysis [J]. Diabetes Care, 2016, 39(11): 1987, 1995.
2. Cho NH, Shaw JE, Karuranga S, et al. IDF diabetes atlas: global estimates of diabetes prevalence for 2017 and projections for 2045 [J]. Diabetes Res Clin Pract. 2018;138:271–81.
3. Mingrone G, Panunzi S, De Gaetano A, et al. Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial [J]. Lancet. 2015;386(9997): 964–73.
4. Aminian A, Brethauer SA, Andalib A, Punchai S, Mackey J, Rodriguez J, Rogula T, Kroh M, Schauer PR Can sleeve gastrectomy "cure" diabetes? Long-term metabolic effects of sleeve gastrectomy in patients with type 2 diabetes [J]. Ann Surg, 2016, 264(4): 674, 681.
5. Brethauer SA, Aminian A, Romero-Talamã s H, et al. Can diabetes be surgically cured? Long-term metabolic effects of bariatric surgery in obese patients with type 2 diabetes mellitus [J]. Ann Surg, 2013, 258(4): 636–637.
6. Buse JB, Caprio S, Cefalu WT, Ceriello A, del Prato S, Inzucchi SE, McLaughlin S, Phillips GL, Robertson RP, Rubino F, Kahn R, Kirkman MS How do we define cure of diabetes? [J]. Diabetes Care, 2009, 32(11): 2133–2135.
7. Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus [J]. Ann Surg, 2003, 238(4): 467–484.
8. Rubino F, Kaplan LM, Schauer PR, et al. The diabetes surgery summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus [J]. Ann Surg. 2010;251(3):399–405.
9. Dixon JB, Zimmet P, Alberti KG, et al. Bariatric surgery: an IDF statement for obese type 2 diabetes [J]. Arquivos Brasileiros De Endocrinologia E Metabologia. 2011;5(3):e171–89.
10. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes [J]. N Engl J Med. 2012;366(17):1567–76.
11. Pournaras DJ, Aasheim ET, Søvik TT, et al. Effect of the definition of type II diabetes remission in the evaluation of bariatric surgery for metabolic disorders. Br J Surg. 2012 Jan;99(1):100–3.
12. Digiorgi M, Rosen DJ, Choi JJ, et al. Re-emergence of diabetes after gastric bypass in patients with mid- to long-term follow-up [J]. Surg Obes Relat Dis. 2010;6(3):249–53.
13. Chikunguwo SM, Wolfe LG, Dodson P, et al. Analysis of factors associated with durable remission of diabetes after Roux-en-Y gastric bypass [J]. Surg Obes Relat Dis. 2010;6(3):254–9.
14. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic [J]. Nature. 2001;414(6865):782–7.
15. Pournaras DJ, Osborne A, Hawkins SC, et al. Remission of type 2 diabetes after gastric bypass and banding: mechanisms and 2 year outcomes [J]. Ann Surg. 2010;252(6):966–71.
16. Rosenthal R, Li X, Samuel S, et al. Effect of sleeve gastrectomy on patients with diabetes mellitus [J]. Surg Obes Relat Dis. 2009;5(4): 429–34.
17. Hall TC, Pellen MG, Sedman PC, et al. Preoperative factors predicting remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass surgery for obesity [J]. Obes Surg. 2010;20(9):1245–50.
18. Aarts EO. Janssen, et al. Preoperative fasting plasma C-peptide level may help to predict diabetes outcome after gastric bypass surgery [J]. Obes Surg. 2013;23(7):867–73.
19. Lee WJ, Ser KH, Chong K, et al. Laparoscopic sleeve gastrectomy for diabetes treatment in nonmorbidly obese patients: efficacy and change of insulin secretion [J]. Surgery. 2010;147(5):664–9.
20. Huang CK, Asim S, Chi-Hsien L, et al. Laparoscopic Roux-en-Y gastric bypass for the treatment of type II diabetes mellitus in Chinese patients with body mass index of 25–35 [J]. Obes Surg. 2011;21(9):1344–9.
21. Sjöström ML, Peltonen M, Jacobson P, et al. Bariatric surgery and long-term cardiovascular events [J]. Jama. 2012;307(1):56–65.
22. Lee WJ, Hur KY, Lakadawala M, et al. Predicting success of metabolic surgery: age, body mass index, C-peptide, and duration score [J]. Surg Obes Relat Dis. 2013;9(3):379–84.
23. National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. Obes Res 1998 Sep;6 Suppl 2: 51S–209S