Clinical Science

The better effect of Roux-en-Y gastrointestinal reconstruction on blood glucose of nonobese type 2 diabetes mellitus patients

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Type 2 diabetes mellitus; Gastric bypass surgery; Blood glucose

Abstract

BACKGROUND: Given the role of gastrointestinal reconstruction, we investigated whether Roux-en-Y gastrointestinal reconstruction (RYGR) and Billroth I reconstruction (B1R) can improve glucose in nonobese type 2 diabetes mellitus patients.

METHODS: Seventy-six nonobese type 2 diabetes mellitus patients underwent open subtotal gastrectomy with RYGR and B1R between January 2005 and January 2010 in our hospital. Besides demographic data, preoperative weight, glucose, hemoglobin A1c, ghrelin, and glucagon-like peptide 1 were determined.

RESULTS: As defined previously, 2 of 35 patients with RYGR were cured, 5 patients were controlled, and 10 patients were improved; similarly, 2 of 41 patients with B1R were controlled, and 3 patients improved 12 months after surgery. The fasting glucose and hemoglobin A1c decreased more significantly in RYGR patients \( (P < .05) \). Moreover, a higher fasting plasma GLP-1 level in RYGR patients and lower ghrelin in B1R patients were noted after surgery \( (P < .05) \).

CONCLUSIONS: RYGR shows a more effective amelioration in nonobese type 2 diabetes mellitus patients.

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The mechanism of bariatric surgery is still unclear. The leading theory aimed at explaining this observation implicates the so-called enteroinsular axis, a group of hormones secreted by the gut that have a significant effect on β-cell secretion of insulin, insulin resistance in the periphery, glycogenolysis, and gluconeogenesis. The changes of gastrointestinal reconstruction could result in hormonal alterations (eg, increased glucagon-like peptide [GLP-1] in Roux-en-Y gastric bypass and decreased ghrelin in sleeve gastrectomy).

In subtotal gastrectomy, Roux-en-Y gastrointestinal reconstruction (RYGR) has a similar gastrointestinal reconstruction of Roux-en-Y gastric bypass including exclusion of the duodenum and the proximal jejunum and early exposure of the rest of the jejunum to undigested food. With Billroth 1 reconstruction (B1R), the duodenal passage remains relatively intact. However, the study and comparisons of the effectiveness between 2 gastrojejunostomies in T2DM patients are still sparse, especially in nonobese patients. Therefore, the purpose of this study was to determine whether the improvement in diabetes observed after bariatric surgery for obesity also occurs in diabetic patients undergoing very similar procedures for reasons other than obesity and to compare the effectiveness of this method.

**Patients and Methods**

Nonobese T2DM patients (ie, body mass index [BMI] < 25 kg/m²) who experienced open subtotal gastrectomy (two thirds to three quarters of the distal stomach) with RYGR and B1R between January 2005 and January 2010 in our hospital were included in our retrospective analysis. We purposely excluded patients who underwent gastrectomy or partial gastrectomy for malignant diseases and co-existed malignant diseases, debilitating disease, unresolved psychiatric illness, or substance abuse because they might affect the metabolism and follow-up work.

Data on patient demographics, BMI, comorbidities, details of the operation, and diabetes mellitus including disease duration, medication use, fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and follow-up clinical notes (until the 12th month) were collected and analyzed retrospectively. Operative details recorded were operation time, duration of hospitalization, and complications noted until the last follow-up session. The plasma of patients was collected from patients directly and using a biobank. The fasting plasma ghrelin and GLP-1 levels were measured using an enzyme-linked immunosorbent assay (Human Ghrelin [active] ELISA and Glucagon Like Peptide-1 [active] ELISA; Millipore, St Charles, MO). The procedural protocols were approved and supervised by the Ethics Committee of Shandong University, Shandong, China.

The effectiveness of the surgery on T2DM was assessed on the basis of the postoperative HbA1c concentration and the fasting glucose level. The patients who did not receive any antidiabetic medication and had an HbA1c concentration less than 6% and FPG less than 6.1 mmol/L were considered as “cured or in remission.” The patients who had an HbA1c concentration between 6% and 7% were considered as “controls.” Patients with an HbA1c concentration greater than 7% but a less than 2-mmol/L decrease in FPG were considered as “improved.” The total effectiveness rate of the treatment was calculated as the sum of the rates of cured or in remission, control, and improved.

**Statistical analysis**

Continuous variables are presented as means ± standard deviation. The 2-sample paired t test, chi-square test, and independent t test were used. All statistics were 2 tailed and calculated with SPSS statistical software (SPSS Inc, Chicago, IL). P values less than .05 were considered statistically significant.

**Result**

**Patients, demographics, and metabolic characteristics**

From January 2005 to January 2010, 76 nonobese T2DM patients underwent subtotal gastrectomy with RYGR or B1R. Fifty patients were diagnosed with peptic ulcers and 26 with benign tumors. Because of the location, the extent of the lesion, and the avoidance of some side effects, the gastrointestinal reconstructions were conducted in different ways. Thirty-five patients accepted RYGR and 41 B1R. There was no significant difference in age, BMI, duration of diabetes, and size of stomach removed between these 2 groups of patients (Table 1). Although the operative time of RYGR was longer than that of B1R (126.3 ± 33.6 vs 95.3 ± 23.1 minutes, P < .05), the average lengths of the hospital stay of patients with RYGR were not significantly different from those with B1R (P > .05, Table 1). No mortality or serious complications occurred in these patients. After surgery, the BMI of patients with RYGR decreased from 22.3 to 20.7 kg/m² (P > .05) and patients with B1R from 22.9 to 19.8 kg/m² (P > .05), but there were no statistically significant differences before and after surgery.

**Effect on diabetes control**

The glucose metabolism of nonobese T2DM patients in 2 groups was significantly improved. As defined previously, 2 of 35 patients were cured, 5 patients were controlled, and 10 patients were improved in the RYGR group 12 months after surgery; similarly, 2 of 41 patients were controlled, and 3 patients were improved in the B1R group (Table 1). The average of fasting glucose in the RYGR group decreased from 11.5 ± 2.4 mmol/L before surgery to 9.7 ± 1.6 mmol/L 6 months after surgery (P < .05) and to 7.5 ± 1.1 mmol/L 12 months after surgery (P < .05). In the B1R group, the glucose decreased from 11.8 ± 2.7 mmol/L before surgery to 10.3 ± 1.9 mmol/L 6 months after surgery; similarly, 2 of 41 patients were controlled, and 3 patients were improved in the B1R group (Table 1).
after surgery ($P > .05$) and to 9.4 ± 1.5 mmol/L 12 months after surgery ($P < .05$, Fig. 1). Moreover, the HbA1c level in the 2 groups showed the same trend (Fig. 1). The average HbA1c level in RYGR patients decreased from 9.8% ± 2.3% to 8.3% ± 1.5% 6 months after surgery ($P < .05$) and to 5.9% ± 0.7% 12 months after surgery ($P < .05$). It also decreased from 9.3% ± 2.1% to 8.8% ± 0.8% 6 months after surgery ($P > .05$) and to 8.3% ± 1.0% 12 months after surgery in patients with B1R ($P > .05$) although there was no statistic difference between before and after surgery.

RYGR showed a more effective amelioration effect of T2DM than B1R in nonobese patients. Although there were no statistic differences between the 2 gastrojejunostomy groups in fasting glucose and HbA1c levels were no statistic differences between the 2 gastrojejunostomy groups in fasting glucose and HbA1c levels were no statistic differences before surgery. The fasting plasma glucose; HbA1c level in RYGR patients decreased from 9.8% to 8.3% after surgery in patients with B1R (P < .05). The HbA1c level in the RYGR group was also statistically lower than that in the B1R group (5.9% vs 8.3%, P < .05).

Changes of fasting glucagon-like peptide-1 and ghrelin levels

Although there were no statistic differences in the fasting plasma level of GLP-1 or ghrelin before surgery between the 2 groups, GLP-1 increased significantly in the RYGR group. It increased from 4.1 ± 0.9 pmol/L before surgery to 5.7 ± 1.1 pmol/L 6 months after surgery ($P < .05$, Fig. 1) and to 6.9 ± 1.3 pmol/L 12 months after surgery ($P < .01$), whereas it did not alter in the B1R group. The fasting levels of ghrelin in the B1R group decreased in the first 6 months after surgery (from 612 ± 135 pg/mL before surgery to 433 ± 95 pg/mL, P < .05) and increased to 515 ± 108 pg/mL 12 months after surgery ($P > .05$). There was no statistically significant difference between the different time intervals in the RYGR group.

Table 1 The baseline and postoperative demographic and metabolic profile of patients

<table>
<thead>
<tr>
<th>Table 1</th>
<th>The baseline and postoperative demographic and metabolic profile of patients</th>
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<tbody>
<tr>
<td></td>
<td>RYGR</td>
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<tr>
<td>Demographics</td>
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<tr>
<td>Male (n)</td>
<td>22</td>
</tr>
<tr>
<td>Female (n)</td>
<td>13</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45.3 ± 8.5</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.3 ± 1.5</td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Operative time (min)</td>
<td>126.3 ± 33.6</td>
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<tr>
<td>Size of stomach removed (%)</td>
<td>70.8 ± 10.5</td>
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<tr>
<td>Hospital stay (d)</td>
<td>13.2 ± 3.7</td>
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<tr>
<td>Diabetes characteristics before surgery</td>
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<tr>
<td>Duration of diabetes (y)</td>
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<td>Treat with insulin (n)</td>
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<tr>
<td>Treat with oral hypoglycemic drug (n)</td>
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<tr>
<td>FPG (mmol/L)</td>
<td>11.5 ± 2.4</td>
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<tr>
<td>Hba1c (%)</td>
<td>9.8 ± 2.3</td>
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<tr>
<td>Diabetes characteristics 12 months after surgery</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>20.7 ± 2.1</td>
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<tr>
<td>FPG (mmol/L)</td>
<td>7.5 ± 1.1</td>
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<tr>
<td>Hba1c (%)</td>
<td>5.9 ± 0.7</td>
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<tr>
<td>Remission rate, % (n)</td>
<td>5.7 (2)</td>
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<tr>
<td>Control rate, % (n)</td>
<td>14.3 (5)</td>
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<td>Improved rate, % (n)</td>
<td>28.6 (10)</td>
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<tr>
<td>Total effectiveness rate, % (n)</td>
<td>48.6 (17)</td>
</tr>
</tbody>
</table>

All data are reported as mean ± standard deviation. 
B1R = Billroth I reconstruction; BMI = body mass index; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; RYGR = Roux-en-Y gastrointestinal reconstruction.

*P < .05 between RYGR and B1R.

Comments

Roux-en-Y gastric bypass can effectively improve the glucose level of T2DM patients. With similar gastrointestinal reconstruction, RYGR was also found to ameliorate T2DM in nonobese patients in this study. In T2DM patients with a BMI below 25 kg/m², the total effectiveness rate of surgery was 48.6%; the fasting glucose level and the HbA1c level decreased significantly after surgery. Because HbA1c is not affected by the wide variation of blood glucose levels throughout the day, a continuous decrease of HbA1c in these patients over 12 months indicates the real amelioration of T2DM in the long-term.

RYGR in subtotal gastrectomy is a similar procedure as bariatric surgery. Therefore, it might share a similar mechanism of improvement of T2MD. Although the reason bariatric surgery induces the remission of T2DM is still not defined, there are many explanations regarding it. Changes in mechanical restriction, hormonal and neural signals generated by the surgery, and its adaptive consequences are supposed to affect other organs and kinds of behavioral changes such as food intake and food preference.

Starvation on its own improves T2DM, which has been reported as far back as the early 1900s. The ability of acute caloric restriction to transiently improve glucose in T2DM is well known. According to this model, when the patients returned to normal eating after Roux-en-Y gastric bypass, the symptoms of T2DM would relapse. However, the glucose and HbA1c levels did not increase although patients’ appetites were restored 12 months after surgery and they did not have significant weight loss. This model cannot explain the superiority of the glycemic control achieved after RYGR versus B1R.

The hypothesis about gut hormones (enteroinsular axis) comes into play here, which is described as the upper and lower intestinal hypothesis. Gut hormones can affect many aspects related to glycemic control, such as glucose-dependent insulin secretion, glucagon inhibition, gastric emptying, and satiety. The upper intestinal hypothesis...
suggests that the excision and exclusion of the duodenum and proximal jejunum may prevent the secretion of a putative signal that promotes insulin resistance and T2DM. For example, ghrelin, manufactured and released in the K cells of the distal stomach, duodenum, and proximal jejunum in response to glucose and fat intake, stimulate insulin counterregulatory hormones, suppress the insulin-sensitizing adipokine adiponectin, and inhibit insulin secretion. The exclusion and excision of the upper intestine could result in the diminution or absence of the stimuli of K cells, leading to decreased levels of ghrelin and an improvement in the glucose level. The amelioration of T2DM in B1R patients and low ghrelin level results support this hypothesis.

An alternative hypothesis, named the lower intestinal hypothesis, proposes that expedited nutrient delivery to the hindgut enhances excessive excretion of anorexigenic hormones, including GLP-1, adiponectin, and peptide YY. Up to two thirds of the insulin normally secreted in connection with food intake is produced by the insulinotropic actions of these hormones. These hormones can also suppress hepatic glucose output by inhibiting glucagon secretion in a glucose-dependent manner, inhibit gastric emptying, and enhance \( \beta \)-cell proliferation and survival in animal models. Our study found that RYGR effectively improves the glucose level of T2DM patients compared with B1R although there was no statistical significance in the sizes of the removed stomach, fasting glucose level, and HbA1c level between the 2 groups before surgery. The fasting level of GLP-1 in RYGR patients was higher than that in B1R patients. This provides strong evidence supporting the lower intestinal hypothesis.

Besides the enteroinsular axis, the gut-brain axis was also proposed. The nucleus neurons could receive and integrate afferent neural and metabolic signals of gastrointestinal reconstruction and then regulate energy homeostasis. We confirmed that more proopiomelanocortin neurons of diabetic rats were activated by GLP-1 after ileal transposition. Active proopiomelanocortin neurons in the hypothalamus can balance energy intake, expenditure, and storage by efferent neural and metabolic signals, conveying information about the energy status of the body. Therefore, the effect of surgery on T2DM is a response of several systems involving several organs.

Because 2 gastrointestinal reconstructions are effective procedures for T2DM and safe procedures, both of them should be considered for clinical use. However, RYGR improved the glucose level of patients more effectively than B1R because it not only removed distal gastric K cells and bypassed the upper intestine but also exposed the lower intestine earlier. It unites 2 theories for the resolution of diabetes: it has the effect of upper gastrointestinal hormone loss, and it lowers the intestinal hormone increase. Thus, RYGR might be a promising option in subtotal gastrectomy for T2DM patients. Although this study has some limitations
The results of our retrospective study show that RYGR can more effectively improve the glucose level of T2DM than B1R in nonobese patients. Thus, it might be preferable in subtotal gastrectomy for T2DM patients.

References