Surgery Today (2019) 49:637–644
https://doi.org/10.1007/s00595-019-1772-x

ORIGINAL ARTICLE

Additional effects of duodenojejunal bypass on glucose metabolism in a rat model of sleeve gastrectomy

Hiroomi Takayama[1] · Masayuki Ohta[1] · Kazuhiro Tada[1] · Kiminori Watanabe[1] · Takahide Kawasaki[1] · Yuichi Endo[1] · Yukio Iwashita[1] · Masafumi Inomata[1]

Received: 4 September 2018 / Accepted: 12 January 2019 / Published online: 31 January 2019

Abstract

Purpose Sleeve gastrectomy with duodenojejunal bypass (SG-DJB) is expected to become a popular procedure in East Asia. The aim of this study was to evaluate the effects of duodenojejunal bypass on glucose metabolism in a rat model of sleeve gastrectomy (SG).

Methods Twenty-four Sprague–Dawley rats were divided into two groups: SG-DJB and SG alone. 6 weeks after surgery, body weight, feed intake, and metabolic parameters were measured, and oral glucose tolerance tests (OGTT) were performed. The mRNA expression of factors related to gluconeogenesis and glucose transport was evaluated using jejunal samples. Protein expression of factors with significantly different mRNA expression levels was evaluated using immunohistochemistry.

Results Body weight and metabolic parameters did not significantly differ between the two groups. During the OGTT, the SG-DJB group showed an early increase in serum insulin followed by an early decrease in blood glucose compared with the SG group. Expression levels of glucose transporter 1 (GLUT1) and sodium-glucose cotransporter 1 (SGLT1) mRNA and protein in the alimentary limb (AL) were greater in the SG-DJB group than in the SG group.

Conclusions The additional effects of duodenojejunal bypass on glucose metabolism after SG may be related to increased expression of GLUT1 and SGLT1 in the AL.

Keywords Sleeve gastrectomy with duodenojejunal bypass · Sleeve gastrectomy · Glucose metabolism · GLUT1 · SGLT1

Introduction

Obesity is a global health problem with increasing prevalence [1]. Diabetes, a disease associated with obesity, is also prevalent worldwide, and has been predicted to steadily increase [2]. One treatment for obesity, bariatric surgery, not only results in weight loss but also causes long-term remission of diabetes more effectively than intensive medical therapy [3]. The Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most commonly performed bariatric procedures [1]. The RYGB is superior to SG for achieving diabetes remission [4]; however, RYGB has typically been avoided in Japan owing to concerns regarding gastric cancer occurrence in the excluded portion of the stomach. Because of this, Kasama et al. developed the SG with duodenojejunal bypass (SG-DJB) procedure in which the limbs of the small intestine are reconstructed in the same manner as for the RYGB [5]. The SG-DJB has been shown to achieve significant weight loss and diabetes remission for a 5 years follow-up period [6]. Recent studies have also demonstrated that this procedure can improve diabetes in non-morbidly obese patients and in morbidly obese patients with type 1 diabetes [7, 8]. A Japanese multicenter study was conducted using the ABCD score to compare the antidiabetic effects of SG-DJB with that of SG alone. The ABCD scoring system predicts the likelihood of diabetes remission using age, body mass index, serum C-peptide level, and the duration of diabetes as predictors [9, 10]. This comparison demonstrated that SG-DJB resulted in greater improvements in diabetes in obese patients with lower ABCD scores (≤ 5) or insulin use than SG alone. As a result, the SG-DJB has been approved in Japan as a highly advanced medical treatment for diabetes since March 2018 and is expected to become a popular bypass procedure in many East Asian countries.

✉ Hiroomi Takayama
t-1603@oita-u.ac.jp

[1] Department of Gastroenterological and Pediatric Surgery, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama-machi, Yufu, Oita 879-5593, Japan

In this study, we investigated the additional effects of duodenojejunal bypass (DJB) on glucose metabolism in a rat model of SG.

Materials and methods

Animals

Twenty-four 3-week-old male Sprague–Dawley rats were purchased from Charles River Japan, Inc. (Yokohama, Japan) and housed in individual cages under pathogen-free conditions. They were given free access to water and a high-fat diet with 60% of its calories from fat (Research Diet D12492; Research Diets Inc., New Brunswick, NJ, USA) for 6 weeks. The rats were maintained in a climate-controlled room at 24–26 °C and 50–60% humidity with a 12 h light/dark cycle. Rats were randomly assigned to undergo SG-DJB or SG alone. Their body weight and feed intake were measured weekly after surgery. All applicable institutional and/or national guidelines for the care and use of animals were followed. This study was approved by the Animal Committee of Oita University and confirmed to the Guidelines for Animal Experimentation of Oita University.

Surgical procedures

The diet-induced obese rats underwent surgery for SG or SG-DJB under anesthesia with 3–4% sevoflurane after overnight food deprivation. SG was performed as previously described [11, 12]. In brief, a 3 cm upper abdominal incision was made, and the greater curvature of the stomach was incised from the antrum to the fundus across the forestomach and glandular stomach. Approximately 90% of the forestomach and 70% of the glandular stomach were removed. The residual stomach was continuously sutured along the incision line using polydioxanone sutures (5-0 PDS®; Ethicon, Tokyo, Japan). SG-DJB was also performed as previously described [13]. In brief, after the SG procedure, the duodenum just distal to the pylorus was transected, and its distal end was closed with 5-0 PDS®. The alimentary limb (AL) was created by transection of the jejunum 10 cm from the ligament of Treitz and connection of the distal end to the pylorus by continuous suturing with 5-0 PDS®. The biliopancreatic limb (BPL) was created by jejunojejunal anastomosis with continuous 5-0 PDS® sutures at 15 cm distal to the duodenojejunal anastomosis [14, 15].

Biochemical tests

All blood samples were collected 6 weeks after the operation. Blood glucose was evaluated immediately after sample collection using a commercial test kit (Accu-Chek; Sanko Junyaku Co., Ltd., Tokyo, Japan). Whole blood samples were centrifuged at 4 °C for 15 min at 1500 × *g*, and the supernatant was collected. Glycoalbumin, albumin, total cholesterol (TC), triglyceride, and free fatty acid (FFA) levels were estimated using an H7180 automatic biochemical analyzer (Hitachi, Tokyo, Japan). Enzyme-linked immunosorbent assay (ELISA) kits were used to evaluate plasma levels of active ghrelin (active ghrelin ELISA kit; Mitsubishi Chemical Medience, Tokyo, Japan) and glucagon-like peptide-1 (GLP-1, rat GLP-1 ELISA kit; Shibayagi, Gunma, Japan). To prevent the degradation of these hormones, total blood was treated with dipeptidyl dipeptidase (DDP)-IV inhibitor immediately after collection. Serum insulin levels were also analyzed with a commercially available ELISA kit (rat insulin ELISA kit; Shibayagi). Total bile acids (TBA) were analyzed by the LC–MS/MS method using a Prominence UFLCXR system (Shimadzu Corporation, Kyoto, Japan) coupled with an API4000 mass spectrometer (AB Sciex, Framingham, MA, USA). To evaluate insulin resistance, the homeostasis model assessment ratio (HOMA-R) was calculated as follows: HOMA-R = fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5 [16].

Oral glucose tolerance test (OGTT)

An OGTT was performed 6 weeks after surgery to evaluate glucose metabolism. After 24 h of fasting, the rats were given 2 g/kg glucose orally. Blood glucose was measured in the conscious rats with a commercial test kit (Accu-Chek; Sanko Junyaku Co., Ltd.) before and 15, 30, 60, and 120 min after glucose administration. Serum insulin levels were simultaneously tested using the rat insulin ELISA kit described previously. The area under the curve (AUC) for the OGTT was calculated by trapezoidal integration.

Quantitative real-time polymerase chain reaction (qRT-PCR) of mRNA expression of factors related to gluconeogenesis and glucose transport in the jejunum

All rats were sacrificed 6 weeks after surgery. Tissue samples were collected from the AL, BPL, and common channel (CC) from the SG-DJB group. For rats in the SG group, tissues were obtained from the sites corresponding to the AL, BPL, and CC of the SG-DJB group. Namely, we created the AL by transection of the jejunum 10 cm from the ligament of Treiz in the SG-DJB group. Therefore, we collected the jejunal samples 17.5 cm distant from the ligament of Treiz in the SG group, corresponding to the center of AL in the SG-DJB group. We collected the samples corresponding to BPL and CC in the same manner. Tissues were immediately frozen in liquid nitrogen, and total RNA isolation was performed as previously described [17]. cDNA was synthesized

from purified total RNA using a Verso cDNA synthesis kit (Thermo Fisher Scientific, Waltham, MA, USA). The mRNA expression was assessed by qRT-PCR using KAPA SYBR FAST qPCR Kit Master Mix (2×) Universal (Kapa Biosystems, Inc., Woburn, MA, USA) with a LightCycler 96 system (Roche Diagnostics, Lewes, East Sussex, UK). Primer pairs were as follows: glucose-6-phosphatase (G6pase), 5′-ctaccttgcggctcactttc-3′ (forward) and 5′-atccaagtgcgaaaccaaac-3′ (reverse); phosphoenolpyruvate carboxykinase (PEPCK), 5′-atacggtgggaactcactgc-3′ (forward) and 5′-tgccttcggggttagttatg-3′ (reverse); farnesoid X receptor (FXR), 5′-cagccacagatctcctcctc-3′ (forward) and 5′-tctttgtcacaggcatctcg-3′ (reverse); glucose transporter 1 (GLUT1), 5′-gtgctcggatccctgcagttcg-3′ (forward) and 5′-gggatggactctccatagcggtg-3′ (reverse); glucose transporter 2 (GLUT2), 5′-caatttcatcatcgccctct-3′ (forward) and 5′-tgcagcaatttcgtcaaaag-3′ (reverse); sodium-glucose cotransporter 1 (SGLT1), 5′-gactgattctcggcttcctg-3′ (forward), and 5′-gtgaggagggagatgaccaa-3′ (reverse). The mRNA expression levels were normalized to that of rat glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Primer3 was used to design the primers [18]. The mRNA expression in the SG-DJB group was expressed in relation to the mean expression in the SG group [19].

Histological analyses

Jejunal samples collected from the AL, BPL, and CC, and the corresponding portions were fixed in formalin, embedded in paraffin, and sectioned at a thickness of 3 μm for histological analyses. The sections were placed on glass slides, deparaffinized, and stained with hematoxylin and eosin for the measurement of villus height, and stained with specific antibodies for immunohistochemistry. The mucosal length was measured under microscopy [20].

Since the qRT-PCR results demonstrated that mRNA expression of GLUT1 and SGLT1 was significantly increased in the AL, anti-GLUT1 (ab115739; Abcam plc., Cambridge, MA, USA) and anti-SGLT1 (ab14685; Abcam plc.) were used as primary antibodies. Binding was detected using the VECTASTAIN Elite ABC kit (Vector Laboratories, Inc., Burlingame, CA, USA) according to the manufacturer's instructions.

Statistical analyses

Data are expressed as means ± standard error of the mean (SEM). All data were analyzed using the Mann–Whitney *U* test. Differences were considered statistically significant if $p < 0.05$. Statistical analyses were performed using the SPSS statistical software program, version 20 (IBM Corp., Armonk, NY, USA).

Results

Body weight and food intake

All rats in both groups survived the surgery. There were no significant differences in body weight between the two groups at the any point after surgery (Fig. 1a). Food intake was significantly lower in the SG-DJB group at 2 and 3 weeks after surgery than in the SG group but from 4 weeks after surgery did not differ between groups (Fig. 1b).

Metabolic parameters and hormones

There were no significant differences in metabolic parameters, including glucose, glycoalbumin, albumin, TC, triglyceride, FFA, ghrelin, GLP-1, insulin, TBA, and HOMA-R, between the SG and SG-DJB groups (Table 1). However, TBA was more than twofold greater in the SG-DJB group

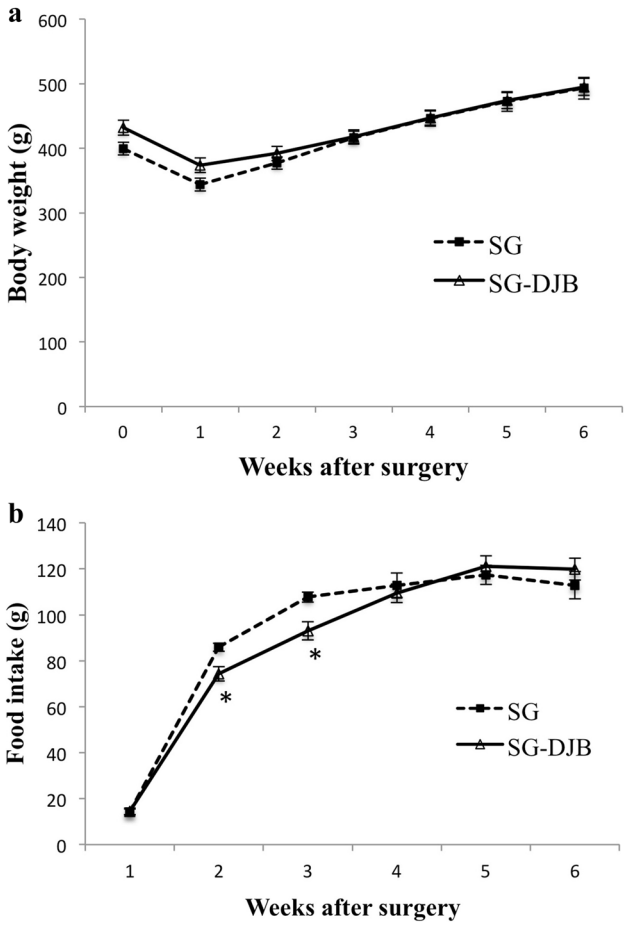

Fig. 1 Changes in body weight and food intake after sleeve gastrectomy (SG) or sleeve gastrectomy with duodenojejunal bypass (SG-DJB). **a** Changes in body weight and **b** weekly food intake after surgery. *$p < 0.05$ versus the SG group

Table 1 Metabolic parameters and hormones 6 weeks after surgery

	SG	SG-DJB	*p* value
Glucose (mg/dl)	117.4 ± 2.8	126.1 ± 2.6	0.061
Glycoalbumin (ng/ml)	8.5 ± 0.4	8.8 ± 0.4	0.799
Albumin (g/ml)	3.6 ± 0.1	3.8 ± 0.1	0.178
TC (mg/dl)	58.1 ± 3	61.8 ± 3.4	0.319
Triglyceride (mg/dl)	36.3 ± 5.7	38.9 ± 2.9	0.160
FFA (μEQ/l)	284.3 ± 21.3	270.3 ± 12.5	0.977
Ghrelin (fmol/ml)	4.8 ± 0.8	4.4 ± 0.9	0.078
GLP-1 (ng/ml)	30.9 ± 4.7	31.6 ± 3.0	0.583
Insulin (ng/ml)	0.86 ± 0.18	0.97 ± 0.32	0.622
TBA (μmol/l)	9.46 ± 2.6	20.3 ± 5.2	0.085
HOMA-R	6.71 ± 1.01	5.44 ± 1.12	0.105

SG sleeve gastrectomy, *SG-DJB* sleeve gastrectomy with duodenojejunal bypass, *TC* total cholesterol, *FFA* free fatty acid, *GLP-1* glucagon-like peptide-1, *TBA* total bile acids, *HOMA-R* homeostasis model assessment for insulin resistance

than in the SG group, suggesting that the bypass procedure resulted in the TBA increase.

OGTT

The OGTT revealed an early decrease in blood glucose in the SG-DJB group resulting in a significantly lower glucose level in the SG-DJB group at 60 min after glucose administration than in the SG group (Fig. 2a). There were no significant between-group differences in the AUC for glucose, but the SG-DJB group tended to have a smaller AUC than the SG group (Fig. 2b, $p = 0.053$). The serum insulin level was significantly higher at 15 min after glucose administration in the SG-DJB group than in the SG group (Fig. 2c).

The mRNA expression of factors related to gluconeogenesis and glucose transport in the jejunum

The mRNA expression of GLUT1 and SGLT1 in the AL was significantly greater in the SG-DJB group than in the SG group (Fig. 3a). There were no significant between-group differences in expression of any factors in the BPL and CC (Fig. 3b, c). The mRNA expression of G6pase in the CC was higher in the SG-DJB group than that in the SG group, but this difference was not significant ($p = 0.299$).

Histological analyses

The SG-DJB group had significantly greater villus height of the AL than did the SG group, but there were no significant differences in the BPL and CC between the two groups (Table 2).

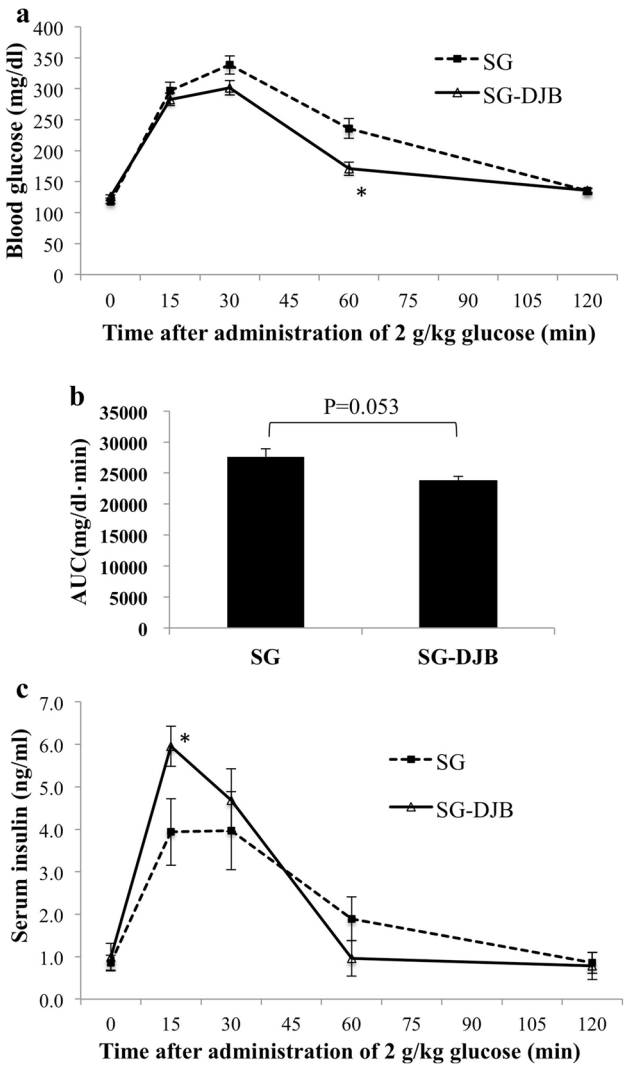

Fig. 2 Oral glucose tolerance test (OGTT) 6 weeks after sleeve gastrectomy (SG) or sleeve gastrectomy with duodenojejunal bypass (SG-DJB). **a** Changes in blood glucose, **b** area under the curve (AUC) for glucose, and **c** changes in serum insulin. Glucose and insulin levels were measured before and 15, 30, 60, and 120 min after oral gavage with glucose solution (2 g/kg). *$p < 0.05$ versus the SG group

Because qRT-PCR demonstrated that mRNA expression of GLUT1 and SGLT1 was significantly increased in the AL of rats in the SG-DJB group, immunohistochemical staining for GLUT1 and SGLT1 were performed on AL samples. Both GLUT1 (Fig. 4a, b) and SGLT1 (Fig. 5a, b) stained more intensely in the SG-DJB group than in the SG group.

Discussion

In humans, improvement in glucose tolerance is observed from the early postoperative period after RYGB, even before decreases in body weight occur [21]. There have been many

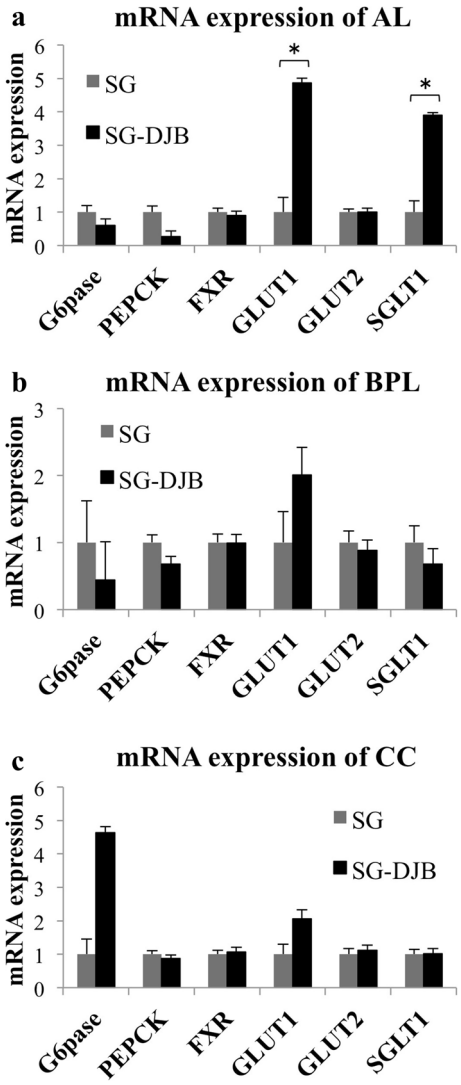

Fig. 3 The mRNA expression of factors related to gluconeogenesis and glucose transport in the alimentary limb (AL), biliopancreatic limb (BPL), and common channel (CC). Glucose 6-phosphatase (G6pase), phosphoenolpyruvate carboxykinase (PEPCK), farnesoid X receptor (FXR), glucose transporter 1 (GLUT1), glucose transporter 2 (GLUT2), and sodium-glucose cotransporter 1 (SGLT1) in the jejunum were quantified by qRT-PCR and expressed relative to their mean expression level in the SG group. *$p < 0.01$

Table 2 Villus height of the jejunum 6 weeks after surgery

	SG	SG-DJB	*p* value
AL (μm)	658.0 ± 28.8	814.8 ± 57.4	0.024
BPL (μm)	705.7 ± 57.6	664.8 ± 39.8	0.792
CC (μm)	627.3 ± 37.7	695.5 ± 38.1	0.289

SG sleeve gastrectomy, *SG-DJB* duodenojejunal bypass with sleeve gastrectomy, *AL* alimentary limb, *BPL* biliopancreatic limb, *CC* common channel

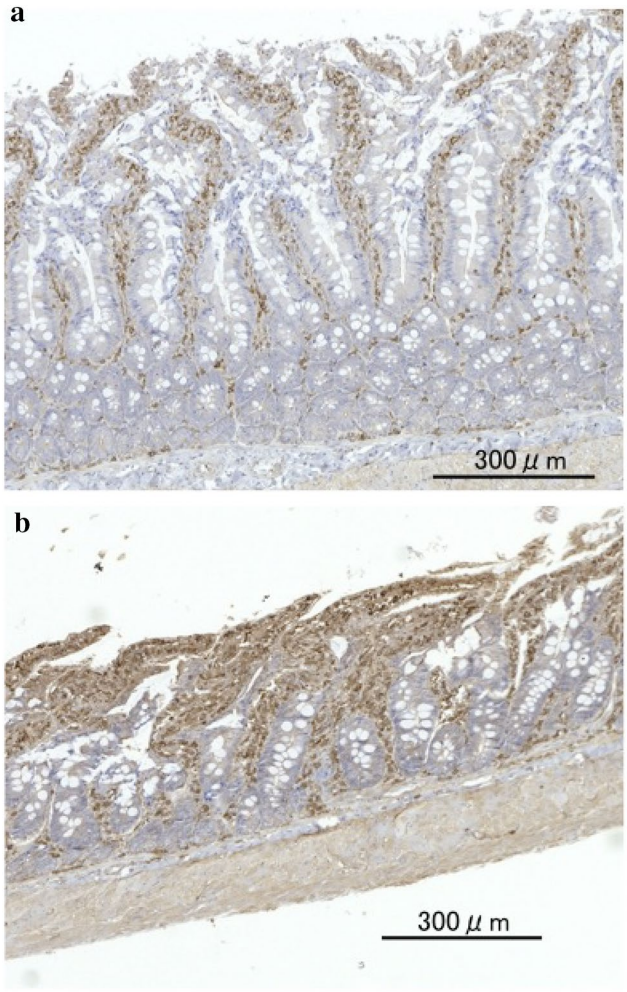

Fig. 4 GLUT1 immunohistochemistry in AL sections (×100). **a** SG group and **b** SG-DJB group

studies of the potential mechanisms by which obesity surgery may cause diabetes remission. Changes in metabolic hormones and mediators such as ghrelin, GLP-1, and FXR, changes in hepatic and intestinal gluconeogenesis, and alterations to the distribution of gut microbiota are all potential causes of the antidiabetic effects of RYGB, but the exact mechanisms remain unclear [20, 22–27].

GLUT1 is a major glucose transporter expressed in most cells, especially the brain and erythrocytes. It regulates the basal uptake of glucose and is rarely expressed in the jejunum [28–30]; however, it is overexpressed in a hypoxic environment [29, 31]. GLUT2 is also a glucose transporter; it transports glucose from epithelial cells to the vascular lumen through the basolateral membrane via facilitated diffusion [32]. SGLT1 is one of the glucose transporters that mediate glucose uptake from the brush-border membrane of epithelial cells in the small intestine [32]. Since GLUT1 is rarely expressed in the jejunum, glucose absorption in the small intestine is usually regulated by SGLT1 and GLUT2.

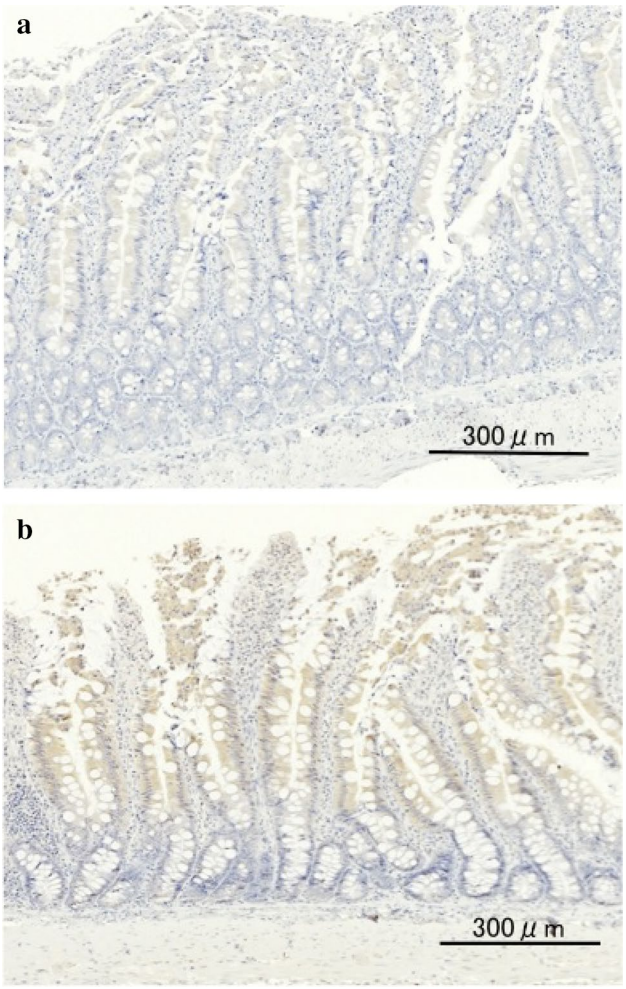

Fig. 5 SGLT1 immunohistochemistry in AL sections (×100). **a** SG group and **b** SG-DJB group

SGLT1 transports glucose from the intestinal lumen to the epithelial cells, and GLUT2 moves glucose from the epithelial cells into the vascular lumen. In addition, SGLT1 acts as a glucose sensor in the intestine and regulates secretion of incretins such as gastric inhibitory polypeptide (GIP) and GLP-1 that promote insulin secretion; therefore, the activation of SGLT1 leads to reductions in hyperglycemia [33].

In this study, we found that the expression levels of GLUT1 and SGLT1 in the AL were upregulated, while GLUT2 expression in the AL remained the same in the SG-DJB group relative to expression levels in the SG group. These expression patterns may be related to the additional effects of DJB on glucose metabolism. Cavin et al. reported similar results after RYGB in rats and in humans. They demonstrated elevated expression of GLUT1, GLUT2, and SGLT1 mRNA in the hypertrophic epithelial cells of the AL 40 days after RYGB in rats compared with expression levels in sham-operated controls [34]. They also demonstrated an increase in the number of GLP-1 secreting cells in the jejunum in both rats and humans, with no significant change in the mean density of the cells after RYGB. After SG, GLUT1 expression was not elevated, but the number of GLP-1 secreting cells and their density were both significantly increased. They hypothesized that glucose consumption was increased in the intestinal mucosa after RYGB, with a resultant increase in uptake of glucose from the blood and intestinal contents. In addition, intestinal absorption of glucose was decreased in the SG mucosa. They concluded that RYGB increased intestinal glucose disposal and SG delayed glucose absorption.

Our study showed that the AL villus height was longer in the SG-DJB group than in the SG group, and that the expression of GLUT1 and SGLT1 in the AL was enhanced after SG-DJB compared with after SG alone. Mumphrey et al. also demonstrated increased mucosal thickness of AL in the RYGB model but not in the SG model [35]. The hypertrophy of the AL after RYGB has been reported previously in numerous rat models [34, 36, 37]. le Roux et al. reported that gut hypertrophy after RYGB was associated with the increased expression of glucagon-like peptide 2 (GLP-2) [36], which may be related to the epithelial hypertrophy in the AL. The reason why the villus height was greater only in the AL after the bypass surgery remains unclear, but it has been suggested that the portion of AL that is first exposed to undigested food may be related to the hypertrophy [38, 39]. Saedi et al. demonstrated the reprogramming of glucose metabolism of AL through the upregulation of GLUT1 after RYGB by exposure to undigested nutrients [37]. Cavin et al. also demonstrated that a hypoxia-inducible gene HIF1 that directly regulates GLUT1 was overexpressed in the hypertrophic epithelial cells of AL after RYGB [34]. They hypothesized that oxygen supply might be insufficient to support the massive hyperplasia in the AL, and suggested that the villus hypertrophy may induce overexpression of GLUT1. The addition of DJB to the SG procedure may induce hypertrophy of AL epithelial cells, and increase glucose transport from the vascular and intestinal tract to epithelial cells and glucose consumption by the epithelial cells; this may contribute to the greater improvements in glucose metabolism seen after SG-DJB than after SG alone. Moreover, the early insulin secretion, possibly due to the activation of GLP-1 by overexpression of SGLT1, may also contribute to the improved glucose metabolism of the SG-DJB group.

FXR may promote the secretion of GLP-1 via the activation of Takeda G-protein receptor 5 and contribute to the improvement of glycometabolism [40]. Since the bypass procedure increases TBA [41], we expected that FXR expression would increase in the SG-DJB group; however, this did not occur. FXR levels in the SG-DJB group were comparable to those of the SG group in this study.

Troy et al. reported rapid improvements in insulin resistance and β-cell function following enterogastric anastomosis

(EGA) in a mouse gastric bypass model [27]. They demonstrated that intestinal gluconeogenesis increased through the activation of G6pase and PEPCK expression after EGA and this improved glucose metabolism. They also showed that gluconeogenesis was related to GLUT2 expression and the hepatoportal sensor pathway. Goncalves et al. also demonstrated that G6pase activity was increased in the duodenum and AL after RYGB compared with its activity in sham-operated controls [19]. However, the EGA model used by Troy et al. did not have an AL, and the limb in which intestinal gluconeogenesis was activated corresponded to the CC in the RYGB model. Therefore, the molecular regulation of intestinal gluconeogenesis after bypass procedure remains unclear. In this study, there were no significant differences in the mRNA expression levels of G6pase and PEPCK between the SG and SG-DJB groups. Intestinal gluconeogenesis was not related to the additional effects of DJB on glucose metabolism in SG; however, our results do not exclude the existence of intestinal gluconeogenesis after bypass surgery.

In this study, we investigated the additional effects of DJB on glucose metabolism in the SG rat model using high-fat diet-induced obese Sprague–Dawley rats. This model has been used as a diabetic model, and it shows a hyperglycemic status and insulin resistance [42, 43]. Our previous report also showed hyperglycemia and insulin resistance in the same rat model [44].

Miyachi et al. reported that the BPL plays an important role in the control of glucose tolerance after DJB in a rat model of diabetes [45]. Plasma bile acids and gut microbiota may be involved in this process. The study showed that BPL length was related to body weight and glycemic control, but AL length was not. However, longer AL groups showed a better tendency of glycemic control among the groups with the same BPL length. Therefore, we consider that the AL might also be related to glycemic control.

This study had some limitations. First, we measured GLP-1 at only one time point after fasting. Serum GLP-1 levels drastically change depending on the timing of the measurement in relation to food intake. Second, we did not directly observe the kinetics of glucose uptake by the epithelial cells through the GLUT1 and SGLT1 transporters. This should be done in the further experiments.

In conclusion, increased expression of SGLT1 and GLUT1 in the AL may be related to the additional effects of DJB on glucose metabolism after SG.

Acknowledgements We would like to thank Ms. Yuiko Aso and Mayumi Wada for their technical assistance with the experiments.

Compliance with ethical standards

Conflict of interest This work was supported by JSPS KAKENHI Grant Number JP16K10505. The authors declare that they have no conflicts of interest.

References

1. Welbourn R, Pournaras DJ, Dixon J, Higa K, Kinsman R, Ottosson J, et al. Bariatric surgery worldwide: Baseline demographic description and one-year outcomes from the second IFSO global registry report 2013–2015. Obes Surg. 2018;28:313–22.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010;87:4–14.
3. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med. 2017;376:641–51.
4. Chang SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. JAMA Surg. 2014;149:275–87.
5. Kasama K, Tagaya N, Kanehira E, Oshiro T, Seki Y, Kinouchi M, et al. Laparoscopic sleeve gastrectomy with duodenojejunal bypass: technique and preliminary results. Obes Surg. 2009;19:1341–5.
6. Seki Y, Kasama K, Haruta H, Watanabe A, Yokoyama R, Porciuncula JP, et al. Five-year-results of laparoscopic sleeve gastrectomy with duodenojejunal bypass for weight loss and type 2 diabetes mellitus. Obes Surg. 2017;27:795–801.
7. Seki Y, Kasama K, Yasuda K, Eri K, Watanabe N, Kurokawa Y. Metabolic surgery for inadequately controlled type 2 diabetes in nonseverely obese Japanese: a prospective, single-center study. Surg Obes Relat Dis. 2018;14:978–85.
8. Uno K, Seki Y, Kasama K, Wakamatsu K, Hashimoto K, Umezawa A, et al. Mid-term results of bariatric surgery in morbidly obese Japanese patients with slow progressive autoimmune diabetes. Asian J Endosc Surg. 2018;11:238–43.
9. Naitoh T, Kasama K, Seki Y, Ohta M, Oshiro T, Sasaki A, et al. Efficacy of sleeve gastrectomy with duodenal-jejunal bypass for the treatment of obese severe diabetes patients in Japan: a retrospective multicenter study. Obes Surg. 2018;28:497–505.
10. Lee WJ, Almulaifi A, Tsou JJ, Ser KH, Lee YC, Chen SC. Laparoscopic sleeve gastrectomy for type 2 diabetes mellitus: predicting the success by ABCD score. Surg Obes Relat Dis. 2015;11:991–6.
11. Lopez PP, Nicholson SE, Burkhardt GE, Johnson RA, Johnson FK. Development of a sleeve gastrectomy weight loss model in obese Zucker rats. J Surg Res. 2009;157:243–50.
12. Masuda T, Ohta M, Hirashita T, Kawano Y, Eguchi H, Yada K, et al. A comparative study of gastric banding and sleeve gastrectomy in an obese diabetic rat model. Obes Surg. 2011;21:1774–80.
13. Sun D, Liu S, Zhang G, Chen W, Yan Z, Hu S. Type 2 diabetes control in a nonobese rat model using sleeve gastrectomy with duodenal-jejunal bypass (SGDJB). Obes Surg. 2012;22:1865–73.
14. Donglei Z, Liesheng L, Xun J, Chenzhu Z, Weixing D. Effects and mechanism of duodenal-jejunal bypass and sleeve gastrectomy on GLUT2 and glucokinase in diabetic Goto-Kakizaki rats. Eur J Med Res. 2012;17:15.
15. Kim M, Son YG, Kang YN, Ha TK, Ha E. Changes in glucose transporters, gluconeogenesis, and circadian clock after duodenal-jejunal bypass surgery. Obes Surg. 2015;25:635–41.
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
17. Tominaga M, Ohta M, Kai S, Iwaki K, Shibata K, Kitano S. Increased heat-shock protein 90 expression contributes to impaired adaptive cytoprotection in the gastric mucosa of portal hypertensive rats. J Gastroenterol Hepatol. 2009;24:1136–41.

18. Untergasser A, Cutcutache I, Koressaar T, Ye J, Faircloth BC, Remm M, et al. Primer3–new capabilities and interfaces. Nucleic Acids Res. 2012;40:e115.
19. Goncalves D, Barataud A, De Vadder F, Vinera J, Zitoun C, Duchampt A, et al. Bile routing modification reproduces key features of gastric bypass in rat. Ann Surg. 2015;262:1006–15.
20. Yan Y, Zhou Z, Kong F, Feng S, Li X, Sha Y, et al. Roux-en-Y gastric bypass surgery suppresses hepatic gluconeogenesis and increases intestinal gluconeogenesis in a T2DM rat model. Obes Surg. 2016;26:2683–90.
21. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. Ann Surg. 1995;222:339–50.
22. Seeley RJ, Chambers AP, Sandoval DA. The role of gut adaptation in the potent effects of multiple bariatric surgeries on obesity and diabetes. Cell Metab. 2015;21:369–78.
23. Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. Diabetes Care. 2016;39:893–901.
24. Langer FB, Reza Hoda MA, Bohdjalian A, Felberbauer FX, Zacherl J, Wenzl E, et al. Sleeve gastrectomy and gastric banding: effects on plasma ghrelin levels. Obes Surg. 2005;15:1024–9.
25. Peterli R, Wolnerhanssen B, Peters T, Devaux N, Kern B, Christoffel-Courtin C, et al. Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann Surg. 2009;250:234–41.
26. Ryan KK, Tremaroli V, Clemmensen C, Kovatcheva-Datchary P, Myronovych A, Karns R, et al. FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature. 2014;509:183–8.
27. Troy S, Soty M, Ribeiro L, Laval L, Migrenne S, Fioramonti X, et al. Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not after gastric lap-band in mice. Cell Metab. 2008;8:201–11.
28. Kahn BB. Facilitative glucose transporters: regulatory mechanisms and dysregulation in diabetes. J Clin Invest. 1992;89:1367–74.
29. Yoshikawa T, Inoue R, Matsumoto M, Yajima T, Ushida K, Iwanaga T. Comparative expression of hexose transporters (SGLT1, GLUT1, GLUT2 and GLUT5) throughout the mouse gastrointestinal tract. Histochem Cell Biol. 2011;135:183–94.
30. Mueckler M. Facilitative glucose transporters. Eur J Biochem. 1994;219:713–25.
31. Ouiddir A, Planes C, Fernandes I, VanHesse A, Clerici C. Hypoxia upregulates activity and expression of the glucose transporter GLUT1 in alveolar epithelial cells. Am J Respir Cell Mol Biol. 1999;21:710–8.
32. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev. 2011;91:733–94.
33. Gorboulev V, Schurmann A, Vallon V, Kipp H, Jaschke A, Klessen D, et al. Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. Diabetes. 2012;61:187–96.
34. Cavin JB, Couvelard A, Lebtahi R, Ducroc R, Arapis K, Voitellier E, et al. Differences in alimentary glucose absorption and intestinal disposal of blood glucose after Roux-en-Y gastric bypass vs sleeve gastrectomy. Gastroenterology. 2016;150:454–64e9.
35. Mumphrey MB, Hao Z, Townsend RL, Patterson LM, Berthoud HR. Sleeve gastrectomy does not cause hypertrophy and reprogramming of intestinal glucose metabolism in rats. Obes Surg. 2015;25:1468–73.
36. le Roux CW, Borg C, Wallis K, Vincent RP, Bueter M, Goodlad R, et al. Gut hypertrophy after gastric bypass is associated with increased glucagon-like peptide 2 and intestinal crypt cell proliferation. Ann Surg. 2010;252:50–6.
37. Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, et al. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. Science. 2013;341:406–10.
38. Hansen CF, Bueter M, Theis N, Lutz T, Paulsen S, Dalboge LS, et al. Hypertrophy dependent doubling of L-cells in Roux-en-Y gastric bypass operated rats. PLoS One. 2013;8:e65696.
39. Mumphrey MB, Patterson LM, Zheng H, Berthoud HR. Roux-en-Y gastric bypass surgery increases number but not density of CCK-, GLP-1-, 5-HT-, and neurotensin-expressing enteroendocrine cells in rats. Neurogastroenterol Motil. 2013;25:e70–9.
40. Pathak P, Liu H, Boehme S, Xie C, Krausz KW, Gonzalez F, et al. Farnesoid X receptor induces Takeda G-protein receptor 5 cross-talk to regulate bile acid synthesis and hepatic metabolism. J Biol Chem. 2017;292:11055–69.
41. Tsuchiya T, Naitoh T, Nagao M, Tanaka N, Watanabe K, Imoto H, et al. Increased bile acid signals after duodenal-jejunal bypass improve non-alcoholic steatohepatitis (NASH) in a rodent model of diet-induced NASH. Obes Surg. 2018;28:1643–52.
42. Bloch O, Broide E, Ben-Yehudah G, Cantrell D, Shirin H, Rapoport MJ. Nutrient induced type 2 and chemical induced type 1 experimental diabetes differently modulate gastric GLP-1 receptor expression. J Diabetes Res. 2015;2015:561353.
43. Lozano I, Van der Werf R, Bietiger W, Seyfritz E, Peronet C, Pinget M, et al. High-fructose and high-fat diet-induced disorders in rats: impact on diabetes risk, hepatic and vascular complications. Nutr Metab. 2016;13:15
44. Kawasaki T, Ohta M, Kawano Y, Masuda T, Gotoh K, Inomata M, et al. Effects of sleeve gastrectomy and gastric banding on the hypothalamic feeding center in an obese rat model. Surg Today. 2015;45:1560–6.
45. Miyachi T, Nagao M, Shibata C, Kitahara Y, Tanaka N, Watanabe K, et al. Biliopancreatic limb plays an important role in metabolic improvement after duodenal-jejunal bypass in a rat model of diabetes. Surgery. 2016;159:1360–71.