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ORIGINAL CONTRIBUTIONS

Residual Gastric Dilatation Interferes with Metabolic Improvements Following Sleeve Gastrectomy by Upregulating the Expression of Sodium-Glucose Cotransporter-1

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Abstract

Objective Sleeve gastrectomy (SG) is widely used in treating obesity because of significant weight loss and anti-diabetic effects, but there are still cases of long-term weight loss failure. Our aim was to explore the weight loss mechanism following SG in mice to learn how initial improvements in glucose metabolism are reversed in the long term.

Methods C57/BL6 mice were divided into two groups, one undergoing SG and the other sham surgery. Body weight, gastric volume, blood glucose level, and the expression of sodium-glucose cotransporter 1 (SGLT1) were assessed at 2 weeks, 1 month, and 2 months after surgery.

Results The SG mice had reduced food intake and lost weight during the 30 days after surgery. However, food intake and weight recovered gradually and even surpassed the sham group after 30 days. SGLT1 expression decreased within 1 month after SG and then increased at 2 months. Although initial SGLT1 expression levels in the stomach were much lower than at intestinal sites, levels increased following surgery and then decreased. The gastric volume decreased after SG, but was significantly increased at 2 months, exceeding the gastric volume in the sham mice.

Conclusions The metabolic benefits of SG are achieved through reduced gastrointestinal glucose absorption as evidenced by decreased expression of SGLT1 without bypassing the proximal intestine as in other forms of bariatric surgery. In addition, SGLT1 expression in the stomach may play a greater role in post-surgical metabolic effects, but further studies are needed.

Keywords Sleeve gastrectomy · Obesity · Weight loss · Type 2 diabetes · SGLT1 · Glucose absorption · Residual gastric volume

Introduction

Obesity is a major public health problem and an economic challenge in both developed and emerging countries [1]. Metabolic surgery for obesity and its associated complications have been widely adopted in modern societies. The sleeve gastrectomy (SG) procedure is becoming more widely used because it is simpler, has a shorter learning curve, fewer complications, and does not involve any reconstruction of the gastrointestinal tract [2]. Both laparoscopic and open SG are

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efficacious for obesity and obesity-related diseases for most patients [3–6], but some face weight regain, poor blood glucose control, and other issues [7]. In a systematic review, regain ranged from 5.7% at 2 years to 75.6% at 6 years [8].

The sodium-glucose cotransporter 1 (SGLT1) is the primary carrier for the transport of glucose in the intestine [9]. The expression level of SGLT1 in the intestinal tract indirectly reflects the body's glucose absorption capacity. SGLT1 expression in mice is diminished after Roux-en-Y gastric bypass (RYGB) surgery with a corresponding reduction in intestinal glucose absorption and decreased body weight [10, 11]. Upregulation of glucose transporters also occurs in humans following RYGB surgery [9, 12]. A clear mechanism for how SG achieves weight loss and improves glucose control is still lacking. For bypass surgery, weight loss was initially considered the major factor in improving glucose metabolism [13], but subsequent studies, the first in 1981, indicated that other factors were probably involved since glucose metabolism improved immediately after surgery [14].

Studies in animal models have indicated that the pronounced antidiabetic effects of RYGB surgery were related to the bypass of the proximal intestine [15], which interrupts glucose sensing and upregulation of SGLT1 [16]. Since exclusion of the proximal intestine is not part of the SG procedure, whether the same mechanism applies to SG remains unclear. A better understanding of the mechanism of weight loss and glucose control in sleeve gastrectomy may provide insight into how to achieve better long-term outcomes in those patients. Thus, we sought to measure expression of SGLT1 in the gastrointestinal tract, gastric cavity volume, and intestinal glucose absorption in an attempt to clarify the mechanisms involved in correcting metabolic disorders following SG in mice.

Materials and Methods

Mice

Male C57/BL6 mice aged 6 to 8 weeks were housed under a strict 12:12-h light/dark cycle (lights on at 7 a.m.) in standard pathogen-free conditions and with ad libitum access to standard rodent food and water. All animal use conformed to the Animal Experiments Committee of the North Sichuan Medical College and was executed according to the guidelines.

Surgical Procedures

The mice were divided into a sham operation group and SG group ($N = 6$). Before undergoing SG, the mice were fasted except for water for 24 h and anesthetized with isoflurane. The lateral 2/3 of the greater curvature of the stomach was excised, leaving a tubular gastric remnant in continuity with the inferior part of the esophagus and the pylorus. In the sham group, the same anesthetic and duration of anesthesia was used for the SG mice. The sham surgical procedure involved analogous isolation of the stomach followed by manually applying pressure with blunt forceps along the line between the esophageal sphincter and the pylorus. After surgery, the mice were put into an incubator for resuscitation, and then were returned immediately to the constant temperature animal room with ad libitum access to standard rodent food and water.

Tissue Harvest

The mice were housed for 2 weeks, 1 month, and 2 months after SG or sham surgery. About 3 cm length tissue from each intestinal segments and the residual stomach were harvested under anesthesia in mice (Fig. 1). Each sample was divided into three parts, two of which were snap frozen in liquid nitrogen and stored at − 80 °C, and the other fixed in 10% formaldehyde over 24 h, then dehydrated and embedded in paraffin.

Oral Glucose Tolerance Test

After fasting for 12 h, a glucose bolus of 3 g/kg glucose (25%, formulated with 9% saline), was then administered directly to the duodenal lumen over 5 min. Blood was obtained for glucometer measurement before administration of the bolus and 20, 40, 60, 80, 100, and 120 min after glucose administration by cutting a small amount of the tail and gently massaging the blood out. Data was recorded in a graph, and the area under the curve was used to describe short-term digestive tract glucose absorption.

Determination of Gastric Cavity Volume

Gastric tissues of the mice were harvested before anesthesia, on day 0, at 14 days, 1 month, and 2 months. At each time point, the stomach cavity was washed, then the level of the fluid level at the time of gastric emptying and the natural filling was measured by acid burette, and the readings were taken. Third, the gastric cavity volume was calculated.

Hematoxylin and Eosin Staining

Ten-micrometer sections were made from tissues embedded in frozen OTC compound and stained with hematoxylin and eosin. The gut villi and crypts were measured in at least three animals in each group.

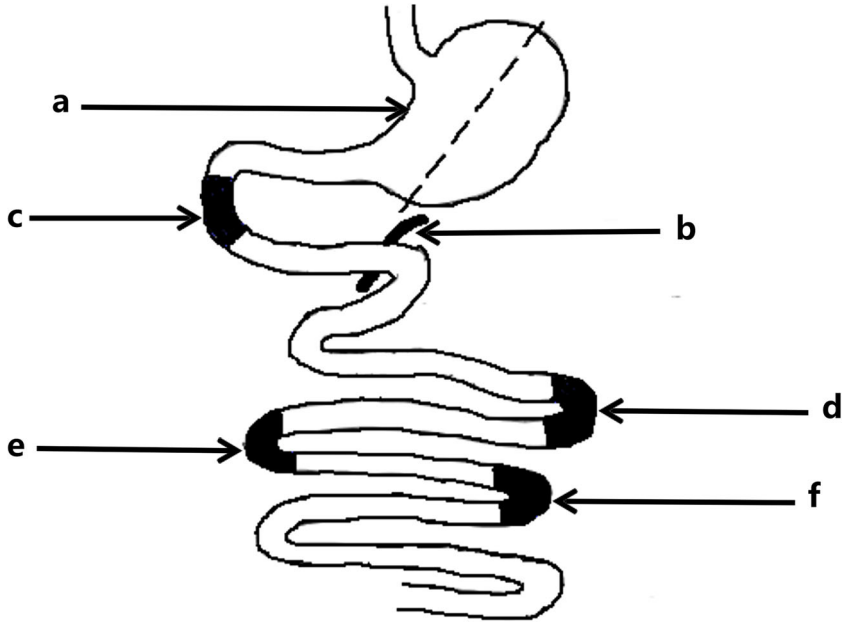

Fig. 1 Position of tissue harvest. a) Residual stomach; b) Treitz ligament; c) duodenum, 3 cm intestinal segment above the ligament; d) proximal jejunum, 3 cm intestinal segment at 4 cm below the ligament; e) distal jejunum, 3 cm intestinal segment at 10 cm below the ligaments; f) proximal ileum, 3 cm intestinal segment at 16 cm below the ligaments

Fluorescence Immunoassay

Ten-micrometer sections were prepared using a freezing microtome, then washed with 0.3% Triton X-100 (diluted in 0.01 M PBS) for 3 × 5 min, and placed in 80 °C citrate buffer (pH = 6) for 8 min. We then added 2% goat serum and sliced the water bath at 37 °C for 30 min. Under 4 degree conditions, we added the primary antibody in sections and placed for 24 h, then the secondary antibody was added and placed for 12 h. Nuclei were stained with DAPI (5 min), and the then sections were dehydrated in 70%, 80%, 95%, and 100% ethanol and xylene solution. We then fixed the sections and observed under a laser confocal instrument.

Quantitative PCR

Primers were designed according to the sequence of the gene and subjected to PCR amplification, and the amplification efficiency and specificity was tested. We set the conditions on the machine for RT-PCR. The following primers were used: SGLT1 5′-CCAAGCCCATCCCAGACGTACACC-3′(forward) and 5′-CTTCCTTAGTCATCCCAGAC GTACACC-3′(reverse) and GAPDH 5′-AGGT CGGTGTGAACGGATTTG-3′ (forward) and 5′-TGTA GACCATGTAGTTGAGGTCA-3′ (reverse).

Statistical Analysis

Data were analyzed using GraphPad Prism 7.0 software (GraphPad Software, San Diego, California, USA) and presented as the mean ± SEM. Differences between experimental groups and controls were assessed by the *t* test with correction where applicable. $P < 0.05$ was considered statistically significant.

Results

Body Weight and Daily Food Intake

At baseline, there was no difference between the two groups in body weight and food intake. However, in the SG group, food intake declined sharply 1 day after surgery and was then restored after 5 days, then gradually increased to the same level as the sham mice after about 45 days. Food intake then increased to more than the sham group after 50 days (Fig. 2a). On average, compared with the sham mice, the mice had lost 17.65% body weight 30 days after SG, and regained gradually and even surpassed the sham group by 15.8% about 60 days after surgery (Fig. 2b).

Oral Glucose Absorption

Oral glucose tolerance tests (OGTT) were performed on mice at 1 month and 2 months after surgery. Compared with the sham mice, at 30 days after surgery, blood glucose levels were significantly reduced in SG mice at each time point during the OGTT (Fig. 3a), and the area under the curve was significantly decreased ($P < 0.001$) (Fig. 3c). However, at 60 days after surgery, blood glucose levels were significantly increased in SG mice compared with sham mice (Fig. 3b), and the area under the curve also increased ($P < 0.001$) (Fig. 2d). In brief, these data indicated that SG reduced intestinal glucose absorption at 30 days after surgery but increased at 60 days.

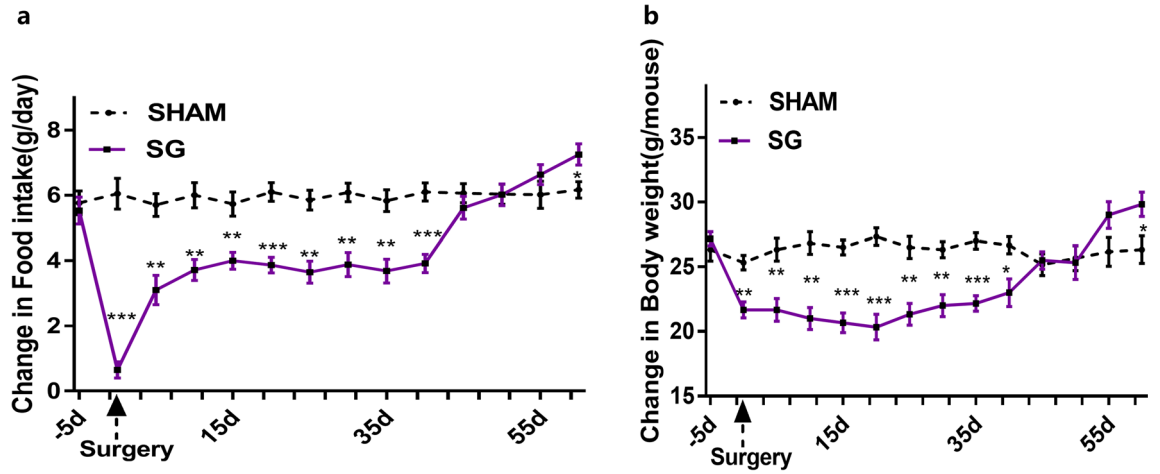

Fig. 2 Food intake and body weight. There was no statistical difference in body weight and food intake between the two groups before surgery. **a** Food intake declined sharply 1 day after SG, then began to restore on the fifth postoperative day. About 45 days after SG, it increased to the sham mice level and to even more than that in the sham group after 50 days. **b** Compared with the sham mice, SG mice lost 17.65% of body weight in 30 days. On the 20th day, body weight began to recover gradually. About 60 days after surgery, it surpassed the sham group by 15.8% ($n = 6$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ SG group vs. sham group)

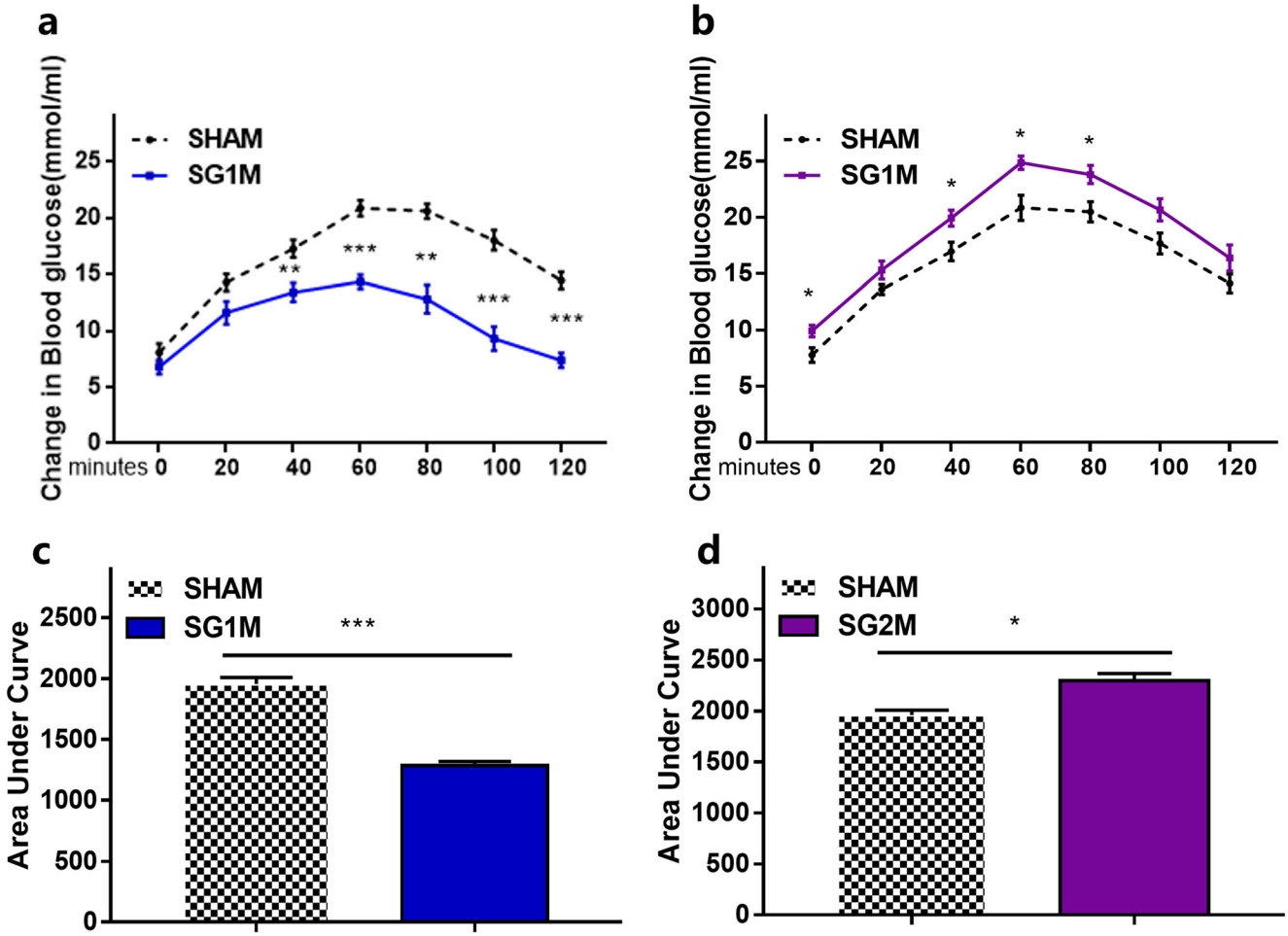

Fig. 3 Oral glucose tolerance test. OGTT was performed in overnight-fasted SG and sham surgery mice at **a** 1 month and **b** 2 months after surgery. Compared with the sham group, at each time point during the OGTT, blood glucose in the SG mice was significantly lower after 30 days, but higher after 60 days. The area under the curve (AUC) for the SG group declined by 34.32% in **c** 30 days and increased by 17.24% in **d** 60 days ($n = 6$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$)

Gastric Cavity Volume and Fasting Blood Glucose

The changes of gastric cavity volume were measured before, and at 2 weeks, 1 month, and 2 months after SG in mice (Fig. 4a). For the same time intervals, changes in fasting blood glucose were also detected. In SG group, gastric volume increased gradually after surgery but did not reach the preoperative size at 14 days and 1 month. However, at 2 months after SG, the gastric volume was larger than the preoperative volume (Fig.4b). The fasting blood glucose decreased 14 days and 1 month after SG, then increased significantly at 2 months and exceeded preoperative levels (Fig. 4c). These results show that fasting blood glucose has the same trend as the gastric cavity volume after SG.

Intestinal Histology

Adaptive changes after SG were observed. Villus heights of the duodenum (DU), proximal jejunum (Proxjej), distal jejunum (Distjej), and proximal ileum (Proxile) in the SG group were significantly lower ($P < 0.001$) than in the sham group (Fig. 5) at 30 days after surgery, but higher at 60 days after surgery. Due to hyperplastic changes, the villus surface area was significantly smaller in the SG mice than in the sham mice. In addition, a thickened gastric wall was observed 60 days after SG.

Real-Time PCR for mRNA Expression

At every time point in the sham group, there was no difference in the abundance of SGLT1 mRNA in each intestinal segment (DU, Proxjej, Distjej, and Proxile), but the expression of SGLT1 mRNA in the stomach was significantly lower than in the intestine (Fig. 6a). Compared with the sham group, mRNA abundance of SGLT1 in the duodenum, proximal jejunum, distal jejunum, and proximal ileum decreased significantly at 2 weeks and 1 month after SG (Fig. 6b–e). At 2 months, the mRNA abundance of SGLT1 in all intestinal segments in SG mice increased beyond the sham group. At 2 weeks and 1 month after SG, SGLT1 in the stomach

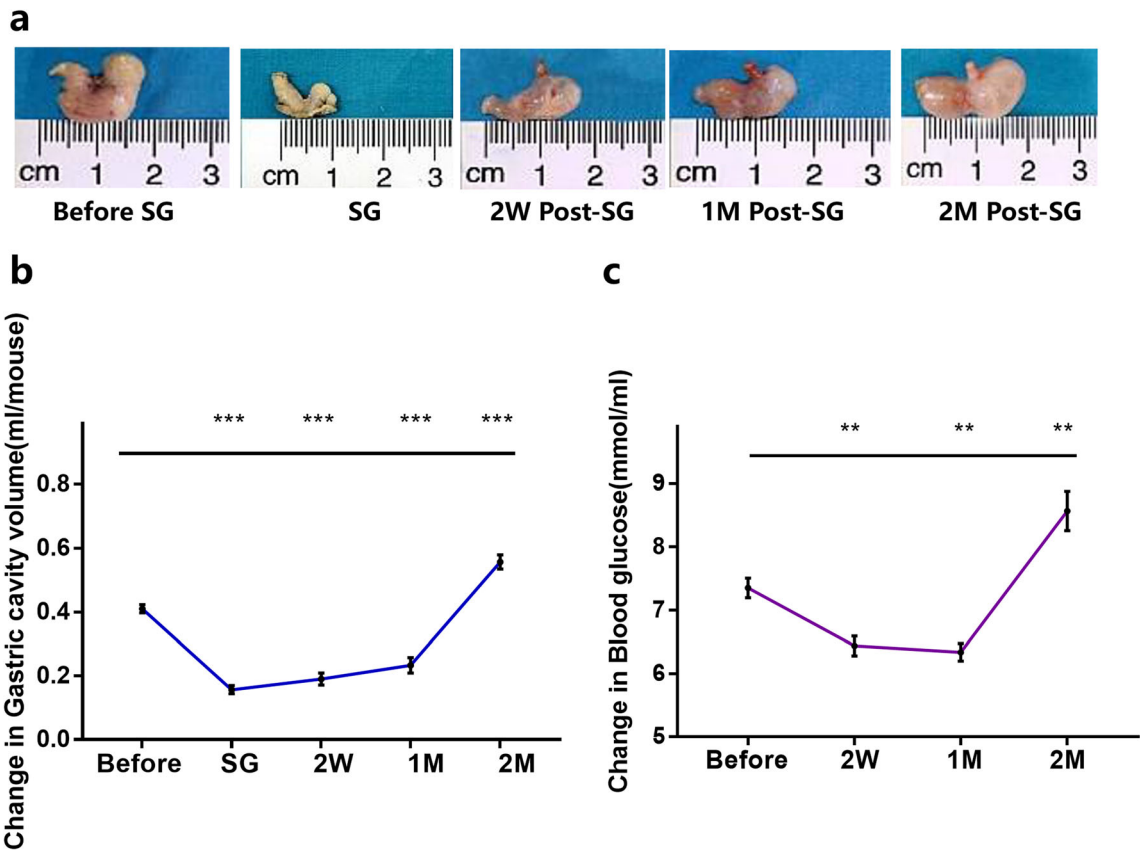

Fig. 4 Gastric cavity volume and fasting blood glucose. **a** 2/3 of gastric tissue was removed during SG surgery. **b** The volume of stomach increased at 14 days after operation and restored to half of the preoperative at 30 days. After 60 days, the gastric volume increased to more than the preoperative size. **c** Fasting blood glucose was measured before and at 14, 30, 60 days after SG surgery in mice. It decreased at 14 days and 1 month after surgery, but increased significantly at 2 months, to even more than preoperative levels ($*P < 0.05$, $**P < 0.01$ $***P < 0.001$)

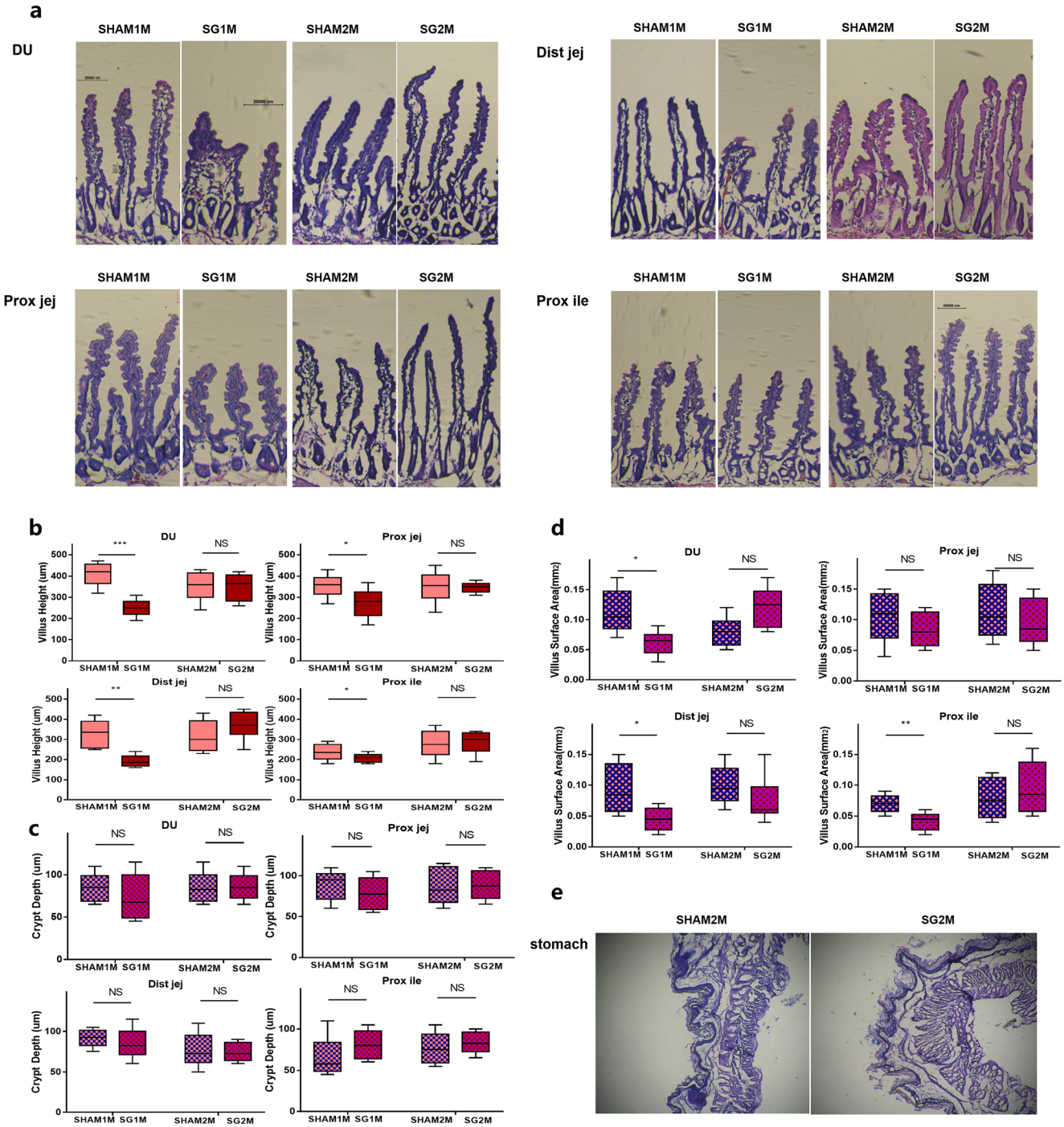

Fig. 5 Intestinal histology. Micrographs of representative sections from mice that underwent SG or sham surgery (hematoxylin and eosin, × 200) (scale bar 20 μm). a–d) The intestinal villus height in the DU (duodenum), Prox jej (proximal jejunum), Dist jej (distal jejunum), and Prox ile (proximal ileum) in the SG group reduced at 30 days but increased at 60 days after SG. Villus surface area of all intestinal segments in SG mice was significantly smaller than that in the sham mice at 1 month. e) The gastric wall thickened in SG mice at 60 days after surgery ($n = 6$, NS indicates no statistically significant difference, $^{*}P < 0.05$, $^{**}P < 0.01$ $^{***}P < 0.001$)

was significantly lower than in the sham group ($P < 0.001$, Fig. 7). However, at 2 months, the expression of gastric SGLT1 increased drastically compared with earlier time points and baseline. Based on the above results, the mRNA abundance of SGLT1 was consistent with the changes in gastric cavity volume.

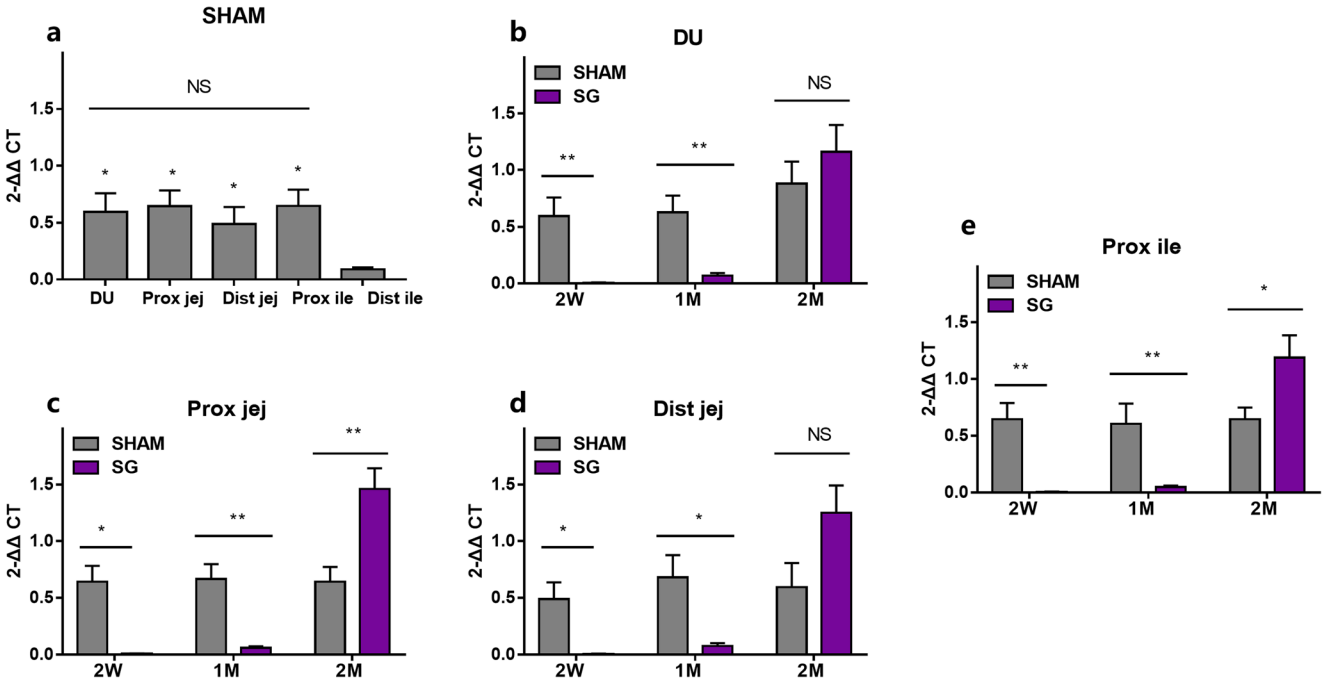

Fig. 6 Expression of SGLT1 in the intestine. **a** In the sham group, mRNA abundance of SGLT1 was no different in each intestinal segment (DU, Proxjej, Distjej, and Proxile) at any time point, but the expression of SGLT1 in the stomach was lower than that in intestinal tissue. **b**–**f** In the DU (duodenum), Prox jej (proximal jejunum), Dist jej (distal jejunum), and Prox ile (proximal ileum) the mRNA abundance of SGLT1 decreased at 2 weeks and 1 month but increased at 2 months after SG. A statistically significant difference was observed only at 2 weeks and 1 month after SG surgery ($n = 6$, $^{*}P < 0.05$, $^{**}P < 0.01$ $^{***}P < 0.001$)

Immunofluorescence

At 2 weeks and 1 month after surgery, reduced SGLT1 expression occurred in the duodenum, proximal jejunum, distal jejunum, and proximal ileum in the SG mice, but increased 2 months after surgery (Fig. 8). These results were consistent with RT-PCR.

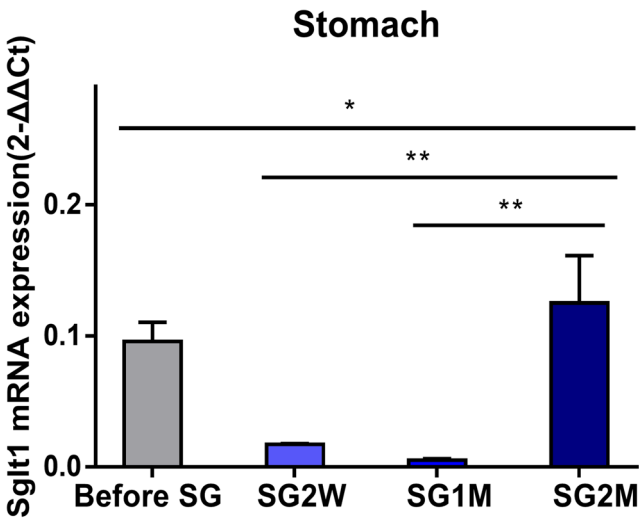

Fig. 7 Expression of SGLT1 in the stomach. The mRNA abundance of SGLT1 decreased at 2 weeks and 1 month but increased at 2 months after SG. Comparisons of expression at 2 months with baseline ($P = 0.0486$), 2 weeks ($P = 0.005$), and 1 month ($P = 0.003$)

Discussion

In this study in mice, SG achieved the same reductions in weight, metabolic improvements, and changes in intestinal structure usually seen in the first month after bypass surgery. We also saw a significant upregulation of SGLT1 2 months after surgery. After 2 months, SGLT1 increased in tissues of the intestine and in the stomach. Several studies indicate that changes in SGLT1 are part of the mechanism involved in weight loss and metabolic improvement following bypass surgery [11, 12, 17]. Those findings also suggest that subsequent upregulation of SGLT1 and other glucose transporters may be responsible for the failure that sometimes occurs over the longer term. Our research shows that changes in SGLT1 expression after SG surgery follow a similar pattern in mice.

In this study, food intake decreased after surgery, and body weight in the SG surgery group was significantly lower than that of the sham surgery group at 1 month, but these effects were reversed at 2 months. In parallel, OGTT showed that SG mice absorbed less glucose than

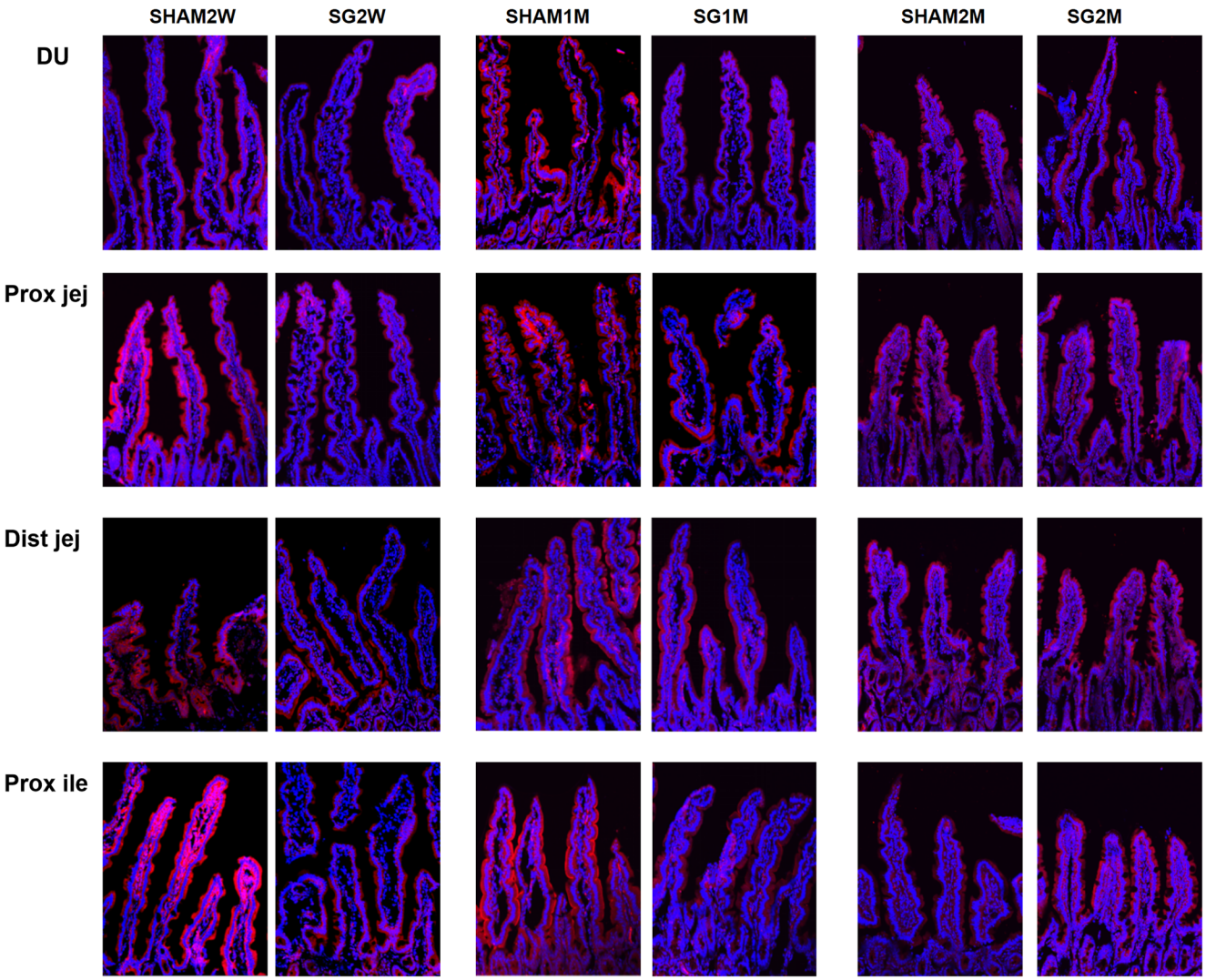

Fig. 8 Immunofluorescence for SGLT1.Compared with the sham group, the SGLT1 protein levels inSG mice in the DU (duodenum), Prox jej (proximal jejunum), Dist jej (distal jejunum), and Prox ile (proximal ileum) decreased at 2 weeks and 1 month after surgery but expression increased at 60 days after surgery

sham-operated mice at 1 month, but the glucose absorption increased at 2 months. HE staining indicated that the depth and density of intestinal villi decreased at 1 month, and there was a decrement in unit area and the total area of intestinal absorption and a reduction in the absorption capacity. The structure and surface area of the villi was restored at 2 months. SG had the same effect as RYGB in that expression of SGLT1 in the intestine decreased significantly in the first month after surgery. Intestinal immunofluorescence results also confirmed that SGLT1 expression was remarkably decreased after SG but increased at 2 months. Although SG does not bypass the proximal portion of the duodenum as in RYGB surgery [18, 19], the reduction in gastric volume leads to adaptive changes in the intestinal tract, which reduces absorptive capacity initially but then restores that capacity later, as in bypass surgery.

Theoretically, SGLT1 is involved in glucose transport throughout the intestinal tract, including the stomach [20]. Our results suggest that glucose transport in the stomach after surgery may play a greater role than previously recognized. SGLT1 expression in stomach tissues after SG in mice has been studied once to our knowledge, but not as carefully, using a sham comparison [21]. Caloric restriction is important [22], but our study indicates that SGLT1 expression and surgical outcomes vary with the size of the gastric sac, although there may be other variables as yet unexplored. We speculate that SGLT1 expression in the stomach, another site for glucose absorption, may play a role in the outcome after SG surgery.

Further experiments are needed to confirm this. Previous studies have confirmed that SGLT1 is expressed in small amounts in the stomach in mice [23], but no changes in postoperative levels have been reported until now.

Our findings suggest that metabolic effects are related to the gastric volume after SG so that maintenance of reduced weight may require greater attention to management of the remnant stomach volume. This suggests that surgeons should be aware of the importance of management of dietary habits, and patients should be made aware of the importance of diet after SG surgery. In bariatric patients, the volume of the remnant stomach seems directly related to the initial metabolic improvement after SG [20]. Other findings suggest that increased gastric volume correlates with the reversal and failure to maintain weight loss after 1 year [24, 25]. If food intake is not limited, the remnant stomach will expand to the original size or even exceed the original size of the gastric sac, which will weaken or reverse the positive effects on weight loss and diabetes. In another study in mice, prevention of postoperative gastric stump dilatation avoided weight gain and recurrence of metabolic disease after RYGB surgery [26].

Limitations

A limitation of this study is that we used non-obese mice in this preliminary study, while most patients who undergo SG surgery are obese and have diabetes. The expression level of SGLT1 in the gut of diabetes patients is higher and thus is not necessarily reflected in a model using non-obese mice [27, 28]. Further studies in a mouse model of obesity and diabetes will be needed to confirm these changes in the expression of SGLT1 in the stomach, intestinal villi, and intestine in the 2 months following SG.

Future Directions

In summary, by reducing the size of the gastric sac, SG alters the expression of SGLT1 in the gut, lowering intestinal glucose uptake, leading to weight loss, and improving glucose metabolism. But more specifically, our findings indicate that the expression of SGLT1 in mice is regulated by changes in residual gastric volume. This study contributes to the research involving animals that has added to our understanding of the effects of bariatric surgery [29]. Effective control and management of gastric volume after SG may be a key factor in prolonging the benefits of surgery. Future research should seek to further clarify this aspect of metabolic changes after sleeve gastrectomy.

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Compliance with Ethical Standards

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

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All applicable institutional and/or national guidelines for the care and use of animals were followed.

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