Obesity Surgery (2019) 29:593–600
https://doi.org/10.1007/s11695-018-3555-7

ORIGINAL CONTRIBUTIONS

Technical Feasibility of a Murine Model of Sleeve Gastrectomy with Ileal Transposition

Lee D. Ying[1,2] · Gregory A. Breuer[1] · Matthew O. Hubbard[1,3] · Geoffrey S. Nadzam[1,3] · John Hwa[1,2] · Kathleen A. Martin[1,2]

Published online: 23 October 2018

Abstract

Background Sleeve gastrectomy with ileal transposition has been shown to be superior to sleeve gastrectomy alone for promoting weight loss in rat and porcine models. The absence of a mouse model for this procedure has impeded efforts to understand the molecular physiology underlying its efficacy. This study demonstrates the long-term survivability of sleeve gastrectomy with ileal transposition in mice.

Materials and Methods In this study of technical feasibility, a sleeve gastrectomy with ileal transposition (SGIT), sleeve gastrectomy (SG), or sham surgery (SH) was performed on 7- to 8-week-old C57Bl/6J mice ($n = 8$ for each). To evaluate long-term survivability, mice were placed on an obesogenic diet and weighed weekly for 10 weeks. The intestinal identity of the transposed segment was assessed with gene expression analysis of duodenal-, jejunal-, and ileal-specific hormones using quantitative polymerase chain reaction.

Results Overall, SGIT better prevented weight gain than the SG or sham procedures (10-week post-operative weight: SH 45.3 ± 1.0 g, SG 41.25 ± 1.6 g, SGIT 35.4 ± 0.8 g). Gene expression pattern analysis of three markers of intestinal identity (gastrin, cholecystokinin, and peptide YY) suggests that the ileal identity of the transposed segment is maintained 10 weeks after transposition.

Conclusions We demonstrate for the first time a reproducible mouse model of sleeve gastrectomy with ileal transposition. Future studies utilizing this model will expand our understanding of the molecular pathways through which the hindgut regulates satiety.

Keywords Mouse metabolic surgery · Sleeve gastrectomy with ileal transposition

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11695-018-3555-7) contains supplementary material, which is available to authorized users.

✉ Kathleen A. Martin
Kathleen.martin@yale.edu

Lee D. Ying
Lee.ying@yale.edu

Gregory A. Breuer
Gregory.breuer@yale.edu

Matthew O. Hubbard
Matthew.hubbard@yale.edu

Geoffrey S. Nadzam
Geoffrey.nadzam@yale.edu

John Hwa
John.hwa@yale.edu

[1] Yale University School of Medicine, New Haven, CT 06511, USA

[2] Yale Cardiovascular Research Center, 300 George St, Room 759, New Haven, CT 06511, USA

[3] Department of Gastrointestinal Surgery, Yale New Haven Health, New Haven, CT 06511, USA

Introduction

Obesity continues to be one of the world's most significant public health challenges [1–4], and metabolic surgery has been increasingly utilized to address this disease and its related co-morbidities [5, 6]. Metabolic surgery has been proven to be safe, reliable, and cost-saving in many instances [7–10]. The sleeve gastrectomy (SG), which was originally developed as a first stage procedure for patients undergoing a duodenal switch [11, 12], has been the most commonly performed metabolic surgery in the USA since 2013 [13]. While the SG is associated with fewer long-term complications than the Roux-en-Y gastric bypass (RYGB), it results in less weight loss [14]. Revision operations including SG to RYGB conversions can sometimes improve weight loss outcomes [15, 16], and as of 2015, revision surgeries accounted for 13.6% of all bariatric procedures [13]. However, revision procedures in general are associated with higher rates of surgical complications [16–19], and SG to RYGB conversions in particular may leave patients with RYGB-associated long-term nutritional deficiencies. As the number of metabolic surgeries performed continues to rise, revision-associated complications are also likely to increase [20, 21]. Further complicating this issue, it is unclear why patients may fail their primary SG, a problem stemming from a lack of consensus regarding the mechanistic basis underlying weight loss following metabolic surgery [22–24].

The sleeve gastrectomy with ileal transposition (SGIT) is a procedure that may provide insights and solutions. Although the mechanisms underlying weight loss after bariatric surgery remain unclear, a central mediator is believed to be the ileal brake. The ileal brake inhibits upper gut motility to decrease food intake and promote satiety and is a neuroendocrine feedback loop that is activated by the detection of nutrients in the hindgut [25, 26]. In the SGIT, a sleeve gastrectomy is combined with a transposition of a segment of the ileum shortly distal to the duodenum. The SGIT is believed to promote greater weight loss than the SG by shortening the distance that intestinal contents must travel before being detected by the "hindgut," thus resulting in earlier satiety [27, 28]. The clinical utilization of this complex procedure as a primary operation has been limited thus far to a few surgeons [29–31], but the outcomes reported by these early pioneers are promising and suggest that the procedure can produce weight loss on par with RYGB [29–31]. Additionally, as the entire length of small bowel is preserved, the procedure is not believed to cause malabsorption-related nutrient deficiencies. However, further molecular characterization of this surgery is necessary to fully understand its physiologic effects and limitations.

Rat models of ileal transposition have been reported since as early as 1984 and have reproducibly demonstrated that the procedure attenuates weight gain when animals are placed on an obesogenic diet post-operatively [32–35]. More recently, studies in diabetic rat models demonstrated that SGIT could enhance weight loss and improve glycemic control compared to SG alone [27, 28]. SGIT has been shown to be similarly effective in porcine models [28, 29, 36], but to date, a mouse model has not been published. To analyze the molecular pathways mediating the weight loss effects of SGIT, gene knockout and editing technologies must be employed, and these platforms are best characterized for murine models. A mouse model of SGIT would allow researchers to study the physiological mechanisms through which SGIT enhances the ileal brake. As the average laboratory rat weighs almost ten times as much as a laboratory mouse of comparable age [37, 38], adapting the procedure to mice is in itself a significant challenge. In this report, we describe for the first time a reliable and reproducible technique for constructing a sleeve gastrectomy with ileal transposition in mice.

Materials and Methods

Animals

All experiments were approved by the Institutional Animal Care and Use Committee of Yale University. Male C57Bl/6J mice (Jackson Labs) were housed in an animal facility with a controlled temperature environment, ad libitum access to food and water, and a 12:12-h light:dark cycle. Ensure® (1.06 kcal/ml with 14% of energy derived from protein, 22% from fat, and 64% from carbohydrate; Abbott Laboratories) was provided during the immediate pre- and post-operative periods as detailed below.

Pre- and Post-Operative Management

Seven- to eight-week-old mice were given a liquid diet (Ensure®) in addition to their chow for 2 days. For the 2 subsequent days, they were given only Ensure® and water, then fasted 6–8 h before surgery. Post-operatively, mice were placed on a circulating water pad and were monitored every 30 min until they resumed normal activity. Animals were provided with water and Ensure® from post-op day 1–7. From day 8–10, mice were provided with high-fat chow in addition to Ensure®. Starting on day 11, Ensure® was removed and the animals were maintained on high-fat diet (60% fat by kcal, D12492, Research Diets Inc.) and water.

Sleeve Gastrectomy Surgery Technique

Numerous techniques for performing a sleeve gastrectomy in mice have been published [39–45], and our technique is based on that described by Hao et al. [44]. Animals were anesthetized with an intraperitoneal injection of a ketamine:xylazine (100:10 mg/ml) at a dose administered per kilogram body

weight. A self-retaining retractor was used to expose the abdominal contents. The stomach was exposed, and the thin mesentery was dissected using straight-tipped Vannas micro-dissecting spring scissors. The stomach contents were washed out through a gastrotomy, and the gastric branches of the splenic artery were identified and cauterized. A custom clamp was applied from the fundus to the pylorus to outline the sleeve, and sutures were placed and the stomach was transected above the clamp. The edges were closed using a continuous suture pattern (7-0 Prolene® Ethicon Inc.), and after releasing the clamp, the suture layer was folded into the stomach and closed with a second continuous layer [44]. The abdominal wall was closed in two layers (7-0 Prolene®). The sleeve surgery required approximately 1 h per mouse.

Sleeve Gastrectomy with Ileal Transposition Surgery Technique

After performing a sleeve gastrectomy as above, a 2-cm segment of ileum located approximately 3–5 cm proximal to the ileocecal valve was isolated (Fig. 1b). Taking care to preserve the vascular stalks, the segment was tied off at its proximal and distal ends with a pair of interrupted sutures (9-0 Ethilon®, Ethicon Inc). The intestine was divided in between each pair of sutures (Fig. 1c), and the free segment was temporarily returned to the abdomen. The most proximal and most distal free segments were joined using an end side-to-end side anastomosis as follows.

First, a small volume of sterile saline was injected into each of the two segments to loosen intestinal debris and to gently inflate the intestine. A 4-mm incision was made on both segments using straight-tipped micro-dissecting scissors, and the intestines were arranged end side-to-end side. Stay sutures were placed on the upper and lower corners of the intestine approximately 1 mm from the intestine edge, and tension was applied with mosquito forceps. The tissue edges were apposed with seven interrupted sutures placed approximately 1 mm from the tissue edge (Fig. 1d). These sutures were tied gently to prevent necrosis at the suture line. When necessary, additional interrupted sutures were placed to close remaining gaps.

After approximating the tissue edge on both sides, a continuous suture was run from the top stay suture to the bottom stay suture. The running suture was locked by bringing the needle through its own loop after reaching the bottom stay suture. This pattern was repeated on the other side until the second stay suture was reached (Fig. 1e) and the knot was secured with three more throws.

Next, the small intestine was transected approximately 4 cm distal to the ligament of Treitz. The isolated ileal segment, with full neural innervation and intact vascular supply,

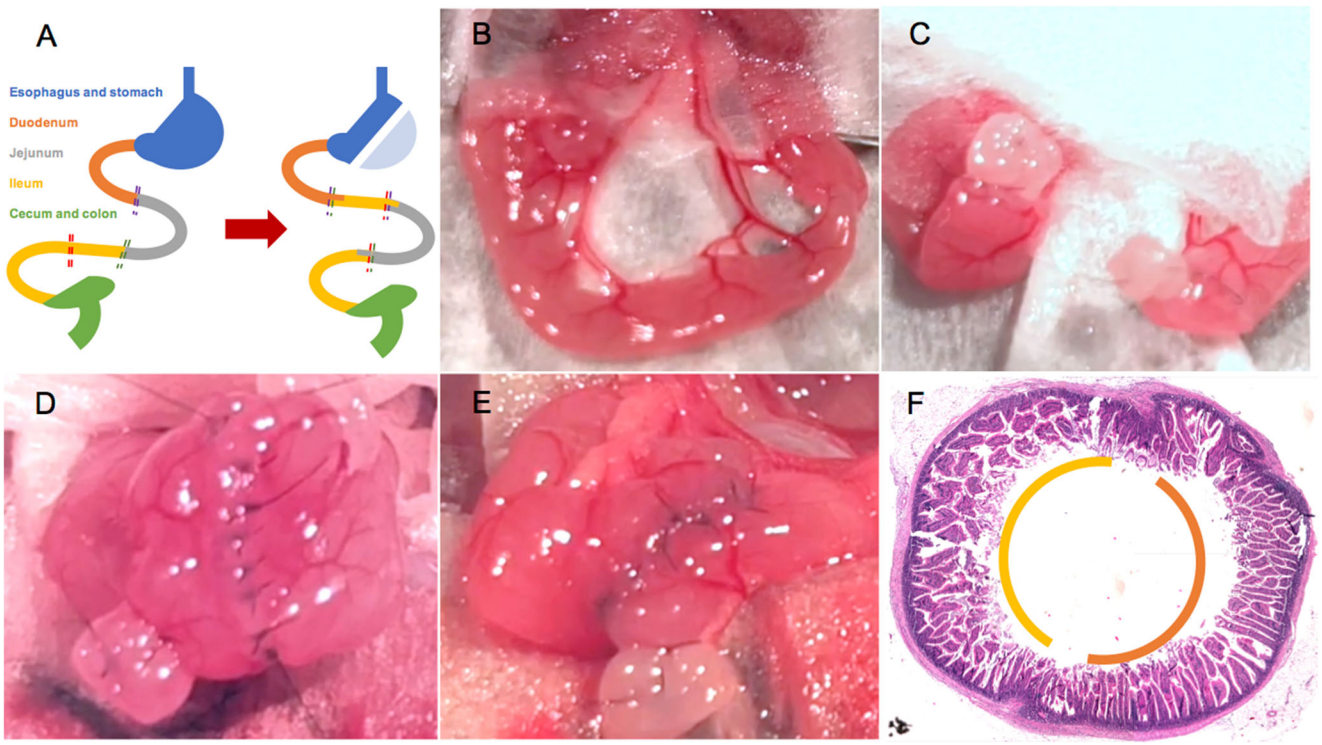

Fig. 1 **a** Sleeve gastrectomy with ileal transposition. **b** The ileal segment is transected at natural breaks in the mesenteric vessels to preserve the vascular supply. **c** The intestine is divided, and the open ends are tied off to prevent adhesion formation. **d** The side-to-side anastomosis is approximated with a layer of interrupted sutures. **e** A second layer of continuous sutures reinforces the watertight seal. **f** Hematoxylin and eosin stain of the anastomosis 10 weeks after surgery. The yellow and orange lines correspond to the ileal and duodenal segments (as depicted in **a**), respectively

was inserted in the original peristaltic direction by making two additional end side-to-end side anastomoses. Finally, the abdominal cavity was thoroughly irrigated prior to closure. The SGIT surgeries took approximately 2 h per mouse and a two-part video (Video part 1, Video part 2) demonstrating this procedure can be found in the electronic supplement.

Sham Surgery Technique

As described [46–50], sham surgeries were performed by externalizing the bowel and applying pressure with forceps at the SGIT anastomosis sites and along the greater curvature of the stomach. The sham surgery (SH) took approximately 45 min per mouse.

Histology

Samples were prepared for hematoxylin and eosin staining as described [51]. Yale Pathology Tissue Services performed sectioning and staining.

Weight and Blood Glucose Measurement

Animals were weighed weekly and mice were fasted for 10 h prior to measuring blood glucose. Statistical significance was evaluated using an ordinary one-way ANOVA, corrected for multiple comparisons using a Tukey's honestly significant difference (HSD) test with $\alpha = 0.05$ (Prism 7, GraphPad Software). The slope of each graph of weight vs time was calculated using a linear regression model, and statistical significance between was determined using a one-way ANOVA with Tukey's multiple comparisons test. Values are reported as the mean ± standard error of the mean.

Gene Expression Analysis

Mice were sacrificed 10 weeks post-surgery. Tissue samples were collected from the duodenum, jejunum, and ileum of the sham mice; jejunum of the SG mice; and the transposed ileal segment of the SGIT mice. RNA was isolated from an aliquot of the intestinal tissue of each mouse using the Direct-zol RNA Miniprep kit (Zymo Research). The RNA was reverse transcribed to cDNA using an iScript cDNA synthesis kit (Bio-Rad), and quantitative polymerase chain reaction (qPCR) was performed to measure gene expression. Primer sequences were obtained through OriGene: Gastrin (MP205267), Peptide YY (MP210680), and Cholecystokinin (MP202464). Gene expression was analyzed using the comparative CT method (ΔΔCT) with 18S as the endogenous control.

Results

Surgical Outcome

Eight mice were randomized to each of the SG, SGIT, and SH groups. The initial mortality rate was 37.5% (3/8) in the SGIT group. The first SGIT animal to be operated on exhibited lethargy and discomfort on the first post-operative day despite standard pain management protocols, and on autopsy, was found to have a leak at the most proximal anastomosis. The second and third mice appeared to recover well after surgery, but were euthanized after they failed to thrive following initiation of high-fat chow. There was no morbidity and mortality in the subsequent 5 SGIT mice. The SGIT procedure has since been performed in over a dozen mice, with a mortality rate of 0%, as well as with a 0% complication rate after being switched to solid chow. Mortality was 0% (0/8) in the sham and sleeve groups.

Anastomosis Histology

Because the anastomoses were constructed side-to-side, a lumenal cross-section containing the transposed ileal tissue as well as the native jejunal tissue to which it is anastamosed can be obtained (Fig. 1f). Hematoxylin and eosin staining shows well-healed intestinal walls, with minimal fibrosis at the two suture lines. Comparison of the intestinal villi shows noticeably different villi morphology, without any areas of degeneration or necrosis. The lumina of the anastomoses were patent at 10 weeks, without any evidence of inflammatory changes or stricture.

Weight Loss and Blood Glucose Measurement

Ten weeks after surgery, the sham group weighed 45.3 ± 1.0 g, the sleeve group weighed 41.25 ± 1.6 g, and the SGIT group weighed 35.4 ± 0.8 g (Fig. 2a). Linear regression analysis was performed on the curves of weight vs time (Sham slope 2.6 ± 0.1, $R^2 = 0.98$; SG slope 2.3 ± 0.07, $R^2 = 0.99$; SGIT slope 1.6 ± 0.1, $R^2 = 0.93$). The slopes of the sham vs SGIT curves and SG vs SGIT curves were significantly different ($p < 0.01$), but the slopes of the sham vs SG curves were not ($p > 0.1$). Average weights of the SH were significantly higher than SG or SGIT at weeks 1–10, and SG was significantly higher than SGIT from weeks 4–10. The SGIT group also had the lowest 10-h fasting blood sugar (SGIT 104 ± 6 mg/dl, SG 123 ± 14 mg/dl, Sham 157 ± 11 mg/dl; Fig. 2b). The difference between the SGIT and sham group was statistically significant ($p < 0.05$).

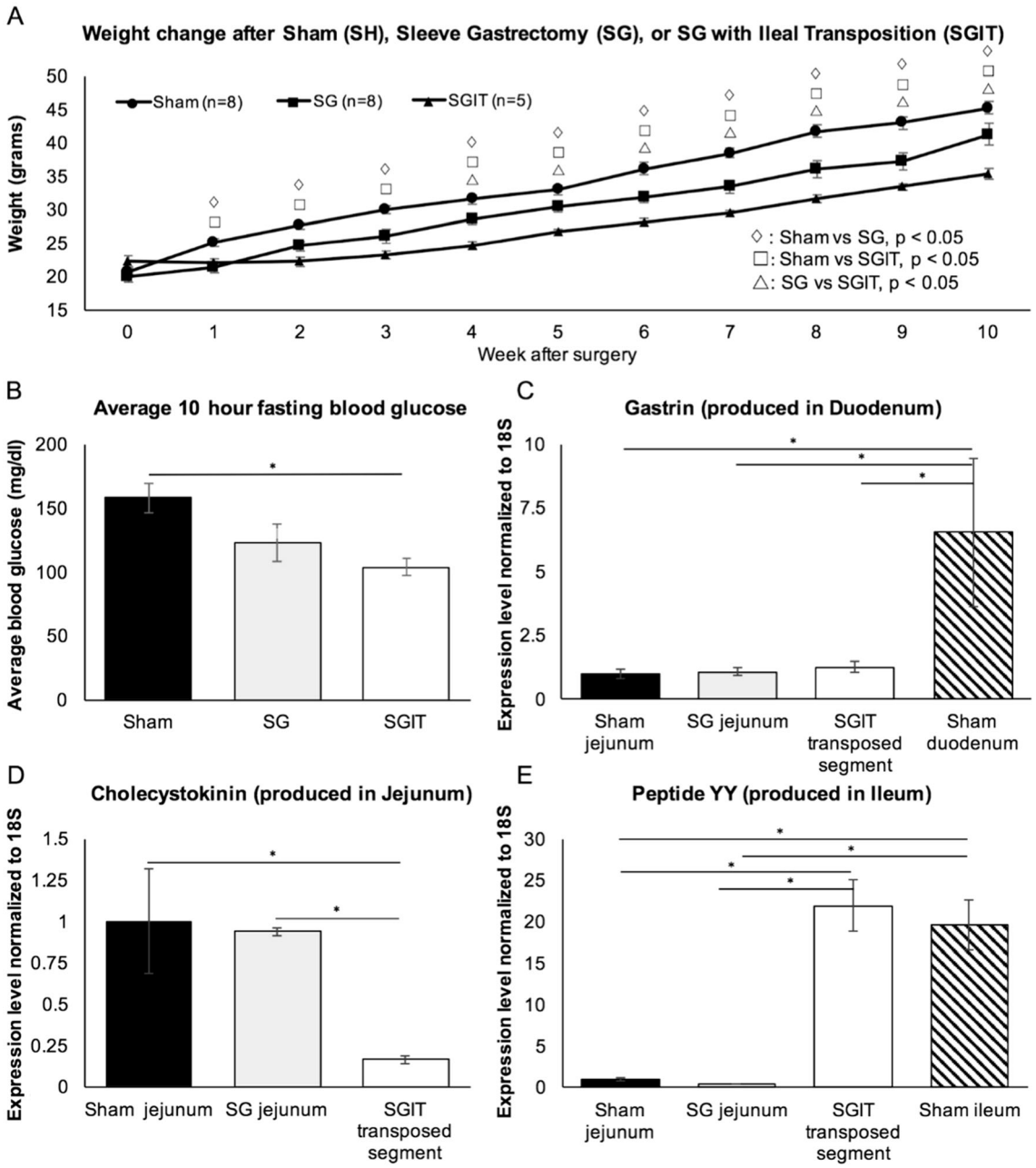

Fig. 2 **a** Weight gain following surgery. All mice were weighed weekly. The sleeve gastrectomy with ileal transposition (SGIT) group gained less weight compared to the sleeve gastrectomy (SG) and sham surgery group. **b** Ten weeks after surgery, the SGIT group had lower blood glucose compared to the SG and sham surgery groups (SH 157 ± 11 mg/dl, SG 123 ± 14 mg/dl, SGIT 104 ± 6 mg/dl). The difference between the SGIT group and sham surgery group was statistically significant ($p < 0.05$). **c** Gene expression for known intestinal hormones was measured in the duodenum, jejunum, and ileum of the sham mice, the jejunum of sleeve gastrectomy mice, and the transposed segment in the SGIT mice. The tissue samples of the jejunum and the transposed segment were taken from the same anatomical location, and thus, the results are normalized to the sham jejunum (expression level ± standard error of mean). The expression of gastrin, a duodenal hormone, was significantly higher in the duodenum than in the jejunum of the sham and SG groups, and the transposed segment in the SGIT group (SH Jejunum 1.0 ± 0.2, SG jejunum 1.1 ± 0.2, SGIT transposed ileum 1.2 ± 0.2, SH duodenum 6.5 ± 3.0. $p < 0.05$ for SH duodenum vs SH jejunum, SH duodenum vs SG jejunum, and SH duodenum vs SGIT transposed ileum). **d** Cholecystokinin, a jejunal hormone, is significantly more highly expressed in the jejunum of the sham and SG mice compared to the transposed segment in the SGIT mice (SH jejunum 1.0 ± 0.3, SG jejunum 0.9 ± 0.02, SGIT transposed ileum 0.2 ± 0.02. $p < 0.05$ for SH jejunum vs SGIT transposed ileum, and SG jejunum vs SGIT transposed ileum). **e** Peptide YY was higher in the transposed segment of the SGIT mice ileum than in the jejunum of the sham and SG mice indicating the transposed segment maintains an ileal-specific gene expression pattern. There was no significant difference between the transposed segment of the SGIT mice and the native ileum of the SH mice (SH jejunum 1.0 ± 0.2, SG jejunum 0.4 ± 0.04, SGIT transposed ileum 21.9 ± 3.1, SH ileum 19.6 ± 3.0. $p < 0.05$ for SGIT transposed ileum vs SH jejunum, SGIT transposed ileum vs SG jejunum, SH ileum vs SH jejunum, and SH ileum vs SG jejunum). Asterisks indicate $p < 0.05$

Gene Expression Analysis of the Transposed Ileal Segment

To determine whether transposition influences the functional identity of the transposed segment, the mRNA expression levels of duodenal-specific, jejunal-specific, and ileal-specific hormones were measured by qPCR. Notably, tissue samples were taken from the same anatomical location: in the SGIT mice, this location corresponded to the transposed ileal segment; in the sham and SG mice, this location corresponded to the jejunum. Tissue from SH duodenum and ileum was also assessed as a positive control for duodenal- and ileal-specific genes. All expression values are presented relative to that of the sham jejunum, which can be considered the "native" tissue at the transposition site. Gastrin, which is produced primarily in the stomach and the duodenum, was higher in the duodenum than in the jejunum of the sham and SG mice, and in the transposed ileum of the SGIT group ($p < 0.05$, Fig. 2c). Cholecystokinin, which is produced in the jejunum, was higher in the jejunal tissue of the sham and SG mice than in the transposed ileum in the SGIT mice ($p < 0.05$, Fig. 2d). Peptide YY (PYY) was more highly expressed in the transposed segment of the SGIT mice than in the intestine from the same anatomical position (jejunum) in the sham and SG mice ($p < 0.01$, Fig. 2e). There was no significant difference between the expression levels of PYY in the transposed segment of SGIT mice and the ileum of SH mice ($p > 0.05$, Fig. 2e).

Discussion

We report for the first time the technical feasibility of a sleeve gastrectomy with ileal transposition in mice. Our technique incorporates previously published surgical techniques for constructing the sleeve gastrectomy and intestinal anastomoses [39–45], and shares similarities in the pre- and post-operative management. However, as opposed to previously reported one-layer closures for the anastomoses [39–45], we employed a two-layer approach. The first interrupted layer assists in precisely aligning the two walls and revealing potential gaps due to small differences in intestine wall length. The second continuous layer creates a strong, watertight seal. Ten weeks after surgery, the anastomoses appear fully matured, with minimal external adhesion formation. The intestinal lumen remains patent, with minimal fibrosis visible at the anastomosis suture line.

As observed in previous studies of SGIT in rat and porcine models [28, 36], after surgery, all three groups experienced some weight gain on the high-fat diet. Post-operative weight gain in even the SG and SGIT groups was expected, as all three groups were placed on a highly obesogenic lard-based diet. Similarly, as previously observed in rat and porcine models of SGIT [28, 36], we confirmed that SGIT can significantly decrease weight gain compared to the sham or sleeve gastrectomy alone. This proof of concept study has thus allowed us to establish a reproducible surgical technique which can be used in future studies to compare SGIT to SG alone in promoting weight loss in obese mice.

The initial mortality rate we observed with this procedure was comparable to the 35.7–44% mortality rate reported for mouse models of RYGB [40, 42, 43], which is the most similar procedure described in the literature. The first mouse to be operated on in the SGIT group succumbed on the first post-operative day following complications arising from leakage at an anastomosis site. This mortality was likely caused by surgeon inexperience. The two mice that succumbed within a week of resuming high-fat chow diet appeared to have poorly tolerated the rapid diet change. By closely monitoring post-operative food intake, as well as providing liquid Ensure® to mice that take longer to begin eating solid chow, we have reduced the overall mortality rate of this procedure to 0%.

We determined that the ileal identity of the intestinal segment was maintained after transposition. In the sham and SG mice, the tissue in this jejunal region had high expression levels of cholecystokinin, a jejunal hormone, but low levels of gastrin and peptide YY, which are more highly expressed in the duodenum and ileum, respectively. On the other hand, the transposed ileum demonstrated an ileal gene expression pattern with high peptide YY expression, and low gastrin and cholecystokinin expression. Whether the act of transposition modifies the gene expression profile of the transposed ileum compared to the native ileum remains to be determined, but we demonstrate that the transposed segment maintains an ileal pattern of gene expression even in its new jejunal environment at 10 weeks after surgery. This is also supported by clear histological differences in the villi structure of the transposed segment, compared to the jejunal tissue to which it was anastamosed.

By establishing the technical feasibility of this model, we provide investigators with a model which can be used in conjunction with murine models of diet-induced obesity to determine whether and how SGIT promotes greater weight loss compared to SG. We believe this model will allow researchers to better explore the molecular mechanisms underlying the ileal brake, which may provide insights into why some patients fail their primary SG. Activation of ileal brakes, such as peptide YY, by earlier exposure of unabsorbed nutrients to the ileum has been proposed as the mechanism explaining weight loss following SGIT [52, 53], and at least one clinical experiment has demonstrated direct evidence of this regulatory mechanism [54]. This mechanism is also referred to as the hindgut hypothesis and has recently garnered increased interest due to its potential mechanistic role in other metabolic surgeries [55–57]. Future studies that utilize this murine model of SGIT may be able to determine the hormones released by the transposed ileum postprandially, as well their contribution

to promoting satiety. We hope this model will allow investigators to better dissect the molecular pathways involved in appetite and satiety regulation and uncover novel insights into mechanism of metabolic-surgery-induced weight loss.

Conclusion

The results of the present study have demonstrated for the first time that a mouse model of sleeve gastrectomy with ileal transposition is technically feasible and is better able to prevent weight gain than sleeve gastrectomy. Additionally, through gene expression analysis, we have confirmed that the transposed segment maintains an mRNA expression pattern characteristic of ileal tissue even 10-weeks after transposition into a jejunal environment. Future studies will use next-generation sequencing techniques to identify potential molecular pathways involved in mediating satiety regulation. Ultimately, we hope this model will improve obesity treatment by increasing our capability to study the role of distal gut hormones in appetite regulation.

Author Contributions L.D.Y. conceived of, performed, and interpreted the research, and wrote and edited the manuscript.

G.B., M.O.H., G.S.N., J.H., and K.A.M. conceived of and interpreted the research, and wrote and edited the manuscript.

Funding Lee D. Ying is supported by the NIH NIDDK (1F30DK112569-01).

Kathleen A. Martin is supported by the NIH NHLBI (HL091013, HL118430, RHL119529).

Compliance with Ethical Standards

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

Ethical Approval All applicable institutional and/or national guidelines for the care and use of animals were followed.

References

1. Flegal KM, Kruszon-Moran D, Carroll MD, et al. Trends in obesity among adults in the United States, 2005 to 2014. JAMA. 2016;315(21):2284–91. https://doi.org/10.1001/jama.2016.6458.
2. Kelly T, Yang W, Chen CS, et al. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond). 2008;32:1431. https://doi.org/10.1038/ijo.2008.102. https://www.nature.com/articles/ijo2008102-supplementary-information
3. Mendez MA, Monteiro CA, Popkin BM. Overweight exceeds underweight among women in most developing countries. Am J Clin Nutr. 2005;81(3):714–21.
4. Haslam DW, James WPT. Obesity. Lancet. 2005;366(9492):1197–209. https://doi.org/10.1016/S0140-6736(05)67483-1.
5. Andersen JR, Aasprang A, Karlsen T-I, et al. Health-related quality of life after bariatric surgery: a systematic review of prospective long-term studies. Surg Obes Relat Dis. 2015;11(2):466–73. https://doi.org/10.1016/j.soard.2014.10.027.
6. Pories WJ, Swanson MS, MacDonald KG, 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(3):339–52.
7. Picot J, Jones J, Colquitt JL, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: a systematic review and economic evaluation. Health Technol Assess (Winch. Eng.). 2009;13(41):1–190,215–357, iii-iv. https://doi.org/10.3310/hta13410.
8. Lopes EC, Heineck I, Athaydes G, et al. Is bariatric surgery effective in reducing comorbidities and drug costs? A systematic review and meta-analysis. Obes Surg. 2015;25(9):1741–9. https://doi.org/10.1007/s11695-015-1777-5.
9. Maciejewski ML, Arterburn DE. Cost-effectiveness of bariatric surgery. JAMA. 2013;310(7):742–3. https://doi.org/10.1001/jama.2013.276131.
10. Chang S, Stoll CT, Song J, et al. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg. 2014;149(3):275–87. https://doi.org/10.1001/jamasurg.2013.3654.
11. Almogy G, Crookes PF, Anthone GJ. Longitudinal gastrectomy as a treatment for the high-risk super-obese patient. Obes Surg. 2004;14(4):492–7. https://doi.org/10.1381/096089204323013479.
12. Silecchia G, Boru C, Pecchia A, et al. Effectiveness of laparoscopic sleeve gastrectomy (first stage of biliopancreatic diversion with duodenal switch) on co-morbidities in super-obese high-risk patients. Obes Surg. 2006;16(9):1138–44. https://doi.org/10.1381/096089206778392275.
13. Surgery ASfMaB. Estimate of bariatric surgery numbers, 2011–2015. Am Soc Metab Bariatric Surg. 2016.
14. Mann JP, Jakes AD, Hayden JD, et al. Systematic review of definitions of failure in revisional bariatric surgery. Obes Surg. 2015;25(3):571–4. https://doi.org/10.1007/s11695-014-1541-2.
15. Brethauer SA, Kothari S, Sudan R, et al. Systematic review on reoperative bariatric surgery: American Society for Metabolic and Bariatric Surgery Revision Task Force. Surg Obes Relat Dis. 2014;10(5):952–72. https://doi.org/10.1016/j.soard.2014.02.014.
16. Chansaenroj P, Aung L, Lee W-J, et al. Revision procedures after failed adjustable gastric banding: comparison of efficacy and safety. Obes Surg. 2017;27(11):2861–7. https://doi.org/10.1007/s11695-017-2716-4.
17. Kellogg TA. Revisional bariatric surgery. Surg Clin N Am. 2011;91(6):1353–71. https://doi.org/10.1016/j.suc.2011.08.004.
18. Khoursheed MA, Al-Bader IA, Al-asfar FS, et al. Revision of failed bariatric procedures to Roux-en-Y gastric bypass (RYGB). Obes Surg. 2011;21(8):1157–60. https://doi.org/10.1007/s11695-010-0229-5.
19. Noel P, Schneck A-S, Nedelcu M, et al. Laparoscopic sleeve gastrectomy as a revisional procedure for failed gastric banding: lessons from 300 consecutive cases. Surg Obes Relat Dis. 10(6):1116–22. https://doi.org/10.1016/j.soard.2014.02.045.
20. Nesset EM, Kendrick ML, Houghton SG, et al. A two-decade spectrum of revisional bariatric surgery at a tertiary referral center. Surg Obes Relat Dis. 2007;3(1):25–30. https://doi.org/10.1016/j.soard.2006.10.010.
21. Hallowell PT, Stellato TA, Yao DA, et al. Should bariatric revisional surgery be avoided secondary to increased morbidity and mortality? Am J Surg. 2009;197(3):391–6. https://doi.org/10.1016/j.amjsurg.2008.11.011.
22. Knop FK, Taylor R. Mechanism of metabolic advantages after bariatric surgery: it's all gastrointestinal factors versus it's all food restriction. Diabetes Care. 2013;36(Suppl 2):S287–S91. https://doi.org/10.2337/dcS13-2032.

23. Madura JA, DiBaise JK. Quick fix or long-term cure? Pros and cons of bariatric surgery. F1000 Med Rep. 2012;4:19. https://doi.org/10.3410/M4-19.
24. Ionut V, Bergman RN. Mechanisms responsible for excess weight loss after bariatric surgery. J Diabetes Sci Technol. 2011;5(5):1263–82.
25. Barreto SG, Soenen S, Chisholm J, et al. Does the ileal brake mechanism contribute to sustained weight loss after bariatric surgery? ANZ J Surg. 2018;88(1–2):20–5. Epub 2017/06/09. https://doi.org/10.1111/ans.14062.
26. Meek CL, Lewis HB, Reimann F, et al. The effect of bariatric surgery on gastrointestinal and pancreatic peptide hormones. Peptides. 2016;77:28–37. Epub 2015/09/08. https://doi.org/10.1016/j.peptides.2015.08.013.
27. Boza C, Muñoz R, Yung E, et al. Sleeve gastrectomy with ileal transposition (SGIT) induces a significant weight loss and diabetes improvement without exclusion of the proximal intestine. J Gastrointest Surg. 2011;15(6):928–34. https://doi.org/10.1007/s11605-010-1369-6.
28. Nausheen S, Shah IH, Pezeshki A, et al. Effects of sleeve gastrectomy and ileal transposition, alone and in combination, on food intake, body weight, gut hormones, and glucose metabolism in rats. Am J Physiol Endocrinol Metab. 2013;305(4):E507–18. https://doi.org/10.1152/ajpendo.00130.2013.
29. de Paula AL, Macedo ALV, Prudente AS, et al. Laparoscopic sleeve gastrectomy with ileal interposition ("neuroendocrine brake")–pilot study of a new operation. Surg Obes Relat Dis. 2006;2(4):464–7. https://doi.org/10.1016/j.soard.2006.03.005.
30. Çelik A, Ugale S, Ofluoğlu H. Laparoscopic diverted resleeve with ileal transposition for failed laparoscopic sleeve gastrectomy: a case report. Surg Obes Relat Dis. 2015;11(1):e5–7. https://doi.org/10.1016/j.soard.2014.09.010.
31. DePaula AL, Macedo ALV, Mota BR, et al. Laparoscopic ileal interposition associated to a diverted sleeve gastrectomy is an effective operation for the treatment of type 2 diabetes mellitus patients with BMI 21–29. Surg Endosc. 2009;23(6):1313–20. https://doi.org/10.1007/s00464-008-0156-x.
32. Kotler DP, Koopmans H. Preservation of intestinal structure and function despite weight loss produced by ileal transposition in rats. Physiol Behav. 1984;32(3):423–7. https://doi.org/10.1016/0031-9384(84)90257-9.
33. Boozer CN, Choban PS, Atkinson RL. Ileal transposition surgery attenuates the increased efficiency of weight gain on a high-fat diet. Int J Obes. 1990;14(10):869–78.
34. Gleeson MH, Cullen J, Dowling RH. Intestinal structure and function after small bowel by-pass in the rat. Clin Sci. 1972;43(6):731–42.
35. Strader AD, Vahl TP, Jandacek RJ, et al. Weight loss through ileal transposition is accompanied by increased ileal hormone secretion and synthesis in rats. Am J Physiol Endocrinol Metab. 2005;288(2):E447.
36. Boza C, Gagner M, Devaud N, et al. Laparoscopic sleeve gastrectomy with ileal transposition (SGIT): a new surgical procedure as effective as gastric bypass for weight control in a porcine model. Surg Endosc. 2008;22(4):1029–34. https://doi.org/10.1007/s00464-007-9685-y.
37. Laboratories J. Body weight information for C57BL/6J.
38. River C. SAS Sprague Dawley rat growth chart.
39. Bruinsma BG, Uygun K, Yarmush ML, et al. Surgical models of Roux-en-Y gastric bypass surgery and sleeve gastrectomy in rats and mice. Nat Protoc. 2015;10(3):495–507. https://doi.org/10.1038/nprot.2015.027.
40. Hao Z, Zhao Z, Berthoud H-R, et al. Development and verification of a mouse model for Roux-en-Y gastric bypass surgery with a small gastric pouch. PLoS One. 2013;8(1):e52922. https://doi.org/10.1371/journal.pone.0052922.
41. Ayer A, Borel F, Moreau F, et al. Techniques of sleeve gastrectomy and modified Roux-en-Y gastric bypass in mice. J Vis Exp. 2017;121 https://doi.org/10.3791/54905.
42. Seyfried F, Lannoo M, Gsell W, et al. Roux-en-Y gastric bypass in mice—surgical technique and characterisation. Obes Surg. 2012;22(7):1117–25. https://doi.org/10.1007/s11695-012-0661-9.
43. Lutz TA, Bueter M. The use of rat and mouse models in bariatric surgery experiments. Front Nutr. 2016;3(25) https://doi.org/10.3389/fnut.2016.00025.
44. Hao Z, Townsend RL, Mumphrey MB, Morrison CD, Münzberg H, Berthoud H-R. RYGB produces more sustained body weight loss and improvement of glycemic control compared with VSG in the diet-induced obese mouse model 2017.
45. Seyfried F, Lannoo M, Gsell W, Tremoleda JL, Bueter M, Olbers T, et al. Roux-en-Y gastric bypass in mice-surgical technique and characterisation 2012. 1117–1125 p.
46. Du J, Tian J, Ding L, et al. Vertical sleeve gastrectomy reverses diet-induced gene-regulatory changes impacting lipid metabolism. Sci Report. 2017;7:5274. https://doi.org/10.1038/s41598-017-05349-2.
47. Ding L, Sousa Kyle M, Jin L, et al. Vertical sleeve gastrectomy activates GPBAR-1/TGR5 to sustain weight loss, improve fatty liver, and remit insulin resistance in mice. Hepatology. 2016;64(3):760–73. https://doi.org/10.1002/hep.28689.
48. Wilson-Pérez HE, Chambers AP, Ryan KK, et al. Vertical sleeve gastrectomy is effective in two genetic mouse models of glucagon-like peptide 1 receptor deficiency. Diabetes. 2013;62(7):2380–5. https://doi.org/10.2337/db12-1498.
49. Pressler JW, Haller A, Sorrell J, et al. Vertical sleeve gastrectomy restores glucose homeostasis in apolipoprotein A-IV KO mice. Diabetes. 2015;64(2):498–507. https://doi.org/10.2337/db14-0825.
50. Shao Y, Shen Q, Hua R, et al. Effects of sleeve gastrectomy on the composition and diurnal oscillation of gut microbiota related to the metabolic improvements. Surg Obes Relat Dis. 2018; https://doi.org/10.1016/j.soard.2018.02.024.
51. Stearns AT, Balakrishnan A, Tavakkolizadeh A. Impact of Roux-en-Y gastric bypass surgery on rat intestinal glucose transport. Am J Physiol Gastrointest Liver Physiol. 2009;297(5):G950–7.
52. Maljaars PJ, Keszthelyi D, Masclee AA. An ileal brake-through? Am J Clin Nutr. 2010;92(3):467–8. https://doi.org/10.3945/ajcn.2010.30180.
53. Strader AD. Ileal transposition provides insight into the effectiveness of gastric bypass surgery. Physiol Behav. 2006;88(3):277–82. https://doi.org/10.1016/j.physbeh.2006.05.034.
54. Maljaars PW, Symersky T, Kee BC, et al. Effect of ileal fat perfusion on satiety and hormone release in healthy volunteers. Int J Obes (Lond). 2008;32(11):1633–9. https://doi.org/10.1038/ijo.2008.166.
55. Cummings DE, Overduin J, Foster-Schubert KE. Gastric bypass for obesity: mechanisms of weight loss and diabetes resolution. J Clin Endocrinol Metab. 2004;89(6):2608–15. https://doi.org/10.1210/jc.2004-0433.
56. Mason EE. The mechanisms of surgical treatment of type 2 diabetes. Obes Surg. 2005;15(4):459–61. https://doi.org/10.1381/0960892053723330.
57. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244(5):741–9. https://doi.org/10.1097/01.sla.0000224726.61448.1b.