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Isolated duodenal exclusion increases energy expenditure and improves glucose homeostasis in diet-induced obese rats

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Muñoz R, Carmody JS, Stylopoulos N, Davis P, Kaplan LM. Isolated duodenal exclusion increases energy expenditure and improves glucose homeostasis in diet-induced obese rats. Am J Physiol Regul Integr Comp Physiol 303: R985–R993, 2012. First published September 12, 2012; doi:10.1152/ajpregu.00262.2012.—Roux-en-Y gastric bypass (RYGB) by implantation of a 10-cm endoluminal sleeve device (ELS-10) induces weight loss and improves glycemic control. We have shown that mimicking the duodenal component of RYGB improves energy expenditure (EE) and increases resting energy expenditure (EE), and improves glycemic control. We have shown that mimicking the duodenal component of RYGB by implantation of a 10-cm endoluminal sleeve device (ELS-10) induces weight loss and improves glycemic control in diet-induced obese (DIO) rats. We sought to determine the mechanisms and structural requirements of these effects. We examined the effects of ELS-10 devices implanted in male DIO rats on weight body, food intake (FI), meal patterns, total and resting EE, and multiple parameters of glucose homeostasis, comparing them with sham-operated (SO) rats and with SO rats weight matched to the ELS-10-treated group. To determine the extent of duodenal exclusion required to influence metabolic outcomes, we compared the effects of implanting 10-, 4-, or 1-cm ELS devices. ELS-10 rats exhibited 13% higher total and 9% higher resting EE than SO controls. ELS-10 rats also exhibited enhanced postprandial GLP-1 secretion and improved glucose tolerance and insulin sensitivity out of proportion to the effects of weight loss alone. Implantation of 4- or 1-cm ELS devices had no effect on EE and limited effects on glucose homeostasis. Complete duodenal exclusion with ELS-10 induces weight loss by decreasing FI and increasing EE and improves glycemic control through weight loss-independent mechanisms. Thus signals originating in the proximal small intestine appear to exert a direct influence on the physiological regulation of EE and glucose homeostasis. Their selective manipulation could provide effective new therapies for obesity and diabetes that mimic the benefits of RYGB.

AS THE PREVALENCE and severity of obesity in the population has grown, so has the number of individuals affected with obesity-associated Type 2 diabetes mellitus (T2DM). Gastrointestinal weight loss surgical procedures (GIWLS) have proven to be an effective treatment for severe obesity and many of its associated metabolic sequelae, including T2DM (3, 24, 34, 35). Among the currently available GIWLS, Roux-en-Y gastric bypass (RYGB) is one of the most effective and commonly performed procedures worldwide (5). After RYGB, patients lose an average 63% of their excess weight, and full remission of T2DM is achieved in 40—85% of patients (4, 24, 34).

The mechanisms of weight loss and T2DM remission after various GIWLS operations remain incompletely understood. Different anatomical modifications of the stomach and intestine may mediate specific physiological outcomes. For example, pair-feeding studies have shown that the weight loss induced by isolated gastric procedures such as vertical sleeve gastrectomy (VSG) or adjustable gastric banding (AGB) results primarily from decreased food intake (FI), without an associated increase in energy expenditure (EE) (15, 36). Improved glycemic control after AGB parallels the associated weight loss implying that weight loss is the primary driver of glycemic improvement after this procedure (10).

In contrast, RYGB is a complex operation that includes modifications of both the stomach and the small intestine that alter the interaction among ingested nutrients, digestive secretions, and the bowel itself (Fig. 1A). In diet-induced obese (DIO) rats, weight loss following RYGB results from both reduced FI and increased resting EE (39). Since isolated gastric procedures do not alter EE, we hypothesized that the intestinal components of RYGB account for its stimulation. Also, substantial improvement in T2DM after RYGB occurs before significant weight loss in humans (28, 33, 42), suggesting a direct effect of RYGB on glycemic control, and recent studies have demonstrated weight loss and food intake-independent improvement in glucose tolerance after this procedure (8). Two intestinal effects of RYGB — nutrient exclusion from duodenum (30, 31) and early delivery of partially digested nutrients to the mid-jejunum (7, 25, 40) — likely mediate these enhanced effects of RYGB on energy balance and glucose homeostasis. In a previous study, we examined the role of these intestinal components in isolation by implanting a scaled model of an endoluminal sleeve (ELS) device in DIO rats. The ELS is a highly flexible, nutrient-impermeable tube that is anchored at its proximal end in the duodenal bulb. After implantation of a 10-cm ELS, ingested nutrients flow through the device lumen, where they are unable to interact directly with the duodenal mucosa. Since biliopancreatic secretions remain external to the device, the ELS reproduces a chemical environment in the duodenum and proximal jejunum similar to that of the biliopancreatic limb of the RYGB. Because of the absence of digestive enzymes within the ELS lumen, place-
Two anatomical components of RYGB. 1) Isolation of the proximal gastric cardia; 2) nutrient exclusion from the distal stomach; 3) nutrient exclusion from the duodenum; 4) accelerated or enhanced contact of partially digested nutrients with the jejunal mucosa; and 5) partial vagotomy. B: 10-cm endoluminal sleeve (ELS) device mimics two anatomical components of RYGB. 1) Ingested nutrients flow through the ELS lumen and are prohibited from direct contact with the mucosa of the duodenum and proximal jejunum. 2) Undigested or partially digested nutrients contact the distal small intestine, while biliopancreatic secretions are distally diverted into the mid-jejunum. A is ELS-anchoring crown; B is highly flexible, nutrient-impermeable tube. C: extent of duodenal exclusion. 1- and 4-cm ELS devices induce more limited nutrient exclusion and rerouting of biliopancreatic secretions than the 10-cm ELS device.

MATERIALS AND METHODS

Animals. To induce obesity, male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were placed on a high-fat diet (HFD; 60% kcal from fat; Research Diets, New Brunswick, NJ) immediately after weaning, as previously described (20). Upon reaching 500 g, rats were individually housed in a barrier animal facility at 19–22°C and 40%-60% humidity with a 12-h light-dark cycle (lights on at 7:00 h). The Massachusetts General Hospital Subcommittee on Research Animal Care approved all experiments described.

Study design. Age- and weight-matched DIO rats (650–700 g) were allocated to one of four groups: sham-operated animals (SO; n = 5), rats implanted with a 1-cm ELS device (ELS-1; n = 5), 4-cm ELS (ELS-4; n = 5), or 10-cm ELS (ELS-10; n = 5). The ELS-1 controls for the effect of the ELS-anchoring crown. It excludes only the duodenal bulb and does not interfere with the immediate mixing of food with biliary and pancreatic secretions as they enter the duodenum. The ELS-4 extends through 50–70% of the duodenum, and the ELS-10 extends through the duodenum and ~3 cm of the jejunum. After surgical implantation of the ELS or a control sham operation, animals were fed a liquid diet that was advanced gradually and replaced by the solid HFD as tolerated but no later than postoperative day 7.

ELS implantation. Surgical implantation of the ELS was performed as previously described (1). Rats were fasted overnight and maintained on inhaled anesthesia throughout the surgical procedure. After a midline laparotomy the proximal intestine was released from the ligament of Trietz, and two enterotomies were performed, one immediately distal to the pylorus (duodenotomy) and the other 1, 4, or 10 cm below the duodenotomy. An introducing catheter was threaded through the distal enterotomy and advanced in a retrograde fashion so as to exit from the duodenotomy. The distal end of the ELS device was then sutured to the tip of the introducing catheter, and the ELS was pulled into the intestine antegrade by withdrawal of the catheter. The duodenotomy was repaired, the crown of the ELS anchored to a surgical pledge embedded between skin and abdominal musculature, and the distal enterotomy and laparotomy repaired. Placement and retention of the ELS device was determined by fluoroscopic imaging of the radio-opaque markers present at the proximal end of the device. The sham operation consisted of laparotomy, release of the proximal intestine from the ligament of Trietz, duodenotomy, and distal enterotomy, each repaired without alteration of the preoperative anatomy.

Body weight and food intake. Body weight (BW) was measured weekly until postoperative week (POW) 8, with change in BW expressed as percentage of preoperative weight. FI was measured weekly from POW 2–8. Cumulative energy intake (kcal) was calculated by multiplying the weight (g) of food consumed by the caloric density of the HFD (5.24 kcal/g).

Nutrient absorption. Nutrient absorption was estimated by determining the difference between calories consumed and excreted in the stool. Eight weeks after surgery, daily FI and fecal output were measured over 5 days, and stool calorie content was determined by direct calorimetry (Parr Instruments, Moline, IL). Percent calorie
absorption was calculated as daily energy intake (kcal) = daily fecal energy output (kcal)/daily energy intake (kcal).

Energy balance measurements. EE was measured by indirect calorimetry (Labmaster, TSE Systems, Bad Homburg, Germany) over 96 h during POW 10. Rats were allowed to acclimate to the metabolic cages for 24 h, after which data were collected for 72 h. Respiratory quotient (RQ), heat production, total EE, and resting EE were calculated from the raw data. Resting EE was determined from the VO2 during periods of inactivity and no FI during 5-h periods within the light (12 PM-17 PM) and dark (20 PM-1 AM) phases of the daily cycle. Spontaneous locomotor activity in three dimensions was measured as total counts over a period of 72 h using infrared light-beam frames surrounding the home cage.

Meal pattern analysis. Ten weeks after surgery, meal patterns were determined over 72 h at the time of indirect calorimetry. Discrete meals were defined as periods of FI ≥0.05 g separated by ≥5 min from the previous meal. The size of an individual meal was defined as the weight of food ingested, and meal duration was defined as the time between initiation and termination of that meal. The intermeal interval was defined as the time between the end of one meal and initiation of the next.

Dietary manipulation. A group of SO rats initially age- and weight-matched to the ELS-10 group was caloric restricted to match the BW of ELS-10 implanted animals (weight-matched sham; WMS). To study the contribution of ELS-10-induced caloric restriction to weight loss, a separate group of SO rats initially age- and weight-matched to the ELS-10 group was fed the same amount of food consumed by the ELS-10 rats the previous day for a period of 7 wk (pair-fed sham; PFS). All rats in the WMS and PFS groups underwent the same sham surgical procedure described earlier in MATERIALS AND METHODS.

Glucose homeostasis. Before assessment of glucose homeostasis, rats were acclimated by saline gavage on at least two previous occasions. Oral glucose tolerance tests (OGTT) were performed after a 12- to 14-h overnight fast between POW 10 and 12. After oral administration of 1 g/kg glucose (50% dextrose), glucose levels were measured in duplicate from blood obtained by tail stick using a hand-held glucometer (Abbot Animal Health, North Chicago, IL) at baseline and at 20, 30, 60, 90, and 120 min. Tail blood was collected with EDTA-coated tubes (Kent Scientific, Torrington, CT) containing a dipeptidyl peptidase IV inhibitor (Millipore, Billerica, MA). After centrifugation, recovered plasma was stored at −80°C for further analysis. Insulin concentrations were determined in duplicate from plasma samples by an enzyme-linked immunosorbent assay (ELISA) (Alpco Diagnostics, Salem, NH) at baseline, 30, 60, and 120 min after glucose infusion. Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) was calculated from fasting glucose and insulin levels, as previously described (12). Glucose-stimulated concentrations of total GLP-1 were determined by ELISA (Wako Chemicals, Richmond, VA) from plasma samples obtained during the OGTT 20 min after glucose administration.

Statistical analysis. Data are presented as means ± SE. Data were analyzed using repeated measures ANOVA or the Kruskal-Wallis H test, as appropriate. Oral glucose tolerance and glucose-stimulated insulin secretion (GSIS) were analyzed by the area-under-the-curve (AUC) analysis using the trapezoidal rule (43). Statistical analysis was performed using SPSS 13 for Windows (IBM, Armonk, NY). Graphs were made using Prism (GraphPad, San Diego, CA).

RESULTS

ELS-10 implantation increases energy expenditure. We previously found that rats implanted with the ELS-10 had reduced body weight and FI compared with SO animals, with no differences in net calorie absorption (1). To determine the contribution of reduced feeding after implantation to overall weight loss, we conducted a pair-feeding experiment. Weight loss in the pair-fed animals was 65% of the weight loss induced by implantation of the ELS-10 (final weights: PFS, 755 ± 14 g vs. ELS-10, 733 ± 11 g, P < 0.05, Fig. 2A), suggesting that implantation of the 10-cm ELS device is associated with an increase in total EE, as the increased weight loss cannot be attributed to differences in calorie absorption. To assess directly whether ELS-10 implantation is associated with increased EE, we measured VO2 and VCO2 by indirect calorimetry in ELS-10-implanted and SO rats. As shown in Fig. 2B, ELS-10-implanted rats exhibited higher VO2, indicative of increased EE. Total EE was increased on average by 13% in ELS-10-treated rats compared with SO controls (ELS-10, 708 ± 12 vs. SO, 625 ± 6 ml·h−1·kg−0.75, P < 0.001; Fig. 2C). In addition, we observed a significant increase in resting EE in ELS-10 rats (ELS-10, 566 ± 5 vs. SO, 517 ± 15 ml·h−1·kg−0.75, P < 0.001; Fig. 2D). Increased total EE was not a consequence of increased activity, as spontaneous locomotor activity was similar between the groups [ELS-10, 154±34 ± 3.826 vs. SO, 159±727 ± 9.001 beam break counts; not significant (NS); Fig. 2E].

CONTRIBUTION OF ELS-10-INDUCED WEIGHT LOSS TO GLUCOSE TOLERANCE IMPROVEMENT. To determine whether duodenal exclusion by ELS-10 implantation improves glucose homeostasis independently of the associated weight loss, we studied key parameters of glucose control in a group of SO rats that were matched by dietary restriction to the final weight of the ELS-10 rats (WMS). Compared with WMS animals, ELS-10 rats exhibited enhanced improvement in fasting glycemia (ELS-10, 113 ± 6 vs. WMS, 138 ± 1.2; SO, 172 ± 8 mg/dl; P < 0.001; Fig. 3A), HOMA-IR (ELS-10, 5 ± 0.05 vs. WMS, 5.4 ± 0.05; SO, 5.8 ± 0.06, P < 0.05; Fig. 3B), and oral glucose tolerance (ELS-10, 18,372 ± 750 vs. WMS, 21,856 ± 502; SO, 23,845 ± 960 AUC units; P < 0.001; Fig. 3C). In contrast, AUC measurements for glucose-stimulated insulin secretion were similarly reduced in WMS and ELS-10 compared with SO rats (Fig. 3D). These results indicate that ELS implantation induces improvement in fasting glycemia, glucose tolerance, and insulin sensitivity above and beyond that induced by a similar degree of weight loss alone.

ELS-10 rats also exhibited a significantly greater increase in GLP-1 secretion 20 min after an oral glucose challenge than either SO or WMS rats (ELS-10, 7.2 ± 0.6 vs. WMS, 3.8 ± 0.4; SO, 4.6 ± 0.2 ng/ml; P < 0.001; Fig. 3E). Thus, unlike diet-induced weight loss, duodenal exclusion induces glucose-stimulated GLP-1 secretion.

Effect of ELS barrier length on energy balance. To determine the extent of duodenal exclusion required for the observed effects of ELS implantation on energy balance, we implanted rats with ELS devices of varying lengths. One week after surgery, all groups exhibited an average loss of 14–16% of their preoperative BW due primarily to the postoperative feeding protocol, with variable recovery of the acute weight loss. Eight weeks after surgery, complete duodenal exclusion using the ELS-10 induced the greatest sustained weight loss, while partial duodenal exclusion with either ELS-1 or ELS-4 induced modest weight loss. On average, ELS-10-, ELS-4-, and ELS-1-treated rats weighed 14%, 9%, and 8% less than SO rats, respectively (ELS-10, 733 ± 11 g vs. SO, 851 ± 26 g; ELS-4, 780 ± 15 g; ELS-1, 772 ± 14 g; P < 0.05; Fig. 4A). Importantly, ELS implantation was not accompanied by calorie malabsorption, as calculated by the percentage of calories
absorbed (SO, 90.2 ± 0.3%; ELS-1, 90 ± 0.2%; ELS-4, 89.8 ± 0.4%; ELS-10, 88.3 ± 0.5%; NS; Fig. 4B).

**Effect of ELS barrier length on food intake and meal patterns.** Ad libitum cumulative FI was similarly reduced in rats implanted with 1-, 4-, and 10-cm ELS devices compared with SO rats (ELS-1, 47,563 ± 227; ELS-4, 4,660 ± 188; ELS-10, 4,589 ± 109 vs. SO, 5,302 ± 150 kcal, *P < 0.001; Fig. 4C). In each case, meal pattern analysis revealed similar 20% reductions in meal size compared with SO rats (SO, 2.4 ± 0.1 vs. ELS-1, 1.9 ± 0.3; ELS-4, 1.9 ± 0.2; ELS-10, 1.8 ± 0.1 g; *P < 0.001; Fig. 4D). Notably, decreased meal size was not accompanied by a compensatory increase in the meal numbers (Fig. 4E). In contrast to ELS-10 rats, rats implanted with ELS-1 or ELS-4 exhibited no increase in total EE (Fig. 4F). Resting EE and locomotor activity after ELS-1 or ELS-4 implantation were no different from those of SO rats (data not shown). Together, these data indicate that partial duodenal exclusion can cause weight loss by inducing a reduction in FI, but exclusion of the full duodenum is required to increase EE, which leads to substantially greater overall weight loss.

**Effect of ELS barrier length on glucose homeostasis.** Using a similar approach, we examined the effect of ELS length on several parameters of glucose homeostasis. Similar reductions in fasting blood glucose were seen after ELS-10, ELS-4, and ELS-1 implantation (ELS-10, 113 ± 6; ELS-4, 116 ± 5; ELS-1, 127 ± 8 vs. SO, 172 ± 8 mg/dl; *P < 0.001; Fig. 5A). Since all three groups lost weight and exhibited similar reductions in FI, these observations suggest that improvement in fasting glucose is related to one or both of these responses. In contrast, fasting insulin concentrations were significantly decreased only in ELS-10-treated rats (ELS-10, 1.59 ± 0.02 vs. SO, 1.72 ± 0.03 ng/ml, *P < 0.001, Fig. 5B), whereas rats implanted with shorter ELS devices exhibited a more modest trend toward decreased fasting insulin concentrations that was not statistically different from that of the SO animals (ELS-1, 1.65 ± 0.02; ELS-4, 1.64 ± 0.03; SO, 1.72 ± 0.03, NS; Fig. 5B).

We similarly observed an ELS length-dependent effect on glucose tolerance and insulin sensitivity. OGTT revealed that ELS-10 rats had the greatest improvement in oral glucose tolerance, with a significantly improved glucose excursion curve compared with rats implanted with a shorter ELS device or SO animals (ELS-10, 18,372 ± 750 vs. SO, 27,753 ± 880; ELS-1, 24,770 ± 1,080; ELS-4, 22,749 ± 1,080 AUC units; *P < 0.001; Fig. 5C, inset). In addition, while ELS-10 animals displayed a significant reduction in GSIS, GSIS after ELS-1 or ELS-4 implantation was not statistically different from that of SO controls (ELS-1, 1.64 ± 0.03; ELS-4, 1.64 ± 0.03; SO, 1.72 ± 0.03, NS; Fig. 5D).

We further examined the impact of ELS implantation on glucose homeostasis by examining the effects of ELS-10 implantation on markers of insulin sensitivity. HOMA-IR was significantly reduced in ELS-10 rats compared with SO rats (ELS-10, 5.0 ± 0.05 vs. SO, 7.5 ± 0.1, *P < 0.001; Fig. 5E). In contrast, ELS-1 or ELS-4 rats did not exhibit a significant reduction in HOMA-IR compared with SO rats (ELS-1, 7.5 ± 0.1; ELS-4, 7.5 ± 0.1; SO, 7.5 ± 0.1, NS; Fig. 5E). These findings suggest that complete duodenal exclusion may be necessary to achieve maximal improvement in insulin sensitivity.
DISCUSSION

In this study, we used implantation of the ELS device to isolate and examine the effects of a specific component of RYGB (duodenal exclusion) on energy balance and glucose homeostasis in DIO rats. We observed that complete duodenal exclusion with a 10-cm ELS device increases total and resting EE and leads to greater weight loss than that induced by caloric restriction alone. Rats pair fed to match the caloric intake of the ELS-10 rats (PFS) exhibited only 65% of the weight loss observed in rats implanted with the ELS-10, demonstrating a substantial contribution of increased EE in the ELS-10-induced weight loss. Similarly, complete duodenal exclusion induces a weight loss-independent improvement in glucose homeostasis and glucose-stimulated GLP-1 secretion. Thus isolated duodenal exclusion appears to mimic the distinctive physiological effects of RYGB on both EE and glucose homeostasis (39).

This study also expands our understanding of the contribution of duodenal nutrient exclusion to improved glucose homeostasis. Previously, we had shown that implantation of a 10-cm ELS improves several parameters of glucose homeostasis including insulin sensitivity, fasting glycemia, and glucose tolerance in DIO rats (1). The present study demonstrates that duodenal exclusion improves oral glucose tolerance and insulin sensitivity to a greater extent than that due to weight loss alone. Thus, similar to RYGB, isolated duodenal exclusion improves glucose homeostasis by both weight loss-dependent and independent mechanisms.

The weight loss-independent effects of RYGB on glycemic control have been shown to be associated with elevated postprandial circulating levels of GLP-1. Given its well-known incretin effects, GLP-1 has been postulated as a key mediator of the antidiabetic effects of RYGB (2, 8, 11, 17, 18). GLP-1 concentrations after oral glucose administration were significantly elevated in ELS-10-implanted rats, indicating a direct effect of duodenal exclusion on GLP-1 secretion, either be-
cause of the loss of normal signaling by nutrients, biliary, or pancreatic secretions in this region or by the signaling changes in response to the accelerated delivery of ingested nutrients, bile, and pancreatic secretions to the mid- or distal jejunum. It is interesting to note that despite the elevated postprandial GLP-1 levels, plasma insulin concentrations were not higher in ELS-10 versus SO rats. This can be explained by the improvement in insulin sensitivity in these previously insulin-resistant animals (1).

Because complete duodenal exclusion with a 10-cm ELS had notable metabolic effects, we were interested in determining the length of the excluded duodenal segment required for these effects. Although ELS-1 and ELS-4 rats exhibited reduced body weight, the extent of weight loss was less than that induced by the ELS-10. Cumulative FI was lower in each ELS-treated group than in SO animals. The ELS effect on FI was mediated primarily through increased satiation, as demonstrated by similar decreases in meal size in all ELS-treated rats. Satiation signals can arise in response to the mechanical distention of the stomach and in response to gut-derived hormones secreted in response to nutrients within the intestine. The ELS effect on FI is similar to the effect of RYGB in rats, which exhibit reduced cumulative FI (13, 14, 39) and increased satiation, with little or no effect on satiety (44). We previously observed that implantation of a 10-cm ELS slowed gastric emptying, which could increase intragastric pressure, and therefore promote satiation (1). Based on these observations and the known physiology of FI regulation, it is likely that the presence of the ELS-anchoring crown immediately distal to the pylorus slows gastric emptying and promotes satiation by marginally increasing intragastric pressure or wall tension. Thus the primary mechanism of FI reduction after ELS implantation may be induced by the presence of the device crown in the first portion of the duodenum.

Similar to the ELS effect on FI, improvement in fasting glucose was observed in all ELS-treated rats, independent of device length, suggesting that the weight loss, rather than duodenal exclusion itself, likely mediates this effect. Taken together, these results suggest that the observed changes in FI result primarily from the effects of the device on gastric motility, and that the decreased fasting glucose is primarily a consequence of the associated weight loss.

There are several potential mechanisms that could explain the significant effects of the 10-cm ELS to increase EE and generate weight-independent improvements in glycemic control. First, implantation of this device creates a physical barrier between ingested nutrients and the proximal intestinal mucosa, while biliopancreatic secretions remain external to the device. Evidence suggests that nutrient exclusion from the duodenum triggers the anti-diabetic effects of RYGB by altering neuroen-
Endoluminal sleeve increases energy expenditure

Endocrine intestinal signals generated in response to duodenal-nutrient interactions (30, 32). It is important to note, however, that this hypothesis has been challenged by the glycemic control obtained after surgical procedures such as ileal interposition and sleeve gastrectomy, in which nutrient transit through the duodenum is maintained and yet glucose homeostasis is significantly improved (21, 37, 41). Together these observations suggest that multiple GI mechanisms contribute to the regulation of glucose homeostasis. Second, the ELS device causes ingested nutrients to be diverted into the midjejunum. Partially digested nutrients are sufficient to trigger a powerful enteroeendocrine response characterized by increased secretion of several gut-derived hormones contributing to metabolic regulation (e.g., GLP-1, PYY) (13, 14, 38). Third, the ELS device prevents interaction between ingested nutrients and biliopancreatic secretions, potentially enhancing the interaction of these secretions with the intestinal mucosa. These secretions likely pass at relatively high concentrations to the mid and/or distal jejunum potentially causing the equivalent of a biliary and pancreatic diversion. Previous studies have shown that rerouting of biliopancreatic secretions within the small intestine modifies plasma levels of bile acids after RYGB in obese human patients, stimulating weight loss and improving glucose homeostasis (27). It is possible that locally increased concentrations of bile acids might contribute to enhanced weight loss and/or improved glucose homeostasis after RYGB or ELS through their ability to stimulate thermogenesis and gut hormone secretions, respectively (16, 23).

We do not yet know whether the 10-cm ELS device produces the maximum effect on these signaling mechanisms or whether they could be further enhanced by a device that extends more distally into the jejunum. The greater effects of biliopancreatic diversion on EE and glucose homeostasis compared with standard RYGB suggest that this indeed may be the case (24). The failure of shorter devices to increase EE or to induce optimal improvement in glucose homeostasis also suggests a threshold effect for the metabolic effects of duodenal exclusion.

While the ELS device mimics much of the intestinal component of RYGB, it is important to note differences between the two procedures. Implantation of the ELS device does not generate an equivalent to the Roux limb, the intestinal segment in RYGB that is exposed to ingested food in the absence of biliopancreatic secretions. Anatomically the ELS procedure more closely mimics an omega-loop mini-gastric bypass (6). In addition, even though food is not interacting with the mucosa of the duodenum with the ELS, there may still be mechanical stimulation of the duodenum from the passage of food through the device lumen, an effect that does not occur in the completely bypassed limb after RYGB.


Perspectives and Significance

We have shown that isolated duodenal exclusion created by ELS implantation mimics several of the key physiological effects of RYGB, including increased EE and weight loss-independent improvements in glycemic control in DIO rats. While these observations do not exclude the possibility of distal GI signals, they strongly implicate signals arising from the duodenum or proximal jejunum as important afferent regulators of energy balance and glucose and insulin signaling. Whether these effects are due to nutrient exclusion from the duodenum, accelerated delivery of nutrients to the distal small intestine, or the presence of unmixed biliopancreatic secretions in the duodenum needs to be further defined. Nonetheless, these observations suggest that the manipulation of these signals by ELS implantation itself will provide important new approaches to treating obesity and T2DM. Moreover, they provide additional evidence that disruption of the normal neuroendocrine responses to nutrient signals contribute to the generation of obesity and T2DM in the first place. Identification of the signals mediating these effects should facilitate the development of new, less invasive therapies that mimic the dramatic beneficial effects of RYGB and related GIWLS on obesity, diabetes, and associated metabolic disorders.

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DISCLOSURES

L.M.K. is a member of the Scientific Advisory Board of GI Dynamics.

AUTHOR CONTRIBUTIONS


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