Duodenal-jejunal bypass protects GK rats from β-cell loss and aggravation of hyperglycemia and increases enteroendocrine cells coexpressing GIP and GLP-1

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Dramatic improvement of type 2 diabetes is commonly observed after bariatric surgery. However, the mechanisms behind the alterations in glycemic control, β-cell mass, islet morphology, and changes in enteroendocrine cell populations in nonobese diabetic Goto-Kakizaki (GK) rats and nondiabetic control Wistar rats. We performed DJB or sham surgery in GK and Wistar rats. Blood glucose levels and glucose homeostasis are still elusive. We examined the effect of duodenal-jejunal bypass (DJB), which maintains the gastric volume intact while bypassing the entire duodenum and the proximal jejunum, on glycemic control, β-cell mass, islet morphology, and changes in enteroendocrine cell populations in nonobese diabetic Goto-Kakizaki (GK) rats and nondiabetic control Wistar rats. We performed DJB or sham surgery in GK and Wistar rats. Blood glucose levels and glucose tolerance were monitored, and the plasma insulin, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide; K cells; L cells; pancreatic and duodenal homoeobox 1; contained co-first authors.

THE EPIDEMIC OF TYPE 2 DIABETES is a top-ranking current health problem around the world and is increasing at an alarming rate (50). Its health consequences significantly decrease both the quantity and quality of life and the cost related to the disease is tremendous (14, 50). Since type 2 diabetes is characterized by a relentless decline of β-cell function (1a), a considerable portion of patients require insulin therapy during the course of the disease (49). Insulin injections are inconvenient and uncomfortable (16), and it is difficult to achieve nearly normal glucose levels by this method such that diabetic complications are common (1, 15). Unfortunately, at this time, there is no means to readily cure type 2 diabetes. However, there is a growing body of evidence for remission of type 2 diabetes. Intensive glycemic control using insulin in patients with newly diagnosed type 2 diabetes was reported to induce prolonged remission in a substantial portion of the patients (48). More obvious and dramatic evidence has been obtained with bariatric surgery conducted in obese patients with type 2 diabetes. A meta-analysis showed that diabetes was completely resolved in 76.8% of patients and resolved or improved in 85.4% of the patients following bariatric surgery (6). Interestingly, the rate of diabetes remission depends on the type of surgery. Whereas gastric banding induced diabetes remission in 47.9% of patients, gastric bypass and biliopancreatic diversion induced remission in 83.7 and 98.9% of patients, respectively (6). The diabetes remission after gastric bypass can be observed within days after operation even before significant weight loss occurs, which contrasts with the results of restrictive surgery, where improvement of glycemic control takes several months (10, 29, 34). Therefore, the mechanisms of rapid improvement of glucose homeostasis after gastric bypass and biliopancreatic diversion are considered to be independent of weight loss or calorie restriction (39, 47), although long-term improvement of glycemic control is dependent on the amount of weight loss (10). Collectively, anti-diabetes mechanisms of gastric bypass may include calorie restriction and changes in hormones from stomach, foregut, and hindgut (39, 47), where none of these components necessarily preclude the others. Among them, the contribution of duodenum and upper jejunum was demonstrated by duodenal-jejunal bypass (DJB) procedures, which preserve the gastric volume intact while bypassing the entire duodenum and the proximal jejunum (32, 33), and endoluminal sleeve procedures, which use a nutrient-impermeable, flexible tube designed for endoluminal implantation to exclude the proximal intestine from alimentary flow (1b, 31). In addition, when a standard liquid meal was given via either oral or gastroduodenal route in a patient who underwent Roux-en Y gastric bypass (a kind of bariatric surgery restricting gastric volume by dividing the stomach into small proximal pouches and separate distal remnants and reconstructing the small bowel with Y-shaped configuration consisting of biliopancre-
atic limb draining digestive juice and Roux limb draining the nutrients from proximal gastric pouch), the oral route, which bypassed the duodenum and upper jejunum, produced increased glucagon-like peptide-1 (GLP-1) secretion, increased insulin secretion, and improved glucose tolerance compared with the gastroduodenal route (9). Collectively, these findings suggest that the intestinal rearrangement is directly responsible for the benefits on glucose homeostasis.

Although the exact mechanism of the improved glucose homeostasis after bypass procedure is largely elusive, an alteration in the enteroendocrine system consisting of the entero-insular axis or incretins is presently considered the most plausible explanation (26, 39, 47). In this regard, enteroendocrine cell populations might be altered following bypass surgery, since anatomic and physiological plasticity of gastrointestinal mucosa is known to take place in several conditions, including bariatric surgery (21, 23, 26, 37, 42). However, to our knowledge, there are not yet any reports examining the enteroendocrine cell population after bariatric surgery. Therefore, we examined the effect of DJB on long-term glycemic control, plasma incretin levels, β-cell mass, islet fibrosis, and changes in enteroendocrine cell populations in the Goto-Kakizaki (GK) rat, a well-known animal model for nonobese type 2 diabetes derived from a Wistar rat colony.

**Fig. 1. Blood glucose (A) and increase in body weight from the baseline (B) in Goto-Kakizaki (GK) rats after surgery.** Blood glucose and body weight were measured under fed conditions at 0900. A, inset, shows mean blood glucose levels during early (0–90 days) and late postoperative periods (91–365 days). Body weight was normalized by its baseline value. •Sham group animals; ◆duodenal-jejunal bypass (DJB) group. Data are shown as means ± SE (n = 4–6 for each group). *P < 0.05 by t-test.

### MATERIALS AND METHODS

**Animals.** Male 9-wk-old GK rats were purchased from Taconic (Hudson, NY), and male 6-wk-old Wistar rats were purchased from the University of British Columbia Animal Care Centre (Vancouver, BC, Canada). All animals were housed in individual cages under constant ambient temperature and humidity in a 12:12-h light-dark cycle and fed a standard rat chow (LabDiet 5012; PMI Nutrition International, Brentwood, MO) throughout the study. All studies were approved by the University of British Columbia Animal Care Committee and carried out in accordance with the Canadian Council on Animal Care guidelines.

**Surgical interventions and monitoring.** After a 1-wk acclimation period, the rats undergoing either DJB (n = 6 for GK and n = 5 for Wistar) or the sham (n = 6 for GK and n = 5 for Wistar) operation were fasted overnight and anesthetized with 2% isoflurane and air/oxygen. The details of the procedure are as illustrated and described previously (32). Briefly, the gastric volume was left intact, whereas the entire duodenum and 10 cm of the proximal jejunum were bypassed. The stomach was separated from the duodenum at the point just below the pylorus. The gastrojejunal anastomosis was made between the pylorus and 10 cm distal to the Treitz ligament by using a 5/0 absorbable suture. The continuity of biliopancreatic secretions was reconstructed by anastomosing the biliopancreatic limb to the alimentary limb of the small bowel 15 cm distal to the gastrojejunal anastomosis in a Roux-en-Y fashion. For the sham operation, transections and reanastomosis of the gastrointestinal tract were per-
formed at the corresponding sites where enterotomies were performed for the DJB, thereby maintaining the physiological conduit of food through the bowel. Weight, food intake, and nonfasting blood glucose were tracked for 1 yr after surgery for GK rats and 12 wk for Wistar rats. During the followup, one rat from the GK-DJB group, one rat from GK sham group, and one rat from Wistar sham group reached a humane end point. Fed-state glucose levels were measured at 0900 from tail vein blood samples with a hand-held glucometer (One Touch Ultra; Life Scan, Burnaby, BC, Canada). Plasma samples from tail vein (100 μl) were also obtained at some time points of glucose measurement and stored at −20°C in a freezer until assays for insulin, GLP-1, and glucose-dependent insulinotropic polypeptide (GIP).

Oral glucose tolerance test and intraperitoneal glucose tolerance test. After overnight fasting, either an oral glucose tolerance test (OGTT) or intraperitoneal glucose tolerance test (IPGTT) was performed using 40% glucose solution (1 g/kg). Glucose levels from tail vein blood samples were measured using a glucometer (One Touch Ultra) at 0, 10, 20, 30, 60, 120, and 180 min after glucose administration. At the same time points, blood (0.25 ml) was collected with heparinized capillary tubes from the tail vein, transferred to micro-tubes, and centrifuged before plasma samples were stored at −20°C in a freezer until assays for insulin, GLP-1, and glucose-dependent insulinotropic polypeptide (GIP).

Mixed-meal tolerance test. A mixed-meal tolerance test was performed following an overnight fast at 38 wk after surgery. A mixed meal (11.7 g/dl carbohydrate, 3.7 g/dl protein, 1.8 g/dl fat, Shapers; Pharmaprix, Toronto, ON, Canada) was administered by oral gavage at a dose of 6 ml/kg body wt. Glucose levels from tail vein blood samples were measured using a glucometer (One Touch Ultra) at 0, 10, 20, 30, 60, 120, and 180 min after meal administration. At the same time points, plasma samples were collected and stored at −20°C until hormone assays.

Insulin tolerance test. After an overnight fast, a dose of 0.4 IU/kg human regular insulin (Novolin; Novo Nordisk, Toronto, ON, Canada) was injected intraperitoneally in conscious rats. Blood glucose levels were measured by a glucometer (One Touch Ultra; Life Scan) at baseline and 10, 20, 30, 60, and 120 min after insulin injection.

Hormone assays. Plasma total GIP levels were assayed by ELISA (Millipore, Billerica, MA). Plasma insulin and total GLP-1 levels (GLP-17-36 amide and GLP-17-37) were assayed using a kit from Meso Scale Discovery (Gaithersburg, MD) according to the manufacturer’s instructions.

Immunostainings. Tissues were fixed in 4% paraformaldehyde in PBS overnight at 4°C and then embedded in paraffin blocks. After dewaxing and rehydration, heat-induced epitope retrieval for immunofluorescence was performed in 10 mM citrate buffer (pH 6 containing 0.05% Tween 20) at 95°C for 10 min using an EZ-Retriever Microwave (Biogenex, San Roman, CA). Sections were incubated overnight at 4°C in the following primary antibodies: guinea pig anti-insulin (1:1,000; Millipore), mouse anti-GIP (1:10,000; kindly provided by Dr. Alison Buchan, University of British Columbia, Vancouver, BC, Canada), rabbit anti-GIP (1:8,000; kindly provide by Dr. Linda Morgan, University of Surrey, Guilford, UK), mouse anti-GLP-1 (1:10,000; kindly provided by Dr. David D’Alessio from University of Cincinnati, Cincinnati, OH), guinea pig anti-pancreatic and duodenal homoeobox 1 (PDX1) (1:1,000; kindly provided by Dr. Wright from Vanderbilt University, Nashville, TN), and rabbit antipaired box gene 6 (PAX6; 1:250; Covance, Emeryville, CA). After washes, sections were incubated for 1 h at room temperature in the following secondary antibodies: biotinylated goat anti-guinea pig IgG (1:250; Vector Laboratories, Burlingame, CA), donkey anti-mouse Alexa Fluor 594, donkey anti-rabbit Alexa Fluor 488, goat anti-guinea pig Alexa Fluor 488, donkey anti-rabbit Alexa Fluor 555 and donkey anti-mouse Alexa Fluor 647 (1:1,000; Molecular Probes, Eugene, OR). Color development for insulin was done with freshly prepared diaminobenzidine (Dako), which yields a brown color. Slides were mounted in Vectashield mounting medium with or without 4’,6-diamidino-2-phenylindole (DAPI; Vector Laboratories, Burlingame, CA). Masson’s trichrome staining was done to identify collagen fibers in pancreatic islets according to the manufacturer’s information (Sigma). Imaging for immunofluorescence was performed using either an Axiovert 200 microscope (Carl Zeiss, Toronto, ON, Canada) connected to a digital camera (Retiga 2000R; QImaging, Burnaby, BC, Canada) controlled with Openlab 5.2 software (Improvision,

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For immunohistochemistry for insulin and Masson’s trichrome staining, the glass slides were scanned by a ScanScope scanner (Aperio Technologies, Vista, CA).

**Histomorphometric analysis.** For each pancreas, three sections separated by 200 μm were analyzed. The β-cell area and the degree of fibrosis were objectively quantified by using a preset positive pixel count algorithm available with ScanScope software (Aperio). The β-cell area was expressed as positive brown pixel counts over total pixel counts corresponding to the total pancreas area in one section. The degree of fibrosis in each islet was expressed as positive blue pixel counts over total pixel counts in an islet, which was defined as the region of interest by marking the islet border with the computer-interfaced freehand tool. To measure the density of K cells expressing GIP, L cells expressing GLP-1, or K/L cells coexpressing GIP and GLP-1, we used three longitudinal sections of the proximal 6 cm of duodenum per animal from DJB and sham groups and the proximal 6 cm of jejunum anastomosed to the stomach from the DJB group and corresponding jejunum from sham group. Densities of the K, L, and K/L cells were calculated as the number of GIP-positive cells, GLP-1-positive cells, and GLP-1- and GIP-copositive cells normalized by the number of total villi in a given longitudinal gut section. The length of villi (from the top of a villus to the top of adjacent crypt) was measured from hematoxylin- and eosin-stained slides. The number of PDX1- and PAX6-positive cells was counted and scored as either GIP positive or GLP-1 positive and then normalized per 10,000 DAPI-positive cells.

**Body composition analysis.** Measurements were performed using a Bruker Biospec 70/30 7 Tesla MRI scanner (Bruker Biospin, Ettlingen, Germany). Nuclear magnetic resonance signal from the body was acquired using a quadrature volume RF coil tuned to 300 MHz. The “free” water component corresponding to body fluids (e.g., urine and cerebrospinal fluid) was typically ≈5% of the total signal. The ratio of lean/fat tissue (wt/wt) was calculated as described elsewhere (22).

**Statistical analysis.** Data analysis was performed using Prism 5.0 (GraphPad, San Diego, CA). Data are presented as means ± SE and were analyzed using Student’s t-test and the Mann-Whitney test where appropriate. A P value <0.05 was regarded as statistically significant.

**RESULTS**

**Nonobese diabetic GK rat study.** Following surgeries, we could not find any difference in blood glucose levels in the fed state between groups until day 90. Thereafter, the DJB group showed lower blood glucose levels than the sham group, and this difference became more evident from ~140 days after surgery and persisted until 1 yr after surgery (Fig. 1A). The mean blood glucose levels during the early and late postoperative period (0–90 days vs. 91–365 days) clearly showed that the bypass had a long-term beneficial effect to prevent progressive deterioration of glucose homeostasis (Fig. 1A, inset).

Body weight gain was slightly attenuated only during the early postoperative period in the DJB group compared with the sham group (Fig. 1B). Food intake per body weight was not different between groups (data not shown). In addition, there was no

![Fig. 3](http://ajpendo.physiology.org/)
difference in lean body mass to fat mass ratio between groups at 52 wk after surgery (data not shown).

OGTTs and IPGTTs were done at 1, 3, 5, 10, and 18 wk after surgery. Contrary to the fed state blood glucose data, the AUCs of OGTT and IPGTT were not different between DJB and sham groups (Fig. 2, A and B). However, consistent with the fed state blood glucose levels, the postprandial blood glucose level at 120 min after mixed-meal challenge 38 wk after surgery was significantly lower in the DJB group than the sham group (Fig. 2C). Insulin sensitivity assessed by insulin tolerance test at 43 wk after surgery was comparable between groups (Fig. 2D).

At 1 wk after surgery, there was no significant difference in plasma insulin and GIP levels during the OGTTs, whereas plasma GLP-1 levels were mildly elevated in the DJB group without any obvious peak being shown (Fig. 3, A–C). At 18 wk after surgery, compared with the sham group, plasma insulin levels during OGTT tended to be higher in the DJB group, although they did not reach statistical significance (P values are in the range of 0.118 to 0.281; Fig. 3D). Interestingly, the plasma GLP-1 and GIP levels during OGTT were significantly higher in the DJB group (Fig. 3, E and F). In the mixed-meal tolerance test, which produced significant differences in postprandial glucose levels (Fig. 2D), plasma insulin and GLP-1 levels were significantly higher in the DJB group than in the sham group (Fig. 3, G and H), whereas there was no difference in plasma GIP levels (Fig. 3I). Consistent with the results of the mixed-meal tolerance test, plasma insulin and GLP-1 levels during the fed state sampled at week 32 were higher in the DJB group compared with the sham group (1,913 ± 288 vs. 641 ± 229 pg/ml for insulin, P = 0.0064, and 31 ± 1 vs. 22 ± 3 pg/ml for GLP-1, P = 0.015, respectively).

Insulin staining in pancreas of GK rats looked irregular with a starfish-like appearance, a well-known characteristic of these animals (20). This irregularity was more prominent in the sham group than in the DJB group (Fig. 4A, top). Masson’s trichrome staining revealed more extensive intraislet fibrosis in the sham group compared with the DJB group (Fig. 4A, bottom). Quantitative planimetry analyses revealed unequivocal differences; the DJB animals had higher β-cell area and lower intraislet fibrosis than sham animals (Fig. 4, B and C).

There was no gross difference in intestinal mucosal appearance and the length of villi in the bypassed duodenum and the jejunum attached to the stomach compared with the corresponding normal duodenum and jejunum (Fig. 5, A–E). To examine whether there were any changes in selected gut endocrine cell populations, we calculated the number of endocrine cells expressing GIP and/or GLP-1 normalized by the number of villi (representative images are shown in Fig. 6A). The cells expressing only GIP (K cells) tended to decrease in the bypassed duodenum compared with the duodenum with intact passage of intraluminal nutrients (Fig. 6B). Interestingly, whereas there was no change in the number of the cells expressing only GLP-1 (L cells) in the bypassed duodenum, the population of cells coexpressing GIP and GLP-1 (K/L cells) in this region appeared to increase relative to the con-
There was a significant increase in the K/L cell number at week 9 in diabetes derived from a Wistar rat colony, is characterized by increased insulin secretion was associated with increased GLP-1 secretion. We also observed increased K/L cell numbers in the jejunum anastomosed to the stomach in GK rats. Collectively, these results provide potential mechanisms explaining the long-term beneficial effects of DJB or foregut exclusion on glucose homeostasis.

One of the most obvious findings in our study was preserved β-cell mass in conjunction with decreased islet fibrosis in DJB-GK rats. Since ileal transposition is also reported to reduce islet fibrosis in GK rats, gut-derived factors might have played an important role in attenuating islet fibrosis in DJB surgery. This β-cell protective effect might be crucial in the long-term remission of type 2 diabetes after gastric bypass surgery in humans. Recently, it was reported that treatment with exenatide, a GLP-1 analog, improved β-cell function assessed by C-peptide secretion up to 2.5-fold after 1 yr of treatment compared with insulin treatment. Given that type 2 diabetes is characterized by a relentless decline in β-cell function, these results, including ours, imply that the anatomic rearrangement of gut to augment GLP-1 secretion might preserve pancreatic β-cell mass and/or function.

Contrary to previous findings, we did not observe an immediate beneficial effect of DJB on either oral glucose tolerance or fed-state glucose levels in GK rats. In our study, the fed-state glucose levels were similar between DJB and sham groups during the early postoperative period. In addition, OGTTs and IPGTTs done at 1, 3, 5, 10, and 18 wk after surgery were comparable between groups. Since the onset of hyperglycemia is known to vary among different colonies of GK rats, the early effect of DJB might be dependent on the degree of islet fibrosis at the time of surgery. Indeed, one colony of GK rats (the Paris colony) was reported to have markedly decreased pancreatic and insulin content (<40% of control) as early as the fetal stage. In humans, the probability of diabetes remission following bariatric surgery is reduced by a longer duration of diabetes, poor preoperative glycemic control, and preoperative insulin use. Suggesting that less deterioration in β-cell mass or function at the time of surgery may maximize the effect of the surgery-induced permutation of gut peptides that enhance β-cell function.

Unlike the early postoperative period, the DJB group showed significantly lower postprandial glucose levels than the sham group in GK rats from 90 days after surgery (especially from ~140 days after surgery). Consistent with this finding, the DJB group showed significantly lower blood glucose levels after a mixed-meal challenge than the sham group. During the mixed-meal tolerance test, the DJB group had higher plasma insulin levels and higher plasma GLP-1 levels. However, plasma GIP levels were similar between groups. In addition, the plasma levels of insulin and GLP-1 at fed state during the late postoperative period were higher in the DJB group compared with the sham group. When a GLP-1 receptor antagonist, exendin (9–39), was given to DJB-GK rats, the beneficial effect of DJB on glucose homeostasis was abolished. Therefore, increased postprandial GLP-1 and insulin levels likely contribute to the decreased blood glucose levels in the late postoperative period. In addition, it is conceivable that augmented by a high-carbohydrate diet and attenuated by GLP-1 treatment. In this study, we found that DJB improved postprandial glycemia in GK rats by attenuating β-cell loss and islet fibrosis. Increased insulin secretion was associated with increased GLP-1 secretion. We also observed increased K/L cell numbers in the jejunum anastomosed to the stomach in GK rats.
eliminating the detrimental effect of chronic hyperglycemia on β-cell function played a role in improving long-term glucose control, since glucose toxicity impairs β-cell function (28).

K/L cells are an enteroendocrine cell population producing both GIP and GLP-1 under transcriptional control of PDX1 and PAX6 (12). We found a significant increase in the K/L cell population in the jejunum anastomosed to the stomach of DJB-GK rats, although we could not attribute this to an increase in the frequency of epithelial cells coexpressing PDX1 and PAX6. Anatomic and physiological plasticity of gastrointestinal mucosa takes place in several conditions, including ileal transposition and enterogastrostomy (21, 23, 26, 37, 42). Interestingly, diet and gut microflora have been reported to influence the distribution of enteroendocrine cells in the rodent intestine (4, 36, 46). Thus regional changes in luminal nutrient and/or microflora contents could contribute to the alteration we observed in the distribution of cells expressing GIP and GLP-1. It was presumed that the increased GLP-1 response to nutrients after bypass surgery might be the result of expedited transport of chyme to the distal gut (26, 39, 47). However, our results suggest an additional mechanism of increased GLP-1 response after bypass surgery. Increased GLP-1 expression in the jejunum anastomosed to the stomach might contribute to the increased GLP-1 response in the absence of intraluminal nutrients.

Although total parenteral nutrition is known to cause intestinal atrophy (5), there was no evidence of mucosal atrophy in the bypassed duodenum in GK rats despite this region not being exposed to luminal nutrients. GLP-2, another L cell hormone, is known to stimulate cell proliferation and inhibit apoptosis in the intestinal crypt compartment (11). Since GLP-2 is secreted in parallel with GLP-1 in equal molar quantities (17), increased GLP-2 levels might play a role in preventing apoptosis of bypassed duodenal mucosa. Contrary to the case of total parenteral nutrition, which impairs bile acid secretion (13), bile flow was not interrupted in the bypassed duodenum in the DJB group. Since oral bile acid supplementation is known to protect from intestinal atrophy (2), uninterrupted bile flow might have played an important role in maintaining intact mucosal structure in the bypassed duodenum.

In the immediate postoperative period (1 wk after surgery), the sham-GK group had a blunted GLP-1 response to the oral glucose challenge, whereas the DJB-GK group showed modestly higher plasma GLP-1 levels. However, subsequent challenges with oral glucose and a mixed meal showed a restored
GLP-1 response. Pacheco et al. (25) also reported a modestly decreased post-glucose challenge plasma GLP-1 level at 1 wk after DJB in GK rats, whereas Kindel et al. (19) reported increased post-meal challenge plasma GLP-1 levels at 30 days after DJB in GK rats. Although DJB was designed to assess the contribution of the upper small intestine in the mechanism of improving glucose homeostasis after Roux-en Y gastric bypass (33), GLP-1 was demonstrated to be critical in mediating the glucose-lowering effect of DJB in a study using exendin (9–39), a GLP-1 receptor antagonist (19). Given the increased K/L cell population in the jejunum attached to the stomach, and perhaps also in the bypassed duodenum, our findings indicate that GLP-1 secreted from this proximal region might contribute to improved glucose homeostasis without the need of expedited nutrient delivery to the hindgut.

Plasma insulin levels during OGTTs performed at 18 wk after surgery tended to be higher in the DJB group than those in sham group in GK rats. Although DJB was designed to assess the contribution of the upper small intestine in the mechanism of improving glucose homeostasis after Roux-en Y gastric bypass (33), GLP-1 was demonstrated to be critical in mediating the glucose-lowering effect of DJB in a study using exendin (9–39), a GLP-1 receptor antagonist (19). Given the increased K/L cell population in the jejunum attached to the stomach, and perhaps also in the bypassed duodenum, our findings indicate that GLP-1 secreted from this proximal region might contribute to improved glucose homeostasis without the need of expedited nutrient delivery to the hindgut.

Consistent with the findings of Rubino and Marescaux (33), we also found that DJB impaired glucose tolerance in nondiabetic, nonobese Wistar rats in the early postoperative period. This finding was associated with delayed acute insulin responses in DJB-Wistar rats compared with sham-Wistar rats, although GLP-1 and GIP responses tended to be greater in DJB-Wistar rats (data not shown). Interestingly, it was reported that duodenal exclusion performed as part of gastrectomy for nondiabetic stomach cancer patients impaired glucose tolerance (35). Collectively, these findings suggest that duodenum and proximal jejunum might contribute to glucose homeostasis.
differently in nondiabetic vs. diabetic states through unknown mechanisms.

In this study, DJB prevented long-term aggravation of glucose homeostasis in diabetic GK rats in association with decreased B-cell loss and decreased islet fibrosis, whereas it impaired glucose tolerance in nondiabetic Wistar rats. The differing effects of DJB in normal vs. diabetic rats warrant further investigation to reveal the mechanisms. In addition, our observations of an increased population of gut cells coexpressing GIP and GLP-1 following bypass suggest that increasing the mass of these enteroendocrine cells should be explored as a method of treating diabetes.

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DISCLOSURES

The authors declare that there is no duality of interest associated with this article.

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