Duodenal mucosal resurfacing: proof-of-concept, procedural development, and initial implementation in the clinical setting

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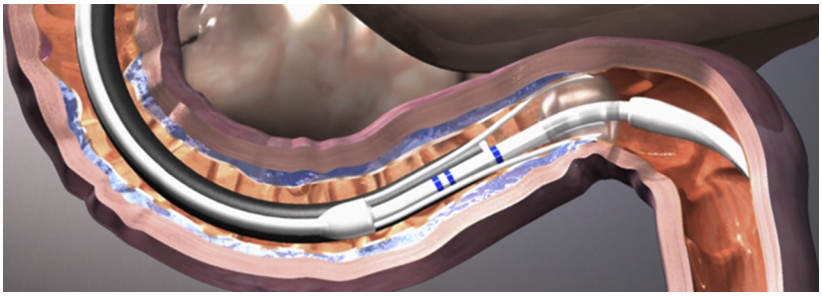
GRAPHICAL ABSTRACT



Background and Aims: We aimed to develop duodenal mucosal resurfacing (DMR), a minimally invasive upper endoscopic hydrothermal ablation procedure, to treat insulin-resistant metabolic diseases.

Methods: We completed a sham-controlled, rodent proof-of-concept study and longitudinal safety study in pigs to demonstrate feasibility to test DMR in humans. Subsequently, the DMR procedure was implemented in an open-label first-in-human (FIH) study of safety and efficacy in patients with type 2 diabetes (T2D).

Results: In rats, duodenal abrasion reduced hyperglycemia by 59 mg/dL on average, compared with no change from baseline in the sham treatment arm ($P < .05$). In pigs, the balloon catheter successfully and safely delivered hydrothermal ablation to the duodenal mucosa and superficial submucosa. Complete mucosal healing was demonstrated by week 6. In the FIH study, hydrothermal ablation was successfully administered with no evidence of perforation, pancreatitis, or hemorrhage. Duodenal biopsy specimens obtained 3 months postprocedure demonstrated full mucosal regrowth. No inflammation was observed, and there was minimal-to-mild collagen banding deposition observed in a proportion of ablation site biopsy specimens with no evidence of fibrotic scarring. Glycemic and hepatic measures improved through 6 months of follow-up.

Conclusions: DMR shows potential as an endoscopic intervention that improves glycemic and hepatic parameters in patients with T2D. Further mechanistic and clinical studies are underway to further explore DMR as a treatment for metabolic disease.

(footnotes appear on last page of article)

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Bariatric surgery (eg, Roux-en-Y gastric bypass) has reversed metabolic disease in patients with type 2 diabetes (T2D) and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis,[1,2] highlighting the important role of the GI tract in regulating systemic metabolism, insulin sensitivity, and inflammation.[3] The mechanisms underlying metabolic improvement are not fully understood, but

bypass of nutrient contact from the duodenum contributes to the metabolic benefits observed.[4,5] Acute reintroduction of nutrients into the bypassed duodenal limb quickly returns patients to their previous dysmetabolic state.[6] Human and animal model studies demonstrated that the duodenal mucosa becomes hyperplastic in response to modern diets, triggering an insulin-resisting signal that may cause metabolic disease.[7,8] Ablation-induced rejuvenation of the duodenal surface could therefore reverse these mucosal changes, mitigating the excessive insulin-resisting signal from the duodenum.[9]

Duodenal mucosal resurfacing (DMR) is a minimally invasive endoscopic procedure using hydrothermal ablation currently in clinical development to treat patients with T2D and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis.[10,11] A first-in-human (FIH), single-arm, single-center study (NCT01927562) evaluated the effect of DMR, and results from the 6-month interim analysis demonstrated that a single DMR procedure was effective in significantly improving hemoglobin A1c in patients with T2D.[9,12] One-year preliminary results from an ongoing 2-year, single-arm, multicenter study (Revita-1; NCT02413567) evaluating safety and feasibility of DMR for the treatment of T2D demonstrated that a single DMR treatment elicited clinically relevant reductions in glycemic (eg, hemoglobin A1c, fasting plasma glucose, and insulin resistance) and hepatic (eg, aminotransferases) parameters ($P < .01$ for all) in patients with T2D on oral glucose–lowering medication.[13] An ongoing randomized, international, multicenter, sham-controlled study (Revita-2; NCT02879383) evaluated DMR efficacy and safety for the treatment of uncontrolled T2D; initial open-label training cases performed under uncontrolled conditions confirmed safe DMR procedure implementation across multiple international centers; and preliminary 1 month results demonstrated DMR lowered plasma glucose.[14] Here we describe concept development in preclinical studies and report procedure implementation from the FIH study.

METHODS

Evolution of DMR technology and procedure

Small animal proof-of-concept study. Two rodent models were used to study the effects of duodenal mucosal abrasion on glucose tolerance: the Goto-Kakizaki (GK) rat model of insulin-resistant diabetes and wild-type (Sprague Dawley rat) nondiabetic controls. The study protocol was reviewed and approved by the Toxikon Institutional Animal Care and Use Committee (Bedford, Mass) and followed the intent of U.S. Food and Drug Aadministration Code of Federal Regulations Title 21 Part 58 (21 CRF Part 58), which details good laboratory practices for nonclinical studies.

Rats (9-week-old; ~300 g) were randomly divided into abrasion (n = 9) and sham (n = 5) procedure groups. Animals were prepped for surgery by standard anesthetic and surgical technique. For mucosal abrasion, a balloon-inflated abrasion device (Fig. 1A) was inserted into the duodenum via laparotomy and gastrostomy. Once positioned in the duodenal bulb, the balloon was inflated with air, and mucosal abrasion was performed via anterograde swipes at successively increasing balloon pressures. For the sham, laparotomy and gastrostomy were performed, and an atraumatic probe was inserted into the duodenum for the same total procedure time without disrupting the mucosa. Animals then underwent oral glucose tolerance testing by oral gavage of 1 g/kg glucose after a 12-hour fast (60 ± 12 hours after abrasion). Tail vein blood was collected at 0, 10, 20, 30, 60, 120, and 180 minutes after oral glucose loading. An unpaired Student *t* test compared preprocedure with postprocedure glucose. In a subset of nonsurvival rats, histologic specimens of the duodenum were obtained, and the mucosal layer was stained with hematoxylin and eosin.

DMR catheter and procedure development

DMR (Fractyl Laboratories, Inc, Lexington, Mass) is a novel tool developed specifically to work in the unique anatomy of the human duodenum—a tortuously curved, distensible organ with a topologically irregular surface and a thin submucosa. The desired effect of DMR is to safely and precisely ablate superficial mucosal tissue in the human duodenum without affecting the deeper muscularis layer below the submucosa (circumferential ablation ~10 cm longitudinal length). The DMR catheter is a single-use hydrothermal balloon catheter that leverages techniques familiar to therapeutic endoscopists to (1) inject saline solution into the submucosa of the duodenum to lift the submucosa, creating a thermal barrier and uniform ablation surface, and (2) ablate the duodenal mucosal surface using heated water recirculating inside the balloon. The ablation hydrothermal profile (Supplementary Fig. 1B, available online at www.giejournal.org) is designed to ensure thermal damage of cells to .6 mm depth (mucosal thickness), sparing cells at 1.0 mm depth (minimum depth of muscularis layer), and stimulate coagulative necrosis of the mucosal tissue without disrupting cell membranes. The DMR procedure requires a high level of endoscopic proficiency. Before treating patients, Fractyl provides therapeutic endoscopists with a full day of training, including a didactic session, bench model simulation, and animal laboratory session. Endoscopists are routinely able to demonstrate competency in all key DMR skills by the end of training.

Initially, 2 separate catheters (6 feet long and made of Pebax [Arkema, Colombes, France]) were developed to perform the functions described above (Fig. 2A). Briefly, the submucosal lift catheter is used to create a longitudinal and circumferential submucosal lifted region in the postpapillary duodenum. Suction selectively draws mucosal tissue into each of the 3 lift ports, needles are

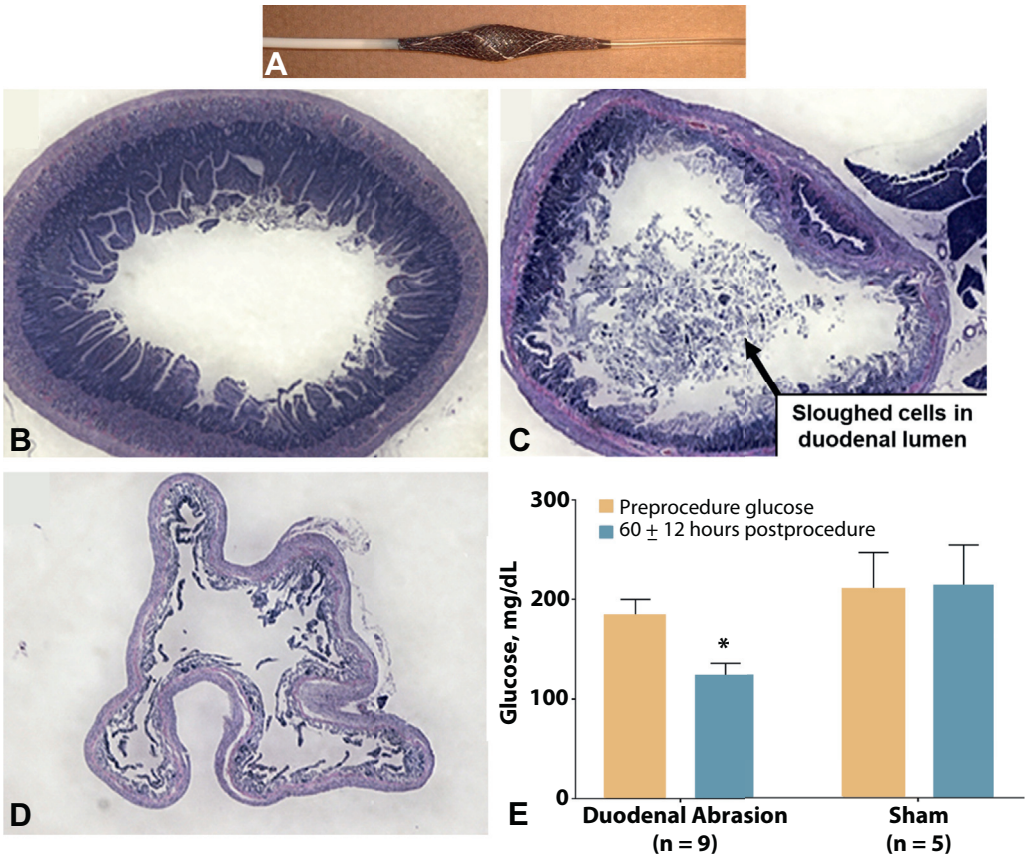

Figure 1. Duodenal mucosal abrasion lowers glycemia in the rodent model. **A,** Balloon-inflated abrasion device. **B,** H&E-stained normal duodenal mucosa. **C,** H&E-stained duodenal mucosal abrasion with sloughed cells in the duodenal lumen. **D,** H&E-stained mucosal abrasion reveals almost no residual mucosa. **E,** Mean (standard error) glucose in Goto-Kakizaki rats preprocedure and 60 ± 12 hours postduodenal abrasion (n = 9) or sham procedure (n = 5). *$P < .05$. Representative histology images were captured with a 4× objective.

advanced into the submucosal space within each port, and 10 mL saline solution is injected through each needle. The catheter is advanced 1 cm between circumferential lifts to achieve at least a 10-cm length of circumferentially lifted duodenum. The submucosal lift catheter is removed, and the mucosal ablation catheter (the balloon is 3 cm in length) performs hydrothermal ablation in the middle of the lifted territory.

Further product development led to a single 6-foot-long catheter made of Pebax (Fig. 2B) that provides both submucosal lift and hydrothermal ablation functions (Supplementary Fig. 1A, available online at www.giejournal.org). Briefly, the DMR catheter is tracked over a guidewire (eg, .035-inch guidewire) and placed in the proximal duodenum distal to the papilla. During the circumferential lift of the mucosa, the tissue is drawn into the needle port and saline solution injected into the submucosal space through the needles. Then, the ablation cycle is started with hot water circulated into the balloon. The balloon is deflated, and the catheter advanced distally to begin treatment of the next segment. The process of expansion, ablation, and repositioning is repeated until the required length (approximately 10 cm) of the duodenum is treated. Animation and endoscopic snapshots of the DMR procedure are presented in Supplementary Figure 2 (available online at www.giejournal.org).

Large animal study. Dual-catheter DMR safety was tested in Yorkshire swine, because of similarities to humans in luminal diameter, mucosal thickness, and endoscopic access. However, unlike humans, Yorkshire swine have a much thinner muscularis propria.[15,16] The study protocol was reviewed and approved by the Pine Acres Rabbitry Farm and Research Facility's animal care and use committee (Norton, Mass) and followed good laboratory practice detailed in 21 CRF Part 58.

Animals (n = 15; weight, 40–65 kg) were fasted for 24 hours before the procedure. Cefazolin (broad-spectrum antibiotic) was administered periprocedurally. A laparotomy and gastrostomy were performed to access the duodenum. The endoscope was inserted into the duodenum, the proximal limit of treatment was marked (≥8 cm from the pylorus), and the internal duodenal lumen diameter was measured using a sizing catheter, which guided appropriate balloon size for the procedure. DMR was performed from the distal duodenum to 8 cm from the pylorus. Routine wellness checks were conducted after the procedure, and blood samples were collected pre- and postprocedure. Follow-up endoscopy was conducted

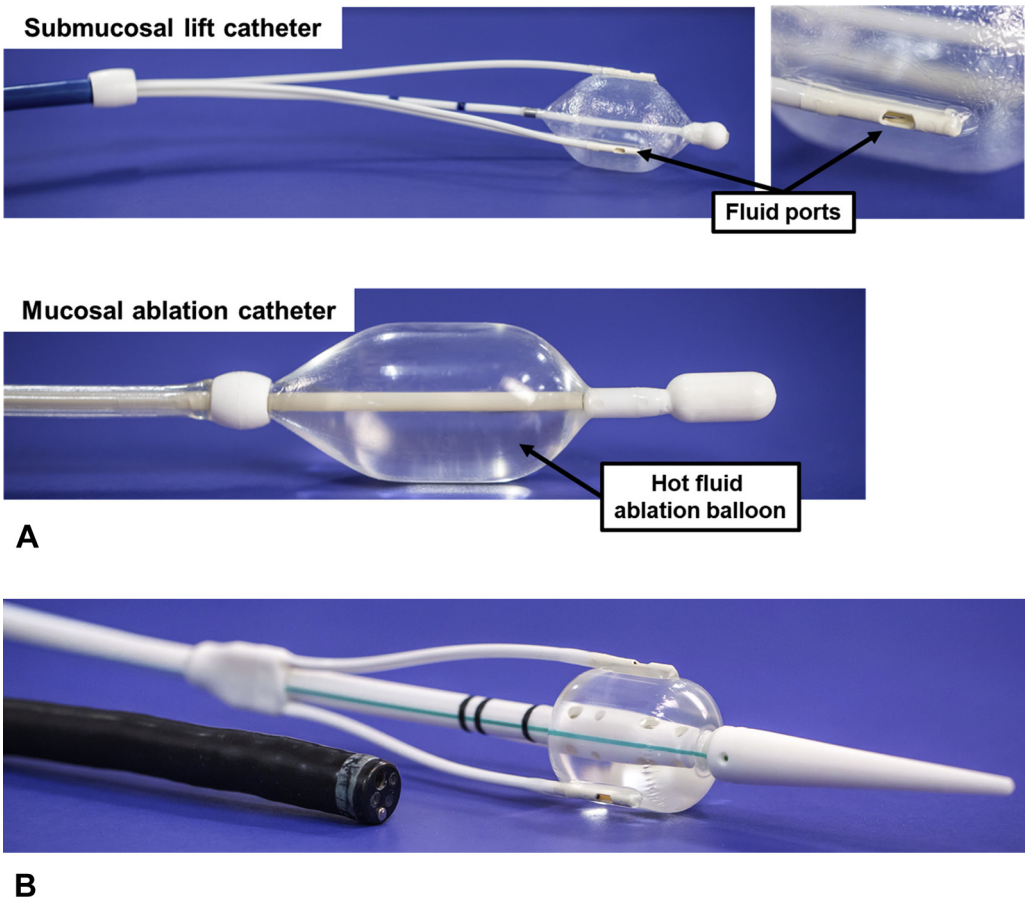

Figure 2. Evolution of the duodenal mucosal resurfacing (DMR) catheter system. **A,** Dual-catheter system used in the first-in-human study. The submucosal lift catheter injects saline solution to protect the muscularis and deeper tissue from damage during mucosal ablation. After mucosal lift, the mucosal ablation catheter hydrothermally ablates the duodenal mucosa. Circumferential hydrothermal ablations lasted approximately 10 seconds at temperatures of approximately 90°C. **B,** Single integrated catheter system. The black device is an Olympus PCF-160AL used in parallel during the current DMR procedure.

to visualize the ablated region and assess for evidence of harm or adverse events (AEs) about 7 days after the procedure.

Animals were killed 3, 14, 28, 42, and 180 days postprocedure (n = 3 per time point). The duodenum was dissected with pancreatic and mesenteric sections still attached and fixed (10% formalin). Histologic analyses (gross appearance, hematoxylin and eosin, and Gomori-trichrome staining) assessed the depth of ablation, tissue-healing response, and presence or absence of infection or pancreatitis (West Virginia University Pathology Laboratory, Morgantown, WV).

FIH clinical study. After successful testing of DMR safety in a large animal model, the FIH single-arm, open-label clinical study to evaluate the safety and efficacy of the DMR procedure was initiated at a single center in Santiago, Chile (CCO Clinical Center for Diabetes, Obesity, and Reflux).[12] The FIH study enrolled 57 patients who were followed through 24 months after the DMR procedure.

Procedure. The dual-catheter DMR system (Fig. 2A) was used initially but was subsequently replaced by the single-catheter system (Fig. 2B). The circumferential submucosal injection was visualized endoscopically during the procedure, and, if initially unsuccessful, the injection was reattempted. To determine whether the superficial mucosal tissue was effectively ablated, the gross appearance of the duodenum was qualitatively assessed immediately after the hydrothermal ablation. The number of ablations performed per patient increased over the duration of the study. On average, dual-catheter patients received 2.4 ablations (using 3-cm balloon) and single-catheter patients received 4.4 ablations (using 2-cm balloon). Patients were categorized as "long-segment" patients (≥3.4 and ≤9.3-cm ablation) or "short-segment" patients (≤3.4-cm ablation).

At procedure completion, patients were treated per standard post–upper endoscopy protocol and discharged home that day or after staying overnight. Patient follow-up was at 1, 3, and 6 months. In a subset, follow-up endoscopy was performed at 1 or 3 months after DMR to examine the treatment site and adjacent tissues and collect duodenal biopsy samples. Biopsy samples taken along the length of the duodenum were fixed (10% formalin)

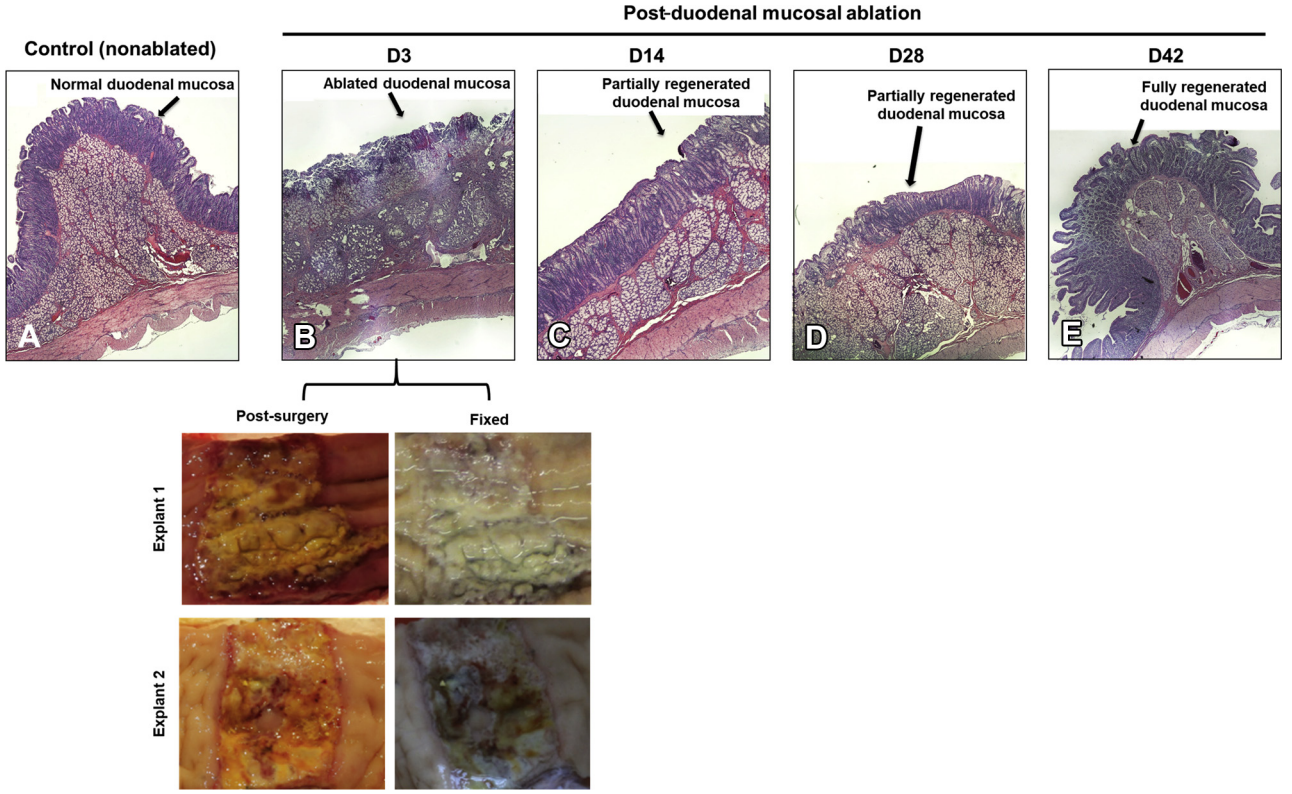

Figure 3. Representative histology of controlled thermal ablation in a large animal porcine model. **A,** Nonablated tissue explant 3 days postprocedure. **B,** Ablated tissue explant 3 days postprocedure. **C,** Ablated tissue explant 14 days postprocedure. **D,** Ablated tissue explant 28 days postprocedure. **E**, Ablated tissue explant 42 days postprocedure. *D*, Day. Representative histology images were H&E stained and captured with a 4× objective.

and hematoxylin and eosin stained. DMR procedural implementation and metabolic outcome data from the dual-catheter long-segment cohort (n = 29) are reported below through 6 months.

RESULTS

Efficacy of duodenal abrasion in rodent model

Abrasion of the duodenal mucosa without disruption of intestinal anatomy was confirmed via duodenal tissue histology in nonsurvival animals (Fig. 1B-D). In the GK rat, duodenal abrasion reduced hyperglycemia compared with sham (P = .0116; Fig. 1E). Nondiabetic control Sprague-Dawley rats showed no change in ambient glycemia after either the sham procedure or duodenal abrasion (data not shown). The procedures were performed without AEs; no changes in bowel or dietary habits were observed in the study animals.

DMR safety and feasibility in a large animal model

In pigs, a single controlled hydrothermal ablation was successfully administered to the duodenal mucosa and superficial submucosa without affecting deeper tissue layers. The DMR procedures were performed safely and without AEs. Blood chemistry and postprocedure blood counts were normal; there were no systemic infections or blood loss from the gut. Follow-up endoscopy and fluoroscopy procedures showed no treatment area obstruction or restriction. Barium flush demonstrated no contrast leakage from the lumen to the peritoneal cavity, confirming absence of bowel perforation.

Histology confirmed safe, controlled thermal ablation (Fig. 3) with no thermal necrosis or damage to the muscularis propria. No abnormalities were seen in the nonablated tissue (Fig. 3A). Animals killed 3 days postprocedure exhibited necrosis in the treated area (Fig. 3B) with full-mucosal-thickness necrosis in ~50% of mucosa; remaining areas demonstrated superficial necrosis. The deepest necrosis reached the superficial submucosa but not the muscularis propria, indicating ablation depth was successfully controlled. Mild-to-moderate inflammatory response was also observed.

Mucosa. Histology demonstrated a progressive regenerative mucosal healing process completed by week 6. At day 14 (Fig. 3C) ablated regions exhibited a variable circumferential regenerative mucosa (16%-35%). By day 28, 35% to 48% of the ablated duodenal circumference was fully regenerated (Fig. 3D) with no sign of necrosis. A healed muscularis propria injury was detected in 1 animal killed at 28 days, also attributed to

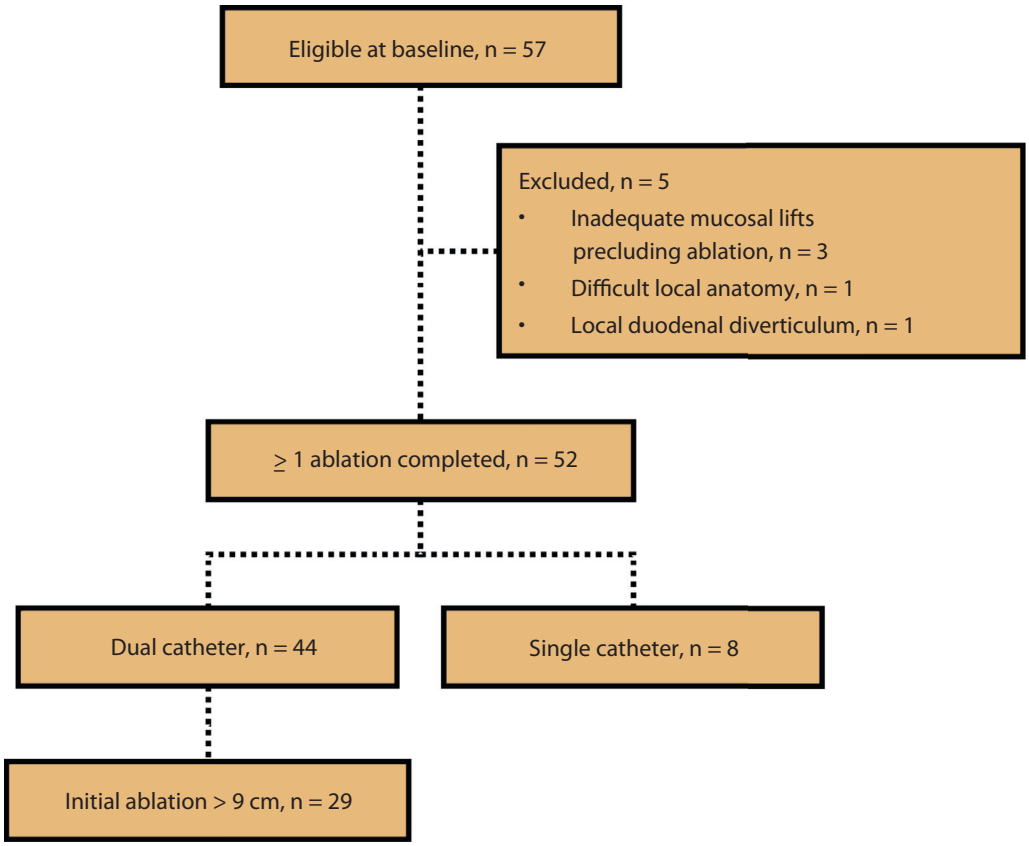

Figure 4. First-in-human study patient disposition.

mechanical damage of the thin-walled muscularis propria. On day 42 the ablation site was not grossly identifiable with fully regenerated mucosa and unremarkable plicae infolding (Fig. 3E).

Submucosa. Three of 15 animals (2 killed on day 14 and 1 on day 28) had increased collagen banding in submucosa of the treated region, although no duodenal scarring was observed. These 3 animals thrived before being killed, suggesting no functional limitations. Minimal inflammation and fibrosis in the ablated region were detected in all animals after week 6 except for 1 animal at month 6, in which submucosal fibrosis was mild to moderate.

Muscularis propria. None of the animals exhibited thermal injury to the muscularis propria in the treated zones. Two of 15 animals (1 killed on day 3 and 1 on day 28) exhibited mechanical injury to the muscularis propria attributed to damage from needle penetration from the saline solution injection. Bench investigation revealed these injuries to be due to the thin-walled porcine duodenum, which is more delicate than the human anatomy for which the device was designed (data on file).

FIH clinical experience and safety of DMR

Patients (n = 29) received ≥9 cm ablations with the dual catheter in the initial single procedure (Fig. 4). In very rare cases (<2% of patients), the initial submucosal injection was unsuccessful and was reattempted successfully. Immediately after the ablation, progressive whitening of the duodenal tissue, indicative of cell death, was observed endoscopically. The median procedure time to completion with the dual-catheter system was 90 minutes (n = 21). Use of the single catheter reduced procedure time to 69 minutes (n = 8).

The procedure was performed without AEs, and no unanticipated device-related AEs or deaths were reported through study completion. Five serious AEs were reported, 2 of which were unrelated to device or procedure (liver tumor and prostate cancer). The remaining 3, cases of duodenal stenosis related to the procedure and/or device, were treated with a single endoscopic dilation without AE or recurrence of symptoms.[12] The 3 cases of stenoses were attributed to inadequate submucosal lift. In the FIH study, the submucosal lift was performed proximal to distal, whereas ablation was applied distal to proximal. Therefore, it is possible that the first segment of the duodenum underwent submucosal lift up to 30 minutes before ablation. Inadequate submucosal lift in the 3 FIH patients may also be partially attributable to the anatomic differences between humans and the porcine model used for initial DMR procedure development.[16] However, after improving the clinical quality and

TABLE 1. Summary of baseline, week 24, and change from baseline for selected variables: first-in-human data

Variable	Baseline	Week 24	Change from baseline	*P* value*
Weight, kg				.0099
Mean ± SD	86.9 ± 11.5 (n = 29)	85.0 ± 11.72 (n = 29)	−1.9 ± 3.7 (n = 29)	
Median (min, max)	85.5 (65.0, 121.0)	83.2 (58.6, 117.6)	−2.0 (−9.6, 4.1)	
HbA1c, %				.0008
Mean ± SD	9.7 ± 1.4 (n = 29)	8.4 ± 1.9 (n = 29)	−1.3 ± 1.8 (n = 29)	
Median (min, max)	9.6 (7.5, 12.3)	8.0 (6.1, 12.4)	−1.4 (−4.5, 3.6)	
FIB-4,† %				.0246
Mean ± SD	1.7 ± .3 (n = 8)	1.3 ± .3 (n = 8)	−.4 ± .41 (n = 8)	
Median (min, max)	1.6 (1.5, 2.2)	1.3 (.8, 1.8)	−.5 (−.8, .3)	
ALT, U/L				.0016
Mean ± SD	36.9 ± 14.9 (n = 29)	26.7 ± 12.7 (n = 29)	−10.2 ± 15.8 (n = 29)	
Median (min, max)	35.0 (18.0, 74.0)	24.0 (12.0, 80.0)	−5.0 (−43.0, 21.0)	
AST, U/L				.0024
Mean ± SD	29.9 ± 11.3 (n = 29)	22.6 ± 5.9 (n = 29)	−7.3 ± 11.9 (n = 29)	
Median (min, max)	28.0 (13.0, 57.0)	22.0 (12.0, 45.0)	−6.0 (−36.0, 14.0)	

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *HbA1c,* hemoglobin A1c; *FIB-4,* fibrosis-4; *SD,* standard deviation.
**P* value from paired *t* test.
†Subset of patients with baseline FIB-4 >1.3.

consistency of the submucosal saline solution lift, no further instances of duodenal stenosis have been observed.

Complete mucosal regrowth was observed by 3 months in all biopsy specimens. At 1 or 3 months after DMR, no inflammation was observed, and 8 of 19 patients had no evidence of fibrosis. Low-to-intermediate fibrosis (minimal [n = 9] to mild [n = 2] submucosal collagen deposition) was observed in 11 of 19 patients. At 24 weeks postprocedure hemoglobin A1c, hepatic transaminases, and fibrosis-4 were reduced (Table 1). Modest weight loss from baseline was observed but was not correlated with change in hemoglobin A1c.

DISCUSSION

DMR is an endoscopic intervention designed to treat insulin resistance–associated metabolic diseases, including T2D and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, by targeting the duodenal mucosa.[17] We report glucose lowering after removal of the duodenal mucosa via mechanical lumen disruption in GK rats. This glucose lowering was not observed in sham GK rats or after duodenal mucosal disruption in nondiabetic Sprague-Dawley rats, indicating that glucose lowering is not because of the surgery itself. DMR was successfully administered and did not cause injury to local tissues or result in systemic sequelae in a large animal porcine model, confirming procedure safety and technique. Although the porcine model does offer advantages over other large animal models regarding its duodenal lumen diameter and mucosal thickness, porcine duodenal muscularis propria is not a good surrogate for the human wall thickness.[15,16]

The DMR procedure we describe benefits from strong endoscopic skills, the ability to accurately identify anatomic landmarks from the ampulla of Vater to the ligament of Trietz, and the use of a catheter system that allows procedural steps to be executed safely and without difficulty. FIH DMR procedure study results demonstrated an encouraging safety and tolerability profile. The streamlined single-catheter system allows greater safety in submucosal lift and ease of use for endoscopists. Notably, procedure time was reduced to <60 minutes in most cases after the transition from the dual- to single-catheter system. The working hypothesis is that the submucosal lift creates a circumferential aqueous submucosal buffer that minimizes inadvertent thermal injury during the procedure and allows anatomic separation of pain fibers from the ablated mucosal surface, minimizing postprocedural pain.[18] Postprocedural GI AEs were mostly mild to moderate in severity and occurred in the days immediately after the procedure, requiring minimal analgesic treatment. More specifically, abdominal pain was not commonly reported as a postprocedural AE, and most patients were pain free (there was no need for opiate analgesia) and returned to normal dietary intake within hours of recovery from the procedure. Submucosal lift allows for safe patient selection in that if the duodenal submucosal lift was not technically possible, ablation was not advised. Although the use of hydrothermal energy for GI mucosal ablation

is novel, this form of surface energy is advantageously well controlled in depth and did not result in postprocedure bleeding.

When developing and evaluating the safety profile of DMR, it was important to take into consideration the inherent risks associated with endoscopic treatments in the duodenum. As part of animal laboratory training for the ongoing Revita-2 study, initial DMR safety testing demonstrated that in a live healthy pig, DMR elicits a superficial ablation of villi and crypts in the duodenum. Studies of the efficacy and safety of gastroduodenal stents and intragastric balloons report serious AE rates around 5%, whereas DMR serious AE rates are approximately 2%.[19-22] Ongoing and future clinical studies will help determine if further catheter iterations are needed to maximize patient safety and ease of use for healthcare providers.

Patients with T2D who underwent DMR experienced a beneficial metabolic effect, impacting both diabetic and hepatic indices; ablation length positively correlated with improvement in metabolic parameters.[12] Glycemic improvement observed in DMR-treated patients is further evidence that the duodenum plays a fundamental role in metabolic control and that resurfacing the duodenal mucosa may abrogate an important and pathologic insulin resisting signal. Modest weight loss (2%-3%) was observed but does not explain the magnitude of glycemic and hepatic improvement.

Although other ablative technologies have been used in the GI tract,[23,24] the choice of submucosal lift and hydrothermal ablation in the duodenum offers several advantages for ablation in the unique anatomy of the small intestine. First, hydrothermal ablation is nondesiccating: The mucosal proteins denature, thus coagulating the duodenal tissue and enabling a gradual sloughing of mucosal tissue without a significant risk of GI bleeding. Second, hydrothermal ablation delivers a consistent temperature–time profile to enable precise control of ablation depth independent of tissue contact against an irregular duodenal surface. Third, circumferential lift is designed to protect deeper tissue structures by separating the superficial intestinal mucosa from the submucosa/muscularis mucosa with saline solution submucosal injection. This protection enables a safe ablation even in the situation of a duodenum with a thin submucosal space. This claim is supported by subsequent safety studies conducted in a porcine model that highlighted the feasibility of hydrothermal ablation, because it was limited to the superficial intestinal mucosa and did not damage the underlying muscularis mucosa or deeper structures.

In summary, DMR safely translated from animal proof-of-concept to early human feasibility studies, resulting in metabolic improvements. Randomized clinical studies are currently ongoing,[13,14] and final reports evaluating the long-term safety, efficacy, and durability of DMR from Revita-1 and Revita-2 studies are forthcoming. Future studies are needed to understand the mechanism by which this unique treatment approach may impact metabolic disease.

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Abbreviations: AE, adverse event; DMR, duodenal mucosal resurfacing; FIH, first in human; GK, Goto-Kakizaki (rat model); T2D, type 2 diabetes.

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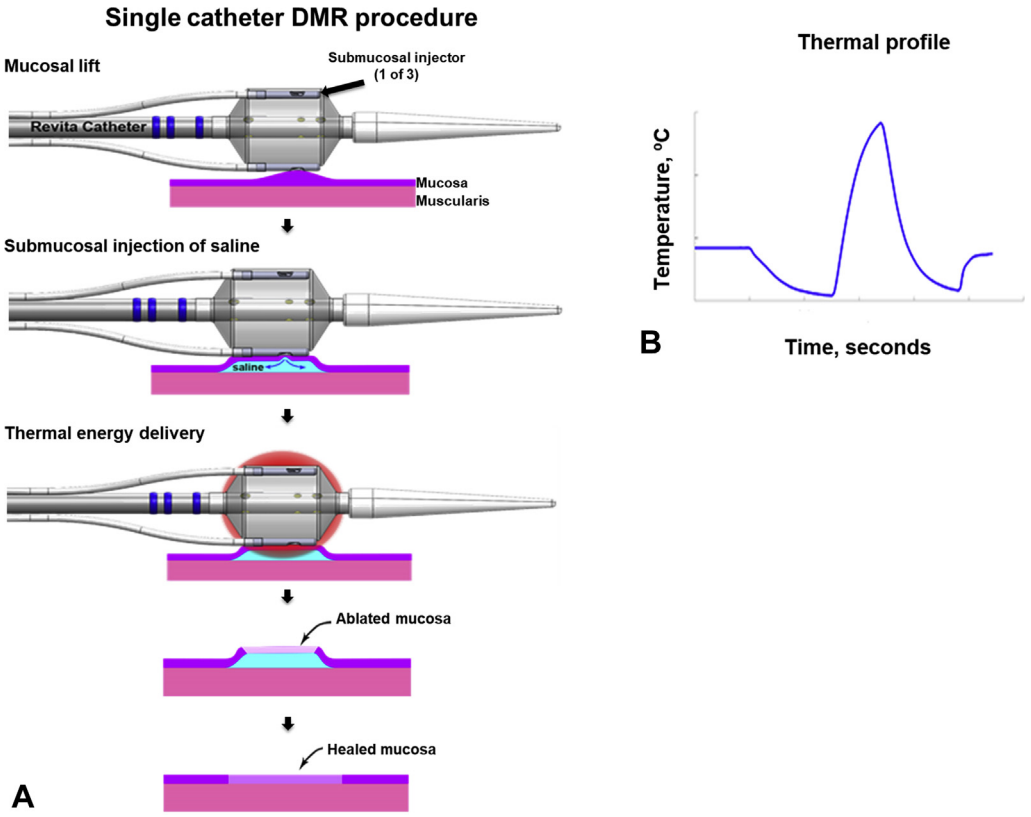
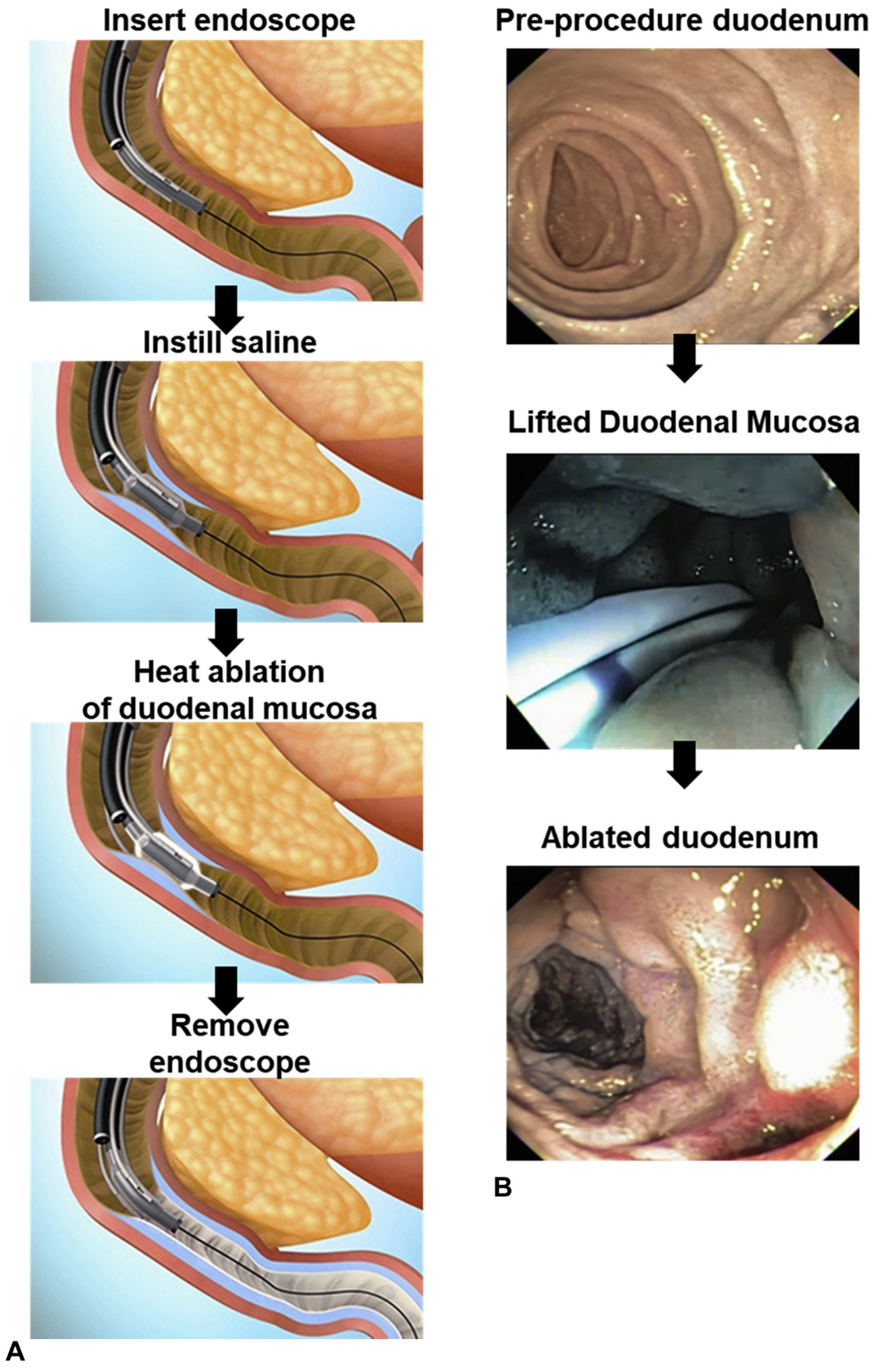


Supplementary Figure 1. DMR Procedure. **A,** The single catheter has a multilumen shaft with a balloon (2 cm in length) attached to its distal end. Affixed to the outside of the balloon are 3 narrow shafts (submucosal injectors) with a port used to draw a vacuum when placing the saline solution during the mucosal lifting portion of the procedure. Within each shaft is a fluid lumen with a miniaturized needle affixed to the distal end. Each needle is wholly constrained within the port, ensuring its safe use. For mucosal lift and ablation, the duodenal mucosal resurfacing (DMR) catheter is placed in the proximal duodenum distal to the papilla. During mucosal lift, the tissue is drawn into the needle port and saline solution is injected into the submucosal space through the needles, resulting in complete circumferential lift of the mucosa. The proximal end of the shaft is fitted with handle, saline solution, and vacuum lines that are affixed to a console unit to control their function. Once complete, the ablation cycle is started with hot water circulated into the balloon to complete an ablation of the lifted tissue (water balloon temperature is approximately 80°C for a duration of 10 seconds). The balloon is then deflated and the catheter advanced distally for the next segment treatment. The process of expansion, ablation, and repositioning is repeated until the required length (approximately 10 cm) of the duodenum is treated. The reusable electromechanical console provides functionality to the submucosal lift and hot fluid ablation steps of the procedure and is controlled through the use of a software user interface monitor. Before use, the console is fitted with a sterile single-use line set that serves as the pathway for the saline solution to be placed into the duodenal submucosa during the procedure. **B,** The hydrothermal energy profile used to perform the DMR procedure.



Supplementary Figure 2. Animation snapshots (**A**) and endoscopic snapshots (**B**) of the duodenal mucosal resurfacing procedure.