Endoscopic Duodenal Mucosal Resurfacing for the Treatment of Type 2 Diabetes: 6-Month Interim Analysis From the First-in-Human Proof-of-Concept Study

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OBJECTIVE

To assess procedural safety and glycemic indices at 6 months in a first-in-human study of duodenal mucosal resurfacing (DMR), a novel, minimally invasive, upper endoscopic procedure involving hydrothermal ablation of the duodenal mucosa, in patients with type 2 diabetes and HbA_{1c} ≥7.5% (58 mmol/mol) on one or more oral antidiabetic agents.

RESEARCH DESIGN AND METHODS

Using novel balloon catheters, DMR was conducted on varying lengths of duodenum in anesthetized patients at a single medical center.

RESULTS

A total of 39 patients with type 2 diabetes (screening HbA_{1c} 9.5% [80 mmol/mol]; BMI 31 kg/m^2) were treated and included in the interim efficacy analysis: 28 had a long duodenal segment ablated (LS; ∼9.3 cm treated) and 11 had a short segment ablated (SS; ∼3.4 cm treated). Overall, DMR was well tolerated with minimal gastrointestinal symptoms postprocedure. Three patients experienced duodenal stenosis treated successfully by balloon dilation. HbA_{1c} was reduced by 1.2% at 6 months in the full cohort ($P < 0.001$). More potent glycemic effects were observed among the LS cohort, who experienced a 2.5% reduction in mean HbA_{1c} at 3 months postprocedure vs. 1.2% in the SS group ($P < 0.05$) and a 1.4% reduction at 6 months vs. 0.7% in the SS group ($P = 0.3$). This occurred despite net medication reductions in the LS cohort between 0 and 6 months. Among LS patients with a screening HbA_{1c} of 7.5–10% (58–86 mmol/mol) and on stable antidiabetic medications postprocedure, HbA_{1c} was reduced by 1.8% at 6 months ($P < 0.01$).

CONCLUSIONS

Single-procedure DMR elicits a clinically significant improvement in hyperglycemia in patients with type 2 diabetes in the short-term, with acceptable safety and tolerability. Long-term safety, efficacy, and durability and possible mechanisms of action require further investigation.

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Type 2 diabetes has reached epidemic proportions in Westernized countries. The current standard of care includes lifestyle or behavioral modification first, frequently coupled with the subsequent use of an array of oral and injectable medications. Despite a wide choice of pharmacological interventions, many patients do not achieve adequate control of hyperglycemia (1). Poor compliance with complex medical regimens (2) and the fact that most available pharmaceutical approaches do not adequately address underlying pathophysiological defects may explain the limited efficacy of current therapies.

Certain forms of bariatric surgery, especially those that involve bypass of the upper intestine, can exert powerful corrective effects on metabolism in obese subjects with type 2 diabetes (3–6). Recently, there has been a groundswell of interest in establishing this form of intervention as an additional approach to managing type 2 diabetes beyond lifestyle modification or pharmacological approaches. A new consensus statement crafted by an international group of diabetes experts and embraced by multiple professional organizations advocates that such metabolic surgeries should be included among current treatment guidelines for patients with type 2 diabetes (7). Experimental evidence demonstrates that intestinal bypass surgery has direct effects on glucose metabolism, highlighting the importance of the small intestine, particularly the duodenum, in the physiology and pathophysiology of glucose homeostasis (8,9). Anatomically, the duodenum is the first site of fuel recognition at the time of nutrient intake. Observations in animal models and humans reveal that the duodenal mucosa exhibits abnormal hypertrophy and endocrine hyperplasia in the presence of diabetes (10). Moreover, gastrointestinal bypass procedures or device-based interventions (i.e., the endoluminal sleeve) that prevent contact between duodenal mucosa, bile, and nutrients improve insulin sensitivity (11) and β-cell function (12). Further, in a rat model and in patients with type 2 diabetes who have undergone Roux-en-Y gastric bypass surgery, the improvement of glucose tolerance is quickly reversed when the bypassed duodenum is acutely re-exposed to nutrients introduced via gastrostomy in the remnant stomach (13,14). These observations underscore the critical glucoregulatory role of the upper intestine. More specifically, exclusion of nutrient contact from an abnormal duodenal surface in type 2 diabetes may elicit beneficial downstream effects on metabolism, perhaps through the reduction of putative anti-incretin mechanisms (15).

Duodenal mucosal resurfacing (DMR) is a novel, minimally invasive, catheter-based upper endoscopic procedure involving hydrothermal ablation of the duodenal mucosa and subsequent mucosal healing. DMR could recapitulate, less invasively, some of the mechanisms of action of gastrointestinal bypass surgery. It may offer a new treatment approach for type 2 diabetes by altering the duodenal mucosal surface itself, thereby altering downstream signaling and eliciting metabolic improvement. Preclinical studies conducted in the Goto-Kakizaki rat, a rodent model equivalent of human type 2 diabetes, support this thesis by demonstrating that selective denudation of the duodenal mucosa conducted by an abrasion device resulted in immediate lowering of glycemia during an oral glucose gavage when compared with preprocedure levels and also to a sham-treated group. Moreover, similarly conducted studies in a nondiabetic rodent model (Sprague-Dawley) showed no lowering of glycemia, indicating that this perturbation of the duodenal mucosa reduced abnormal hyperglycemia but did not impact normoglycemia (unpublished data, Fractyl Laboratories, Inc.). Additional studies in a pig model also demonstrate that the DMR procedure achieves a predictable ablation of the intestinal mucosa surface without damage to the underlying muscularis mucosa or deeper structures (unpublished data, Fractyl Laboratories, Inc.). We therefore conducted a first-in-human clinical study of single-procedure DMR in patients with type 2 diabetes. Here we report on safety, tolerability, and effectiveness from the 6-month interim analysis.

RESEARCH DESIGN AND METHODS

Study Design

This was a phase I, first-in-human, open-label, proof-of-concept study with a single-arm, nonrandomized design performed at a single center in Santiago, Chile (CCO Clinical Center for Diabetes, Obesity and Reflux). All procedures were performed by physicians trained in endoscopy (L.R., P.B., and M.P.G.N.) between August 2013 and November 2014. The study protocol defines a projected follow-up of 3 years, and we report here data from the first 6 months of postprocedure follow-up.

Study Oversight

The study protocol was approved by an independent ethics committee (Metropolitano Comité de Ética Cientifico Oriente) in Santiago, Chile, and complied with the recommendations of the Declaration of Helsinki. All patients provided written informed consent.

Procedural Development and Length of Treated Duodenal Segment

During a period of procedural development from August 2013 to December 2013 (dose escalation phase), consecutive patients were treated with a single application of thermal energy ablation over a maximum of 3 cm of duodenum length with complete circumferential application. The length of the ablated region and number of applications during a single procedure were increased in subsequent procedures over the course of the study, with the goal of achieving complete circumferential ablation of the postpapillary duodenum, covering ~12 cm in length. From January 2014 to November 2014, at least 9 cm of the duodenum was treated in all patients, except when precluded by duodenal anatomy.

Patients

Eligible patients were adults with type 2 diabetes aged 28–75 years, with a BMI 24–40 kg/m^2 and HbA_{1c} 7.5–12% (58–108 mmol/mol) on at least one oral antidiabetic agent. Additional eligibility criteria included fasting c-peptide >1 ng/mL and type 2 diabetes diagnosis made within 10 years prior to enrollment. Patients were excluded if they had type 1 diabetes (including anti-GAD positivity), current use of injectable antidiabetic medication, history of previous gastrointestinal surgery or anatomical abnormalities that would preclude the DMR procedure, treatment with antiplatelet agents that could not be temporarily discontinued, or pregnancy.

Study Procedure

DMR is an endoscopic treatment consisting of intestinal luminal sizing, submucosal expansion with saline (designed to provide a uniform ablative surface and a thermally protective layer of saline between the ablated mucosa and deeper tissue layers), and circumferential thermal ablation along a length of the duodenum. In the current study, novel polyethylene terephthalate balloon treatment catheters (Revita system; Fractyl Laboratories, Inc.) were introduced into the duodenum via a trans-oral endoscopic approach in anesthetized patients. The first catheter was used to determine the size of the duodenum and inject saline into the submucosal space via three vacuum-assisted needle injectors oriented at 120° from one another around the circumference of the balloon. Circumferential mucosal lift was performed along the length of the postpapillary duodenum from 1 cm distal to the ampulla of Vater (hepatopancreatic ampulla) to proximal to the ligament of Treitz. After removal of the initial catheter, a second balloon catheter was introduced to perform thermal ablation on the lifted area. Under direct endoscopic visualization, discrete circumferential thermal ablations of ~10 s each were applied at temperatures of ~90°C to obtain up to five longitudinally separated ablations along the length of the postpapillary duodenum. Care was taken to avoid the ampulla of Vater to prevent damage to the biliary tree and to avoid treatment in or beyond the ligament of Treitz.

Patients were discharged within 24 h after the procedure and prescribed a progressive diet (liquids → pureed foods → soft foods) for 2 weeks. Although no specific recommendations were made, physicians were requested to minimize alterations in antidiabetic medications except when medically indicated. Medications and doses were recorded by the investigators at all follow-up time points. Background antidiabetic medication use was assigned into "stable," "increased," and "decreased" categories over time to allow subset analysis of the patient cohort.

Outcome Measures and Assessments

The first-in-human study evaluated procedural safety and efficacy. Efficacy was assessed using mixed-meal tolerance testing (MMTT) and measuring fasting plasma glucose (FPG), fasting plasma insulin, and HbA_{1c}.

Comparisons were made between preprocedure (screening) and postprocedure metabolic parameters and also between patient cohorts based on the length of the treated duodenal segment (short vs. long), HbA_{1c} levels, and changes in background medication use.

Preprocedure measurements at screening consisted of patient history, vital signs, physical examination, medication review, blood analysis (including HbA_{1c}, fasting glucose, fasting insulin, cholesterol, and other pancreatic and liver markers), and MMTT. All participants underwent a screening endoscopy, with a follow-up endoscopy 3 months after the treatment procedure.

Patients were seen on days 7 and 14 after the procedure for a physical exam, standard blood analysis, collection of data on medication use, and surveillance for adverse events. These assessments and MMTT were also performed at 1, 3, and 6 months after the procedure, with the exception of repeat endoscopy and duodenal biopsy, which was performed within 3 months to assess mucosal healing in the first cohort of treated patients.

Statistical Analysis

All statistical tests were two sided at the α level of 0.05 unless stated otherwise. No adjustments for multiple hypothesis testing were made. For the efficacy analyses, a mixed model with repeated measures was used to analyze change from preprocedure levels when more than two postprocedure measures were assessed. Safety data were tabulated by patient and events overall and by severity and relationship to device, including the number of overall adverse events, serious adverse events, and unanticipated adverse device effects by severity. Where applicable, comparisons are reported as means ± SEM. All statistical analyses were performed using Statistical Analysis System (SAS) release 9.4 or higher (SAS, Cary, NC).

RESULTS

We report data for the first 44 patients enrolled in the study who underwent screening endoscopy in preparation for the DMR procedure (intent-to-treat population). Among these patients, four did not receive thermal ablation (two failed screening endoscopy, one had tortuous anatomy, and one had the procedure stopped prior to ablation to prevent prolonged anesthesia), and one subject underwent the procedure but was subsequently excluded from the efficacy analysis (although included in the safety analysis) due to anti-GAD positivity indicative of type 1 diabetes documented after the index procedure. One additional treated patient withdrew consent before the final 6-month visit but was included in both the safety and efficacy analyses. Clinical characteristics of the

Table 1—Clinical characteristics at screening (intent-to-treat population)

Patient characteristics	Value (n = 44)
Age, years (range)	53.4 ± 7.5 (38–65)
Sex, *n* (%)	
Female	16 (36)
Male	28 (64)
Weight (kg)	84.4 ± 11.9
Height (cm)	165.3 ± 8.4
BMI (kg/m^2)	30.8 ± 3.5
Systolic blood pressure (mmHg)	122.0 ± 14.2
Diastolic blood pressure (mmHg)	77.0 ± 8.1
Duration of type 2 diabetes, years (range)	5.7 ± 2.2 (0.2–9.7)
HbA_{1c}	
%	9.6 ± 1.4
mmol/mol	81 ± 16
FPG (mg/dL)	187 ± 58
Oral antidiabetic medications	
Metformin	42 (98)
Sulfonylurea	16 (37)

Data are mean ± SD or *n* (%), unless otherwise indicated.

intent-to-treat population at screening are presented in Table 1.

A total of 39 treated patients were included in the efficacy analysis. The average time between screening and treatment in this efficacy cohort was 5.5 weeks.

All treated patients received circumferential ablation of between 3 and 15 cm of the postpapillary duodenal mucosa. The mean procedure time from beginning of submucosal saline expansion to completion of thermal ablation was 54 min (interquartile range 47–69). The mean length of treated duodenal mucosa in the full cohort was 7.8 cm. Over the course of the study, 28 patients had ablation of a long segment of duodenal mucosa (LS-DMR; ≥9 cm of ablation) and 11 had a short segment ablated (SS-DMR; <6 cm of ablation). SS-DMR was performed either in the course of early procedural development or later due to complicated duodenal anatomy. The average length of duodenal mucosa ablated was 9.3 cm in LS-DMR and 3.4 cm in SS-DMR.

Safety and Tolerability

The DMR procedure was completed without complication in all 40 treated patients. There was no gastrointestinal bleeding, perforation, pancreatitis, severe hypoglycemia, or evidence of malabsorption (i.e., calcium abnormalities or iron deficiency anemia), either in the period immediately following the procedure or at later follow-up visits. No patients experienced difficulty tolerating the oral diet in the days immediately following the procedure.

The most common study-related adverse event was transient, postprocedural abdominal pain (in 8 of 40 patients) due to air insufflation and/or endotracheal intubation, for which analgesic medications were neither administered nor required. No patient reported experiencing discomfort by 48 h after the procedure.

Three patients developed a duodenal stenosis that presented as epigastric pain and vomiting 2–6 weeks after the procedure. These patients were treated with endoscopic balloon dilation with full resolution of symptoms and no further sequelae. Root cause analysis revealed assignable faults in each case for which device improvements and procedural changes have since been instituted.

Follow-up endoscopies and duodenal biopsies (1 month: endoscopy [*n* = 19] and biopsy [*n* = 19]; 3 months: endoscopy [*n* = 39] and biopsy [*n* = 9]) showed mucosal healing in all evaluated patients. Figure 1 shows the appearance of the duodenal mucosa prior to the procedure, immediately after hydrothermal ablation, and 1 month after the procedure as seen during follow-up endoscopy. No patients experienced any signs of infection.

Efficacy

DMR elicited significant improvements in glycemic indices. FPG reductions were noted within 1 week of the procedure (Fig. 2*A*) and HbA_{1c} reductions were observed as early as 1 month (Fig. 3) after DMR and were still present in a significant proportion of subjects (29 of 39 patients) at 6 months of follow-up. These reductions were observed without a change in fasting plasma insulin (screening 11.7 ± 1.0 mIU/L, 3 months 11.8 ± 1.5 mIU/L, and 6 months 11.6 ± 1.3 mIU/L for LS-DMR cohort [*n* = 28]).

HbA_{1c} was reduced by 1.2 ± 0.3% at 6 months in the full cohort ($P < 0.001$). More potent glycemic effects were observed in LS-DMR patients (Fig. 2*A*). LS-DMR patients experienced a 2.5 ± 0.2% reduction in mean HbA_{1c} at 3 months, compared with a 1.2 ± 0.5% reduction among the SS-DMR cohort at the same time point ($P < 0.05$ between groups). This trend was continued through 6 months of observation, with a mean HbA_{1c} reduction of 1.4 ± 0.3% in the LS-DMR cohort and 0.7 ± 0.5% in the SS-DMR cohort ($P = 0.3$ between groups). This occurred despite net medication reductions in the LS-DMR cohort between 0 and 6 months.

Individual patient data plots for FPG for the LS cohort show that the majority of patients had a robust glucose-lowering response after DMR (Fig. 2*B*). MMTT results suggest that the improvement in glycemic indices manifested through improvements in both fasting and postprandial glycemia (Fig. 2*C* and *D*), with the majority of the effect seemingly attributable to improvements in fasting hyperglycemia. The procedure also appeared to exert glycemic improvements over a wide range of screening

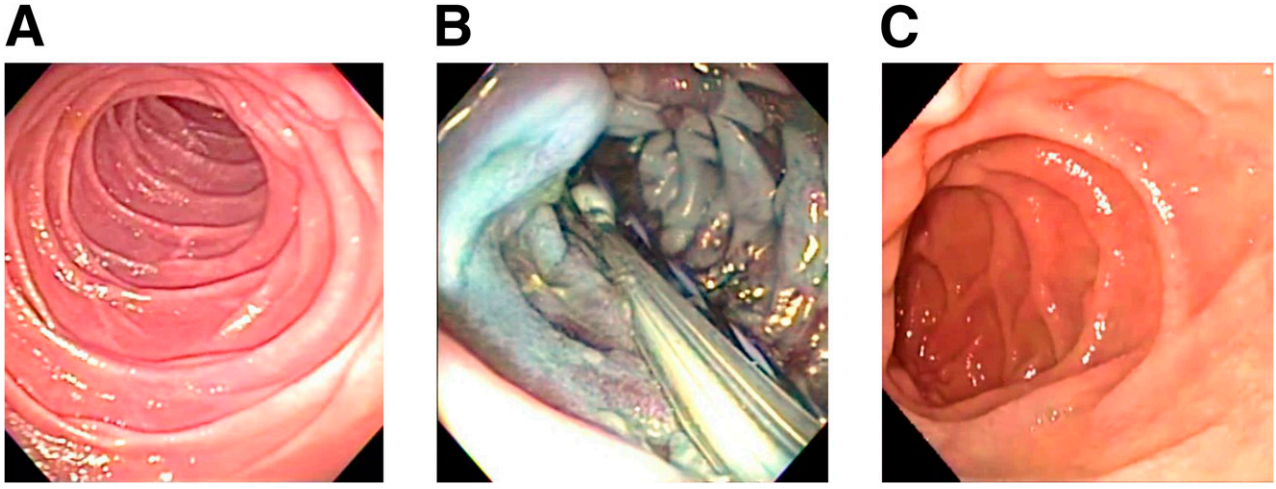

Figure 1—The duodenal mucosa prior to DMR (*A*), immediately after hydrothermal ablation (*B*), and 1 month after the procedure (*C*) as seen during follow-up endoscopy.

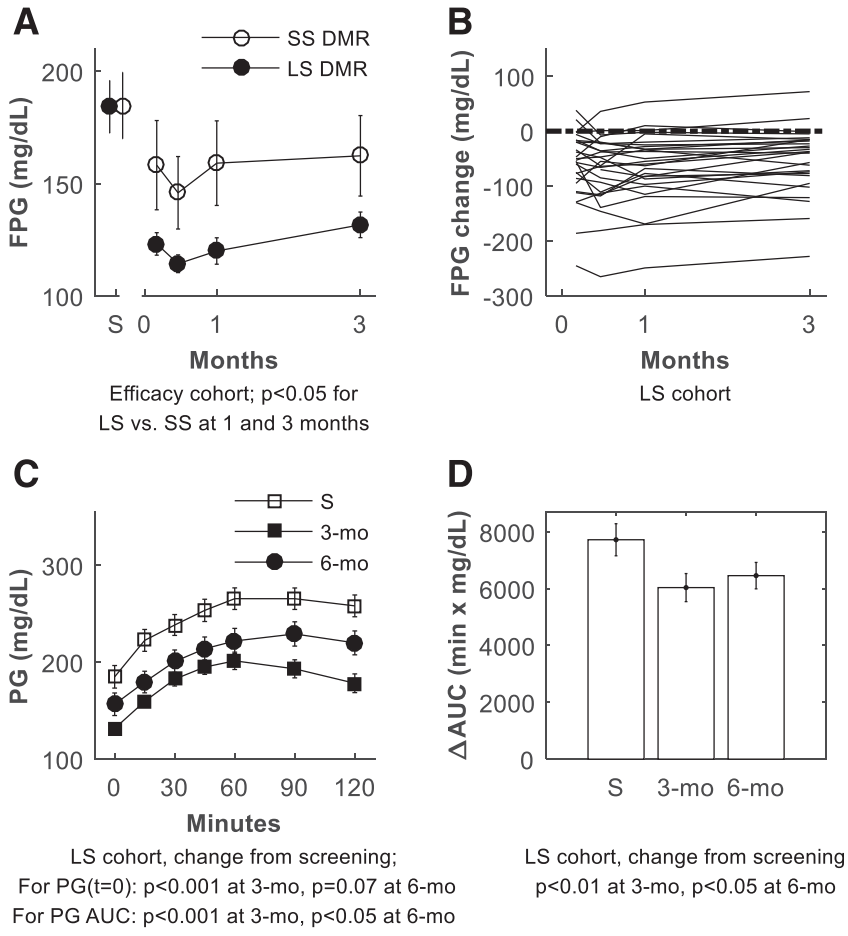

Figure 2—Effect of DMR on ambient glycemia. *A*: Effect of SS (white circles) and LS (black circles) DMR treatment on FPG plotted to 3 months (n = 39). *B*: FPG change from screening plotted to 3 months in individual subjects who received LS-DMR (n = 28). *C*: Meal challenge plasma glucose (PG) from fasting to 120 min after meal ingestion in LS-DMR subjects at screening (white squares, n = 28), 3 months (black squares, n = 27) (no 3-month MMTT data for one subject), and 6 months (black circles, n = 28). *D*: Change from fasting in area under the curve (AUC) for MMTT at screening, 3 months, and 6 months in LS-DMR subjects (n = 28). Values for *A*, *C*, and *D* are reported as mean ± SEM. mo, month; S, preprocedure levels (screening).

HbA_{1c} values, including values of 10% (86 mmol/mol) and greater (Fig. 3*A*). However, some erosion of the glycemic effect was observed between the 3- and 6-month follow-up, as seen in Fig. 2*C* and Fig. 3.

During the 6-month follow-up period, concomitant medication use changed in some patients in both the SS (3 increased, 3 stable, and 5 decreased) and LS cohorts (0 increased, 14 stable, and 14 decreased), with a trend toward greater improvements in glycemic control in patients whose usage of antidiabetic medication remained stable (Fig. 3*B* and Fig. 4) (P = 0.11 at 6 months). Among LS patients with a screening HbA_{1c} 7.5–10% (58–86 mmol/mol) and on stable antidiabetic medications postprocedure (n = 8), HbA_{1c} was reduced by 1.8 ± 0.5% at 6 months ($P < 0.01$) and was accompanied by a modest weight reduction of 3.9 ± 0.5 kg at 3 months ($P < 0.001$) and 2.5 ± 0.1 kg at 6 months ($P < 0.05$). There was no statistically significant correlation between degree of weight loss and magnitude of HbA_{1c} improvement.

CONCLUSIONS

In this first-in-human study, a single procedure endoscopic DMR ablation elicited a substantial improvement in glycemia in medically treated patients with suboptimally controlled type 2 diabetes followed for 6 months, with an acceptable safety and tolerability profile observed to date.

DMR appeared to exhibit dose dependency, with LS ablation exerting more potent glycemic effects, as seen by the statistically significant difference in glycemic effect between SS-DMR versus LS-DMR at 3 months ($P < 0.05$). This is stated with some caution, as the study was not designed to formally examine ablation dose dependency (i.e., SS vs. LS ablation), and the optimal length of ablated duodenum requires additional study. As one would anticipate with a novel, procedure-based intervention, this first-in-human study was conducted in an iterative manner where procedural feasibility and patient safety were of prime importance in the earlier cases. As procedural expertise increased, LS ablation became more feasible, but with ongoing attention to patient safety. In the LS cohort, DMR exerted improvements in glycemia as early as 1–2 weeks postprocedure, similar to the prompt effects seen after bariatric surgery and suggesting the possibility of similar mechanisms of action (9,16). Patients in this study were asked to adhere to only modest dietary modification in the first 2 weeks after DMR, and no recommendations on diet or caloric restriction were made beyond that time. Therefore, the early improvement in glycemic control induced by DMR is unlikely to be explained by decreased caloric intake. In addition, the lack of substantial weight loss through 6 months of follow-up also suggests that decreased caloric intake is not a major mechanism.

Beyond the early improvement in glycemia, DMR led to plasma glucose and HbA_{1c} improvement over the 6-month follow-up. Meal challenge data suggest that the predominant effect of DMR was on fasting hyperglycemia, with a less striking improvement in postprandial excursion. It is interesting that a gut-related intervention targeted at the duodenum would exert predominant effects on fasting, not postprandial, glycemia. This suggests a potential effect on hepatic glucose production, possibly through an insulin-sensitizing mechanism, in line with previous observations in duodenal-jejunal bypass (17) and Roux-en-Y gastric bypass surgery (18–20). The overall glucose-lowering effect of DMR appears less potent than that observed with bariatric surgery, but the intended targeted intervention of DMR (an alteration of nutrient exposure to the duodenal surface) would only approximate one of the multiple anatomical modifications that come with Roux-en-Y gastric bypass surgery. It is

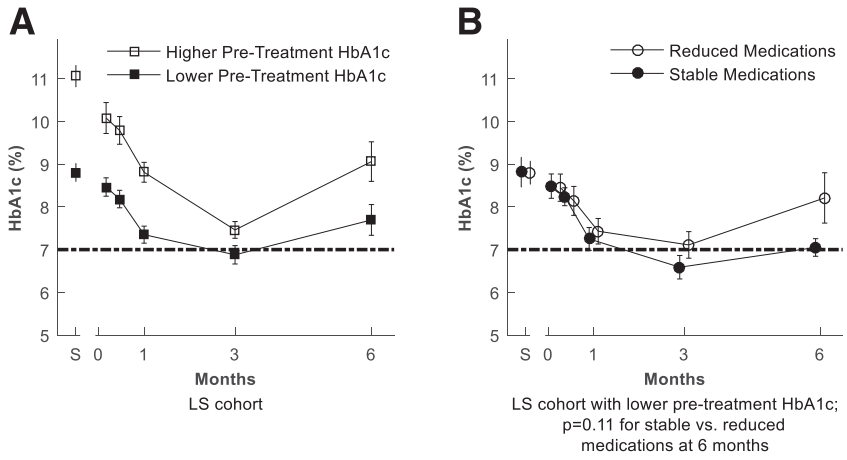

Figure 3—DMR effect on HbA_{1c}. *A*: Mean change in HbA_{1c} in LS-DMR subjects with higher (>10% [86 mmol/mol], white squares, *n* = 10) and lower (≤10% [86 mmol/mol], black squares, *n* = 18) pretreatment HbA_{1c} levels. *B*: Effect of LS-DMR in subjects with lower (≤10% [86 mmol/mol], *n* = 18) pretreatment HbA_{1c} levels where background antidiabetic medication remained stable (black circles, *n* = 8) or was reduced (white circles, *n* = 10) during the 6-month follow-up period (for one subject, 6-month medication data were not recorded). All values are reported as mean ± SEM. S, preprocedure levels (screening).

interesting nevertheless that a targeted intervention by endoscopic procedure can elicit glycemic improvement without the more extensive anatomical disruption of surgical approaches. Future development of DMR will focus on the underlying mechanism and efforts to more predictably manifest a metabolic benefit.

Examination of the overall glycemic effects in this study suggests some erosion of effect in the latter phase of study. A closer examination of glycemic response by individual patient in the LS cohort with pretreatment HbA_{1c} levels of ≤10% (86 mmol/mol) (Fig. 4) shows that whereas some patients experience an almost complete erosion of the effect by the 6-month follow-up (6 of 18 LS subjects with pretreatment HbA_{1c} ≤10% [86 mmol/mol] had <0.5% reduction in HbA_{1c} at 6 months), many patients manifest a sustained effect on glycemia throughout the 6-month period (10 of 18 LS subjects with pretreatment HbA_{1c} ≤10% [86 mmol/mol] had an HbA_{1c} <7.5% [58 mmol/mol] at 6 months). In addition, erosion of the glycemic effect in some cases can be explained by a withdrawal of or nonadherence to prescribed concomitant antidiabetic medication. This includes the single patient in Fig. 4 who had reduced antidiabetic medication use and experienced a significant deterioration in glycemic control.

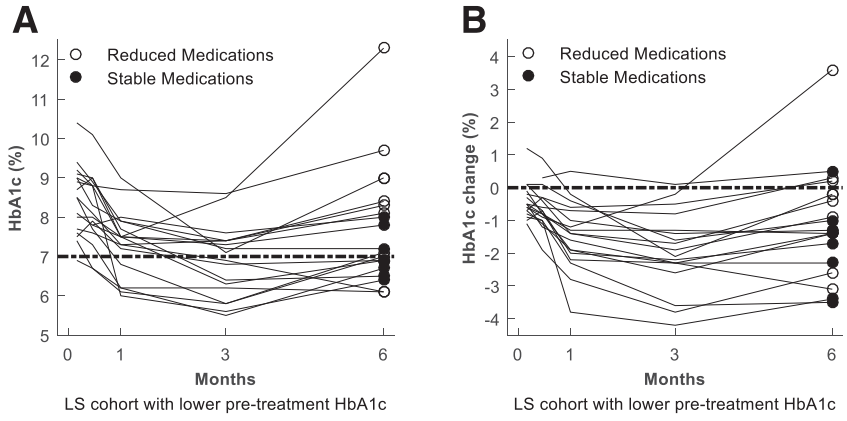

Figure 4—HbA_{1c} in individual subjects who received LS-DMR and had lower (≤10% [86 mmol/mol]) pretreatment HbA_{1c} levels plotted to 6 months (*n* = 18) and displayed as absolute HbA_{1c} levels (hatched line indicates American Diabetes Association treatment goal of 7%) (*A*) and change from pretreatment HbA_{1c} levels (*B*). Individual subject antidiabetic medication status is represented as stable (black circles) or reduced (white circles).

The more precise mechanism through which DMR elicits beneficial metabolic effects likely relates to the pathogenic changes observed in the gut of subjects with type 2 diabetes. The duodenal mucosa becomes abnormal with high fat/hexose feeding (10,21–25), which in turn disturbs local nutrient absorption (26) and neuronal and hormonal signaling (24,25,27). This appears to also involve the overgrowth of certain mucosal cell types, including the K cell (10,23), which is recognized for its glucoregulatory role in secreting the incretin hormone GIP. Duodenal biopsy from humans with diabetes also shows hypertrophy, thickening, and an overgrowth of entero-endocrine cell types (22). In addition, an as yet unidentified factor isolated from proximal intestinal cells may directly impact systemic insulin sensitivity, as myocytes become insulin resistant when exposed in vitro to proteins produced by duodenal/jejunal mucosa from subjects with diabetes (28). Moreover, studies in animals and humans show that duodenal exclusion ameliorates the metabolic disturbance (9,29,30) of type 2 diabetes, and in humans and rats, an intestinal device that prevents nutrient contact with the duodenal mucosa also leads to improvement in metabolic measures (31–33).

The Revita DMR procedure appeared to be safe and well tolerated in this first-in-human trial. The procedure consists of duodenal sizing, saline expansion of the submucosal space, and hydrothermal treatment of the mucosa at denaturation temperatures to ablate superficial layers and trigger a rejuvenative healing response. The DMR procedure is analogous to the commonly performed radiofrequency ablation of the esophagus, where ablation and subsequent healing of esophageal mucosa is used to treat Barrett esophagus and esophageal dysplasia (34,35). DMR treatment targets the mucosal surface of the duodenum distal to the ampulla of Vater and proximal to the ligament of Treitz. There were gastrointestinal symptoms noted postprocedure, but these were transient and of mild or moderate severity. There were no cases of perforation, pancreatitis, or bleeding and no apparent evidence of malabsorption. Three cases of duodenal

stenosis were reported, occurring within 6 weeks of the procedure and presented with epigastric pain and vomiting. All were addressed with endoscopic balloon dilatation with no longer-term sequelae. Since that time, the catheter system has been further optimized to reduce the risk of stenosis, but this is a particular safety event that will require further surveillance. On an additional safety note, DMR does not appear to manifest potential for inducing hypoglycemia within the first 6 months after the procedure, as this complication was not observed in the absence of background hypoglycemic medication use, despite an overall reduction of ambient glycemia.

Any first-in-human study comes with shortcomings, in part because aspects of the intervention are new and untested. That stated, the outcome of this first-in-human study is cautiously optimistic. This unique, single-procedure intervention not only exerts robust effects on glycemia in patients with type 2 diabetes but does so with minimal perturbation to the patient and with a relatively reassuring safety profile to date. The majority of patients were able to receive the full intended ablation, but full ablation with DMR was not feasible in some patients owing to anatomical limitations.

Our findings suggest that minimally invasive upper gastrointestinal intervention through DMR can improve glycemia in type 2 diabetes and represents an interesting potential adjuvant or alternative to pharmacological treatment. The DMR approach may overcome treatment adherence and compliance issues, a major shortcoming of all pharmacological approaches. DMR also provides a window into the intriguing and specific role of the duodenum in regulating downstream metabolism. Further work is necessary to better understand the clinical utility of this procedure-based intervention in controlled trial conditions in larger numbers of patients.

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Duality of Interest. H.R. and J.C. are employees of Fractyl Laboratories, Inc. and own shares in the company. A.D.C. is a scientific advisor/consultant to Biocon, Eli Lilly and Company, Fractyl Laboratories, Inc., Hanmi, Islet Sciences, Merck, Metavention, Novo Nordisk, NuSirt Biopharma, Profil Institute for Clinical Research, Inc., Sensulin, Silver Lake, Thermalin Diabetes, Thetis Pharmaceuticals, vTv Therapeutics, ViaCyte, Viking, and Zafgen; receives research support from Eli Lilly and Company, Merck, Metavention, Novo Nordisk, Silver Lake, and Thermalin Diabetes; and has equity/stock options in Fractyl Laboratories, Inc., Metavention, Sensulin, Thetis Pharmaceuticals, and Zafgen. C.C.T. is a scientific advisor/consultant to Apollo Endosurgery, Covidien, Fractyl Laboratories, Inc., Olympus, and USGI Medical; receives research support from Apollo Endosurgery, Aspire Bariatrics, and USGI Medical; receives laboratory support from Olympus; and has an ownership interest in GI Windows. L.M.K. is a scientific advisor/consultant to Fractyl Laboratories, Inc., GI Dynamics, Janssen, MedImmune, and Novo Nordisk. F.R. is a scientific advisor/consultant to Ethicon, Fractyl Laboratories, Inc., Medtronic, and NGM Biopharmaceuticals and has received speaker honoraria from Sanofi. G.M. is a consultant for Novo Nordisk and Fractyl Laboratories, Inc. and has received research funds from AstraZeneca, Fractyl Laboratories, Inc., and Metacure. P.B., P.R., P.V., and L.R. have received research support from Fractyl Laboratories, Inc. M.P.G.N. serves on the scientific advisory board of and receives research funding from GI Dynamics and Fractyl Laboratories, Inc. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. H.R. participated in the design of the study and the data analysis and wrote, edited, reviewed, and approved the manuscript. A.D.C. and L.M.K. provided critical review of the manuscript and reviewed, edited, and approved the manuscript. C.C.T. and F.R. provided critical review of the manuscript and edited and approved the manuscript. G.M. participated in the design of the study, provided critical review, and edited and approved the manuscript. P.B. and L.R. performed the study procedures and reviewed, edited, and approved the manuscript. P.R. served as study coordinator at the study site, assisted during study procedures, and reviewed, edited, and approved the manuscript. P.V. saw patients at the site for screening and follow-ups, made determinations regarding medication management, and reviewed, edited, and approved the manuscript. J.C. participated in the design of the study, contributed to the manuscript draft, provided critical review, and edited and approved the manuscript. M.P.G.N. performed the study procedures, provided critical review, and edited and approved the manuscript. H.R. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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