Durable Glycemic and Hepatic Improvements After Duodenal Mucosal Resurfacing in Patients With Type 2 Diabetes

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Introduction

- Insulin resistance (IR) and progressive failure of insulin production underlie type 2 diabetes (T2D), which has reached pandemic proportions in Westernized countries[1–3]
- Current pharmacotherapies for T2D require continuous administration, and even with optimal compliance, eventually become insufficient because they do not adequately address pathophysiologic defects underlying IR[4–6]
- High-fat/sugar diets cause hyperplasia of the duodenal lining, altering both hormonal signaling and nutrient absorption from the duodenum, which can lead to abdominal obesity, IR, impaired glucose metabolism, hyperinsulinemia, dyslipidemia, and high blood pressure[7,8]
- Duodenal mucosal resurfacing (DMR) is a novel, minimally invasive, outpatient, endoscopic procedure that uses submucosal lift and hydrothermal ablation of the hyperplastic duodenal mucosa to promote epithelial regrowth and restore insulin sensitivity in patients with T2D[9,10]
  - Primary results from the multicenter, international, open-label, prospective REVITA-1 study demonstrated that a single DMR procedure safely and effectively elicits glycemic improvement over 12 months in patients with suboptimally controlled T2D[11]

Objective

- To study the durability of response through 24 months in patients with T2D who underwent a single DMR procedure in the REVITA-1 study

Methods

Patients

- Aged 28–75 years with T2D, body mass index (BMI) 24–40 kg/m^2, hemoglobin A1c (HbA1c) levels of 59–86 mmol/mol (7.5%–10.0%), and on stable diabetes treatment with ≥ 1 oral glucose-lowering drug for ≥ 3 months at enrollment
- Exclusion criteria included:
  - Clinical diagnosis and/or positive glutamic acid decarboxylase antibodies for type 1 diabetes
  - History of ketoacidosis, low endogenous insulin production (fasting C-peptide levels < 0.333 nmol/L), use of injectable glucose-lowering medication, severe hypoglycemia, autoimmune disease, gastrointestinal (GI) surgery that could impact treatment of duodenum, chronic or acute pancreatitis, active hepatitis or liver disease, upper GI bleeding conditions, or illicit substance use
  - Receiving anticoagulation therapy, P2Y12 inhibitors and/or nonsteroidal anti-inflammatory drugs, corticosteroids, or drugs known to affect GI motility, or taking weight-loss medications
  - Estimated glomerular filtration rate (< 30 mL/min/1.73 m^2) or modification of diet in renal disease, persistent anemia (hemoglobin levels < 10 mg/dL), active systemic infection, or malignancy within ≤ 5 years

REVITA-1 Study Design and DMR Procedure

- REVITA-1 was a multicenter, international, open-label, prospective study of DMR (REVITA®, Fractyl Laboratories, Lexington, MA, USA) efficacy and safety in patients with uncontrolled T2D (NCT02413567) **(Figure 1)**
- Safety endpoints
  - Incidence rate of serious adverse events (SAEs), unanticipated adverse device effects (UADEs), procedure- and device-related SAEs and UADEs, number of events (blood glucose levels < 56 mg/dL [3.1 mmol/L], or requiring third-party assistance)
- Efficacy endpoints
  - Mean change from baseline in HbA1c levels
  - Proportion of patients achieving ≥ 1% reduction in HbA1c levels
  - Overall reduction in HbA1c levels
  - Mean change in fasting blood glucose levels
  - Proportion of patients who achieved a decrease in alanine aminotransferase (ALT)
  - Overall reduction in ALT
  - Change in oral antidiabetic medication use
  - Beta cell function (fasting plasma glucose, fasting plasma insulin, and C-peptide)
- * The need for insulin was determined based on the judgment of the clinical investigators. Specifically, insulin therapy was indicated for patients with an HbA1c > 7.5% and taking ≥ 2 oral glucose-lowering medications (if metformin, patients had to be taking a maximally tolerated dose)
- The primary results at 6 months and durability through 12 months post-procedure have been previously reported[11]
- Here, long-term follow-up results are presented through 24 months post-DMR

DISCLOSURES
ACG van Baar has nothing to disclose. **JC Lopez-Talavera, H Rajagopalan, V Bhambhani,** and **K White** are full-time employees of Fractyl Laboratories Inc., and may hold Fractyl stock and/or stock options. **J Bergman** received research support from Fractyl for IRB-based studies and received a consultancy fee for a single advisory board meeting for Fractyl in September 2019.

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Fractyl participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this poster for submission. All authors had access to the data; participated in the development, review, and approval of the poster to present at the Diabetes Technology Meeting. Fractyl funded the research for this study and provided writing support for this abstract. Medical writing assistance, funded by Fractyl, was provided by Caroline W Cazares, PhD, of JB Ashtin.

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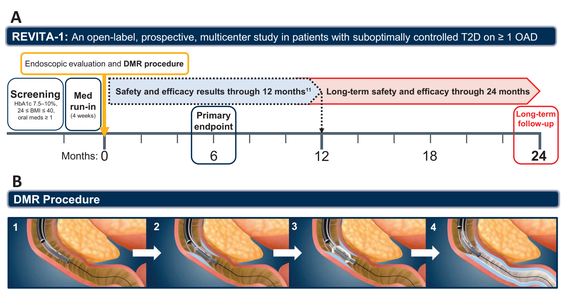
Figure 1. REVITA-1 Study Design and DMR Procedure



(A) REVITA-1 study design schematic. Oral antidiabetic medication run-in 4 weeks prior to DMR. Prescribed medication regimen was not changed at screening, with the exception of discontinuing glucose concentration-independent insulin secretagogues. The medication run-in was used to confirm lack of blood glucose control in conjunction with medication compliance and nutritional counseling. Glucose lowering medication was kept stable for 6 months post-DMR, thereafter protocoled medication changes based on HbA1c levels were allowed. (B) DMR procedure schematic. DMR was performed as previously described[9–11] Briefly, under general anesthesia or conscious sedation, the Revita DMR catheter was placed in the proximal duodenum distal to the papilla using a guidewire (Step 1). Then, the balloon was inflated, and the vacuum drew the intestinal mucosal tissue onto the ports on the balloon, and the console delivered saline into the submucosa through the needles within the lumens of the catheter to create a complete circumferential lift of the mucosa (Step 2). The ablation cycle was started, and hot water was then circulated into the balloon to ablate the previously expanded tissue (Step 3). The balloon was deflated, and the process of expansion, ablation, and repositioning was repeated distally until the needed length of duodenum was treated. Finally, the catheter and endoscope were removed (Step 4). BMI = body mass index; DMR = duodenal mucosal resurfacing; DTM = Diabetes Technology Meeting; HbA1c = hemoglobin A1c; OAD = oral antidiabetic drug; T2D = type 2 diabetes.

Statistical Analysis

- A 2-sided paired student's *t* test was used to assess significance between baseline and 24 months for HbA1c and ALT levels at the 0.05 level
- Mean (standard deviation [SD]) was calculated for continuous variables, and n (%) was calculated for categorical variables
- Per-protocol (PP) population, defined as a complete circumferential mucosal ablation ≥ 9 cm, was the analysis population

RESULTS

Patients

- A total of 34 patients underwent complete DMR PP **(Table 1)**
- At baseline, mean (SD):
  - Age was 56.2 (7.6) years
  - Diabetes duration was 6.5 (2.4) years
  - HbA1c was 8.5% (0.7)
  - ALT was 38.1 (21.1) mg/dL

Table 1. Demographics and Baseline Characteristics (PP Population)

Parameter	DMR (N = 34)
Age, years	56.2 (7.6)
Diabetes duration, years	6.5 (2.4)
Weight, kg	n = 31 88.9 (11.8)
BMI, kg/m^2	n = 31 30.4 (3.7)
HbA1c	8.5 (0.7)
Fasting glucose, mg/dL	n = 33 198.4 (41.2)
Fasting insulin, pmol/L	n = 30 16.7 (9.9)
C-peptide, nmol/L	n = 12 3.1 (1.3)
HOMA-IR	n = 30 8.6 (5.9)
ALT, mg/dL	38.1 (21.1)
Oral antidiabetic medication, n (%)	
Metformin	31 (91)
Meglitinide	2 (4)
DPP-4 inhibitor	8 (24)
SGLT-2 inhibitor	6 (18)

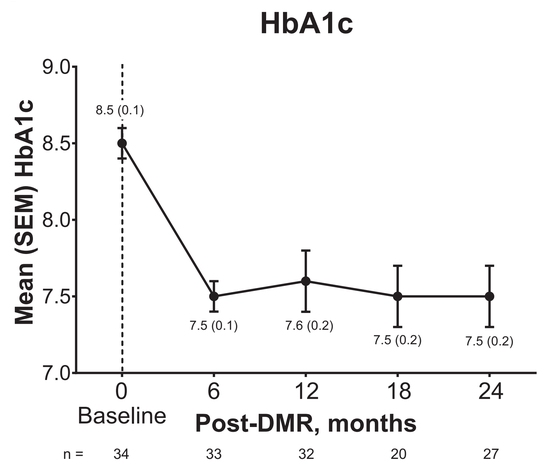
Data are presented as mean (SD), unless otherwise noted. *Three patients had major protocol deviations between 12 and 24 months post-follow-up and were excluded from the PP population and 1 patient that was excluded from the previously reported 12-month data[11] due to medication adherence was included in this 24-month analysis. Therefore, a difference of 2 patients exists between the 12-month analysis and this 24-month analysis. ALT = alanine aminotransferase; BMI = body mass index; DMR = duodenal mucosal resurfacing; DPP-4 = dipeptidyl peptidase-4; HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment of insulin resistance; SD = standard deviation; SGLT-2 = sodium-glucose Cotransporter-2.

Efficacy

Reduction in glycemic parameters sustained through 24 months post-DMR

- Glycemic indices improved immediately post-DMR and HbA1c levels reached 7.5% (0.8) at 6 months
- The reduction in HbA1c levels was maintained through 24 months with mean HbA1c levels of 7.5% at 24 months post-DMR (n = 27; *P* = 0.0020; **Figure 2**)
- HbA1c levels were stable between 12 and 24 months
- At 24 months post-DMR, the mean (SD) fasting glucose level was 165.9 (41.6) mg/dL (n = 28)

Figure 2. Mean HbA1c Reduction

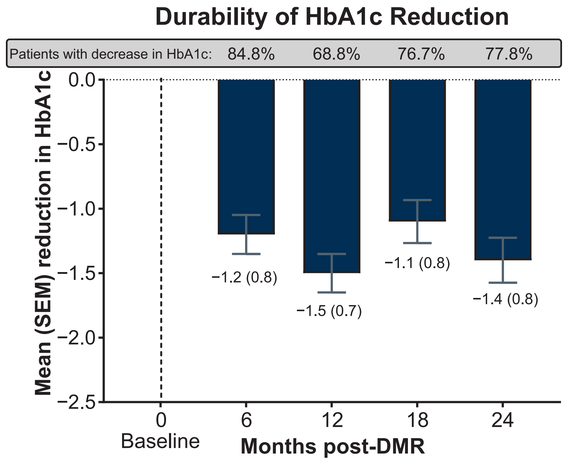


DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; SEM = standard error of the mean.

Durability of HbA1c reduction

- After a single DMR procedure, approximately 80% of patients experienced an improvement in HbA1c levels by month 6, which persisted through 12 months **(Figure 3)**
  - 90% of patients with an HbA1c improvement from baseline at 12 months maintained that improvement to 24 months; mean reduction was 1.4% at 24 months **(Table 2)**
- This analysis demonstrated an improvement in glucose control at 24 months in a high proportion of patients who underwent a single DMR procedure

Figure 3. Durability of HbA1c Response Through 24 Months



Responders were defined as patients with any improvement from baseline in HbA1c levels at any given time point. DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; SEM = standard error of the mean.

Table 2. Durability of Response to DMR in Patients With Improvement in HbA1c (PP Population)

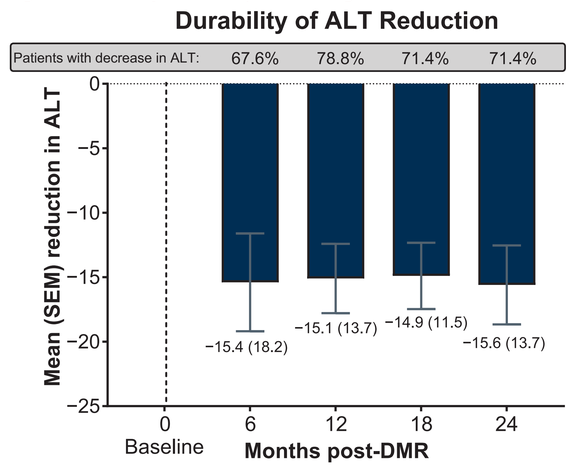
Patients with HbA1c improvement from baseline at:	Magnitude of improvement from baseline (N = 34)	
	n/N (%)	Mean (SD)
6 months	28/33 (84.8)	–1.2 (0.8)
Maintained at 12 months	20/26 (76.9)	–1.5 (0.7)
12 months	22/32 (68.8)	–1.5 (0.7)
Maintained at 18 months	17/20 (85.0)	–1.3 (0.8)
Maintained at 24 months	18/20 (90.0)	–1.5 (0.8)
18 months	23/30 (76.7)	–1.1 (0.8)
Maintained at 24 months	17/20 (85.0)	–1.4 (0.8)
24 months	21/27 (77.8)	–1.4 (0.8)

DMR = duodenal mucosal resurfacing; HbA1c = hemoglobin A1c; PP = per-protocol; SD = standard deviation.

ALT reduction sustained through 24 months post-DMR

- Approximately 75% of patients experienced a reduction in ALT levels after a single DMR procedure by 6 months, which was maintained through 24 months **(Figure 4)**
  - 24 months post-DMR, mean ALT was 32.5 (22.1) U/L (N = 28; *P* = 0.0127)
- Roughly half of the treated patients had a "normal" ALT at baseline (average 38 mg/dL)
- Reductions in ALT levels in treatment responders persisted, suggesting sustained and meaningful reduction in liver injury and inflammation through 24 months post-DMR

Figure 4. Durability of ALT Response Through 24 Months



Responders were defined as patients with any improvement from baseline in ALT levels at any given time point. Roughly 33% of patients entered the study with "normal" ALT levels. ALT = alanine aminotransferase; DMR = duodenal mucosal resurfacing; SEM = standard error of the mean.

- 71.4% of patients experienced an improvement in ALT levels from baseline to 18 months; of those responders, 16 (84%) maintained that improvement at 24 months **(Table 3)**

Table 3. Durability of Response to DMR in Patients With Improvement in ALT Levels (PP Population)

Patients with ALT improvement from baseline at:	Magnitude of improvement from baseline	
	n/N (%)	Mean (SD)
6 months	23/34 (67.6)	–15.4 (18.2)
Maintained at 12 months	20/23 (87.0)	–18.2 (14.2)
12 months	26/33 (78.8)	–15.1 (13.7)
Maintained at 18 months	18/23 (78.3)	–15.8 (11.7)
18 months	20/28 (71.4)	–14.9 (11.5)
Maintained at 24 months	16/19 (84.2)	–17.9 (14.5)
24 months	20/28 (71.4)	–15.6 (13.7)

ALT = alanine aminotransferase; DMR = duodenal mucosal resurfacing; PP = per-protocol; SD = standard deviation.

Oral antidiabetic medication use and beta cell function

- In most patients (68%), oral antidiabetic medication use remained stable (13/31)[a] or decreased (8/31)[a] from screening at 2 years post-DMR
- Almost 50% (14/31)[a] of patients had an indication for insulin treatment at screening, whereas only 16% (5/31)[a] used insulin at 24 months*
- Beta cell function was assessed 2 years post-DMR **(Table 4)**

[a]Medication use was unknown for 3 patients who were not included in these analyses.

Table 4. Beta Cell Function 2 Years Post-DMR (PP Population)

Parameter	n/N	Mean (SD) change from baseline
Fasting plasma glucose, mg/dL	27/34	–34.7 (36.0)
Fasting plasma insulin, IU/mL	24/34	2.7 (17.6)
C-peptide, ng/mL	11/34	–0.7 (1.0)

DMR = duodenal mucosal resurfacing; PP = per-protocol; SD = standard deviation.

Safety

- No device- or procedure-related adverse events or unanticipated adverse device events were noted between 12 and 24 months post-DMR

Conclusions

- **Disease modification in patients with T2D can be achieved with a single DMR procedure, as demonstrated by durable glycemic and hepatic improvements that persisted through 24 months**
  - **> 80% of patients who experience an improvement in glycemic and/or hepatic parameters at 12 months after a single DMR procedure maintain improvements through 24 months post-procedure**
  - **HbA1c improvements are clinically relevant, with 1%–1.5% reductions through 24 months**
  - **ALT reductions over 24 months suggest additional benefit of DMR on biomarkers of nonalcoholic fatty liver disease**
- **In summary, DMR is a potentially favorable and durable treatment option for patients with T2D and/or nonalcoholic fatty liver disease**

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