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Durable metabolic improvements 2 years after duodenal mucosal resurfacing (DMR) in patients with type 2 diabetes (REVITA-1 Study)

Annieke C.G. van Baar[a], *Jacques Devière*[b], *David Hopkins*[c], *Laurent Crenier*[d], *Frits Holleman*[e], *Manoel P. Galvão Neto*[f], *Pablo Becerra*[g], *Paulina Vignolo*[g], *Leonardo Rodriguez Grunert*[g], *Geltrude Mingrone*[h,i], *Guido Costamagna*[h,j], *Max Nieuwdorp*[k], *Caterina Guidone*[l], *Rehan J. Haidry*[m], *Bu Hayee*[c], *Cormac Magee*[m,n], *Juan Carlos Lopez-Talavera*[o], *Kelly White*[o], *Vijeta Bhambhani*[o], *Emily Cozzi*[o], *Harith Rajagopalan*[o], *Jacques J.G.H.M. Bergman*[a,*]

[a] *Gastroenterology and Hepatology, Amsterdam University Medical Centers, Academic Medical Center, Amsterdam, the Netherlands*
[b] *Gastroenterology, Erasme UnCiversity Hospital, Brussels, Belgium*
[c] *Institute of Diabetes, Endocrinology, and Obesity, King's Health Partners, London, UK*
[d] *Department of Endocrinology, Erasme University Hospital, Brussels, Belgium*
[e] *Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands*
[f] *Bariatric Endoscopy Service, Gastro Obeso Center, Sao Paulo, Brazil*
[g] *CCO Clinical Center for Diabetes, Obesity and Reflux, Santiago, Chile*
[h] *Fondazione Policlinico Universitario A. Gemelli IRCCS - Università Cattolica del Sacro Cuore, Rome, Italy*
[i] *Department of Diabetes, School of Life Course Sciences, King's College London, London, UK*
[j] *Università Cattolica del Sacro Cuore, Rome, Italy*
[k] *Internal and Vascular Medicine, Amsterdam University Medical Centers, location AMC, Amsterdam, the Netherlands*
[l] *Internal Medicine, Fondazione Policlinico A. Gemelli IRCSS, Rome, Italy*
[m] *Department of Gastroenterology, University College Hospital, London, UK*
[n] *Center for Obesity Research, Department of Medicine, University College London, London, UK*
[o] *Fractyl Laboratories Inc, Lexington, MA, USA*

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ABSTRACT

Aims: Duodenal mucosal resurfacing (DMR) is an endoscopic procedure developed to improve metabolic parameters and restore insulin sensitivity in patients with diabetes. Here we report long-term DMR safety and efficacy from the REVITA-1 study.

Materials and Methods: REVITA-1 was a prospective, single-arm, open-label, multicenter study of DMR feasibility, safety, and efficacy in patients with type 2 diabetes (hemoglobin A1c [HbA1c] of 7.5–10.0% (58–86 mmol/mol)) on oral medication. Safety and glycemic (HbA1c), hepatic (alanine aminotransferase [ALT]), and cardiovascular (HDL, triglyceride [TG]/HDL ratio) efficacy parameters were assessed (*P* values presented for LS mean change).

Results: Mean ± SD HbA1c levels reduced from 8.5 ± 0.7% (69.1 ± 7.1 mmol/mol) at baseline ($N = 34$) to 7.5 ± 0.8% (58.9 ± 8.8 mmol/mol) at 6 months ($P < 0.001$); and this reduction was

* Corresponding author at: Amsterdam University Medical Centers, location Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands.
E-mail address: j.j.bergman@amsterdamumc.nl (J. J.G.H.M. Bergman).

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sustained through 24 months post-DMR (7.5 ± 1.1% [59.0 ± 12.3 mmol/mol], $P < 0.001$) while in greater than 50% of patients, glucose-lowering therapy was reduced or unchanged. ALT decreased from 38.1 ± 21.1 U/L at baseline to 32.5 ± 22.1 U/L at 24 months ($P = 0.048$). HDL and TG/HDL improved during 24-months of follow-up. No device- or procedure-related serious adverse events, unanticipated device effects, or hypoglycemic events were noted between 12 and 24 months post-DMR.

Conclusions: DMR is associated with durable improvements in insulin sensitivity and multiple downstream metabolic parameters through 24 months post-treatment in type 2 diabetes.

Clinical trial reg. no. NCT02413567, clinicaltrials.gov.

1. Introduction

Type 2 diabetes mellitus (T2D) is considered a multiorgan metabolic disease hallmarked by impaired beta cell function and insulin signaling, dyslipidemia, inflammation, and incretin resistance [1]. Insulin resistance in peripheral tissues is initially compensated for by increased insulin production to maintain normoglycemia; as T2D progresses, beta cells can no longer compensate for insulin resistance, leading to impaired glucose homeostasis and multiorgan complications [1–4].

Unfortunately, most patients with T2D do not achieve optimal glycemic control with lifestyle interventions alone and thus require pharmaceutical intervention. Twelve different drug classes are approved by the US Food and Drug Administration to treat T2D, including medications that increase pancreatic insulin secretion, peripheral tissue insulin sensitivity, and glycosuria to reduce hyperglycemia [1]. Despite available options, T2D progressively worsens in most patients, with about 25% eventually requiring insulin therapy to maintain glycemic control [5,6]. Furthermore, less than half of patients are able to maintain adequate glycemic control over the long term with current treatment options [7]. Active treatment with daily (or weekly) administration is a requirement with current available T2D therapies, since beta cell function deteriorates and hyperglycemia returns upon therapy withdrawal [8,9]. Durable, disease-modifying, and adherence-independent therapeutic interventions for T2D are urgently needed.

Hyperplasia of the duodenal lining induced by a high-fat and high-sugar diet alters hormone signaling and nutrient absorption from the duodenum, which can lead to dysmetabolic states, including abdominal obesity, insulin resistance, impaired glucose metabolism, hyperinsulinemia, dyslipidemia, and hypertension [10,11]. Moreover, surgical bypass of the duodenum (e.g., Roux-en-Y gastric bypass) in patients with T2D drastically and immediately improves the metabolic profile of patients in a weight-independent manner. These observations point to the duodenum as a key signaling center that regulates metabolic homeostasis and underlines its importance as a treatment target for metabolic diseases [12].

Duodenal mucosal resurfacing (DMR) is a novel, minimally invasive, outpatient, endoscopic procedure designed to promote mucosal regeneration and restore insulin sensitivity in patients with metabolic diseases [8,9,13]. Results from the first-in-human study demonstrated that DMR is feasible and safely improves glycemic parameters in patients with T2D [14,15]. Primary results from the multicenter, international, open-label, single-arm, prospective REVITA-1 study demonstrated that a single DMR procedure safely elicits durable and clinically relevant glycemic and hepatic improvements over 12 months post-treatment in patients using oral glucose-lowering medication with suboptimally controlled T2D [16]. Here we report follow-up results through 24 months post procedure, to further evaluate the long-term safety and durability of DMR.

2. Subjects

Eligible patients were aged 28 to 75 years with T2D diagnosed within the last 10 years, BMI 24 to 40 kg/m^2, hemoglobin A1c (HbA1c) levels of 7.5 to 10.0% (59 to 86 mmol/mol), and stable diabetes treatment with $\geq$ 1 oral glucose-lowering drug for $\geq$ 3 months at enrollment [16]. Patients were excluded if they had a clinical diagnosis of type 1 diabetes and/or positive glutamic acid decarboxylase antibodies, low endogenous insulin production (fasting C-peptide levels < 0.333 nmol/L), if they used injectable glucose-lowering medication (e.g., glucagon-like peptide-1 analogues or insulin), had undergone gastrointestinal surgery that could impact treatment of duodenum, had chronic or acute pancreatitis, active hepatitis or liver disease, or upper GI bleeding conditions. The complete list of eligibility criteria is provided in **supplementary Table 1**. All patients provided written informed consent at screening.

3. Materials and methods

3.1. *Study design and treatment*

REVITA-1 was a multicenter, international, open-label, prospective, single-arm study of DMR feasibility, safety, and efficacy in patients with uncontrolled T2D (**Supplementary Fig. 1**) [16]. The study was conducted across seven sites in the Netherlands, Belgium, Italy, United Kingdom, and Chile in accord with Good Clinical Practice Guidelines as defined by the International Conference on Harmonization, The Declaration of Helsinki, and all applicable national, state, and

local regulations and respective Independent Ethics Committees, as appropriate. The REVITA-1 study is registered at clinicaltrials.gov (NCT02413567).

3.2. Procedure

The DMR procedure was performed as previously described (Supplementary Fig. 2) [14–16].

3.3. Assessments

3.3.1. Safety

The safety end points assessed were the incidence of serious adverse events (SAEs), unexpected adverse device effects (UADEs), procedure- and device-related SAEs and UADEs, and hypoglycemic events (blood glucose levels < 56 mg/dL [3.1 mmol/L] or requiring third-party assistance) reported from screening through 24 months post-DMR. The SAEs were defined as adverse events that lead to death, serious deterioration in health, or fetal distress, congenital abnormality, or birth defect. The UADEs were defined as any serious adverse effects on health or safety, caused any life-threatening problem, or resulted in death caused by or associated with the device not previously identified. Treatment-emergent adverse events, defined as events that started or worsened in severity after start of the procedure, were also assessed through 24 months post-DMR by device/procedure relatedness and severity. Adverse events were assessed as procedure related or device related by the local investigator (**Supplementary Table 2**).

3.3.2. Efficacy

To assess the long-term impact of DMR on glycemic parameters, the change from baseline in HbA1c (determined by high-performance liquid chromatography [HPLC]), fasting plasma glucose (FPG), fasting plasma insulin (FPI), C-peptide (determined using a radioimmunoassay [RIA]), homeostatic model assessment of insulin resistance (HOMA-IR), and weight were assessed through 24 months post-DMR. To assess the long-term impact of DMR on hepatic parameters, the change from baseline in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were assessed. To assess the long-term impact of DMR on markers of cardiovascular health, the change from baseline in triglycerides (TG), HDL, LDL, TG/HDL ratio, total cholesterol, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were evaluated.

Oral medication used to lower glucose levels was managed as previously described throughout 24 months post-DMR.[16] Briefly, the regimen for oral glucose-lowering medication that was established during the run-in period was continued without change until the 24-week follow-up visit, unless rescue therapy was required (**Supplementary Table 4**). At each follow-up visit, the number of prescriptions for diabetes medication and the number of tablets per day was recorded. Change in diabetes medication compared with the original medication prescribed at baseline (increased, decreased, or unchanged) was assessed. Per protocol, there was an indication for insulin therapy in case of HbA1c levels $\geq$ 7.5% (58 mmol/mol) despite patient's taking $\geq$ 2 oral glucose-lowering medications (if metformin, patients had to be taking the highest tolerable dose).

Change from baseline in patient-perceived satisfaction was assessed at 12 and 24 months post-DMR using the diabetes treatment satisfaction questionnaire status (DTSQs) scale [17].

3.4. Statistical analysis

The number of patients was based on medical and procedural considerations. The initial study closed at 49 patients when the DMR procedure had matured to a level for initiating a sham-controlled study. Analysis revealed that 49 patients was sufficient to detect a significant difference in HbA1c at 24 weeks (primary efficacy endpoint) [16]. The primary analysis population was considered the per-protocol (PP) population, which included patients who received a full DMR procedure (five complete ablations or circumferential mucosal ablation 9–10 cm) and excluded patients with major protocol deviations. The safety population included all treated patients. "Treatment durability" was defined as any patient who experienced a measured reduction from baseline at 6 months and maintained reduction (from baseline) at 24 months. A "responder" was defined as any improvement from baseline at the subsequent timepoints (i.e. 12 months, 24 months). An assessment of increases, decreases, and stable glucose lowering medications was conducted in the PP population. Analyses were completed in patients with follow-up data at each time point assessed (in contrast to our previous report, where missing data was imputed) [16]. A mixed model with repeated measures was used to assess significance between baseline and 24 months at the 0.05 level for parameters except DTSQ. A paired *t* test was used to assess statistical significance between baseline and 24 months at the 0.05 level for the DTSQ parameter. Mean ± SDs were calculated for continuous variables, and n (%) was calculated for categorical variables. HOMA-IR was calculated as (FPG (mg/dL)*fasting insulin (μIU/mL))/22.5. Due to the exploratory nature of the study, there was no imputation of missing data. *P* values are presented for least squares (LS) mean change from baseline for continuous variables. Statistical analyses were performed using Statistical Analysis Software version 9.4 or higher (SAS institute, Inc., Cary, NC, USA).

4. Results

4.1. Patients

As previously reported, the DMR procedure was completed in 37 of 46 patients treated. In this analysis, 33 patients were included in the PP population analysis at 6 months and 32 patients were included in the PP population analysis at 12 months post-DMR. At 24 months post-DMR, 27 patients were in the PP population (Fig. 1). Three patients were excluded from the 24-month PP population analysis due to major protocol deviations between 12 and 24 months post-DMR. Due to intermittent insulin use during the first months after DMR, 1 patient was excluded from the initial 12-month PP analysis since this interfered with the end points during

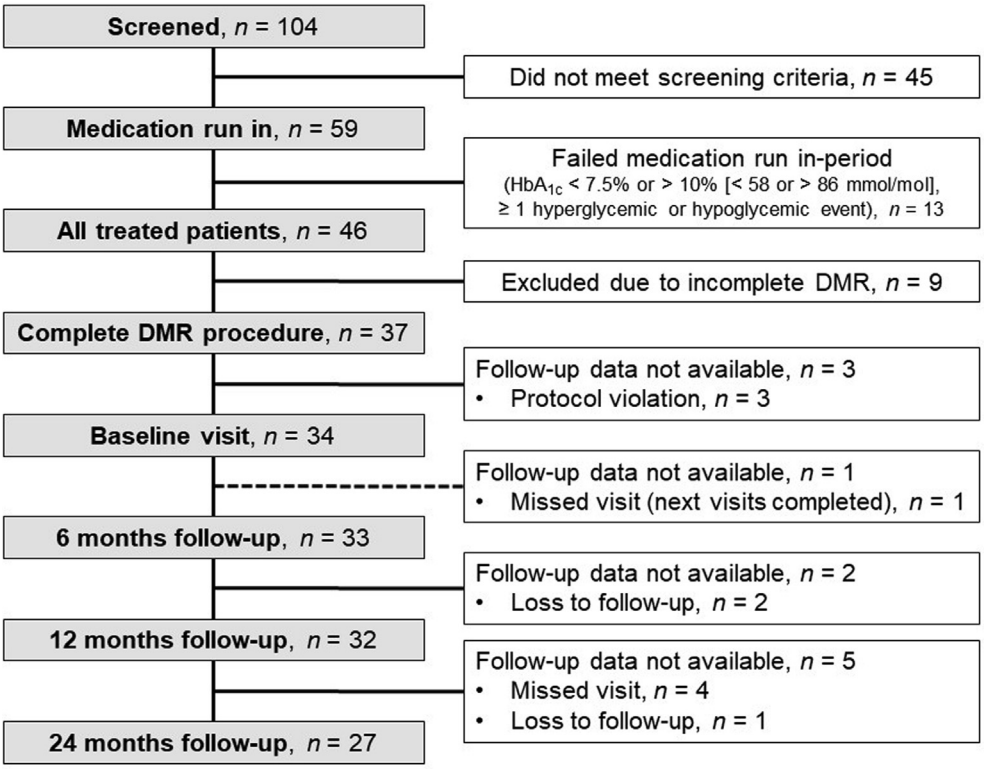

Fig. 1 – Patient disposition. **A total of 46 patients were treated (safety population), the DMR procedure was completed in 37 patients, 36 patients were in the PP population at 12 months post-DMR, and 34 patients remained in the PP population at 24 months post-DMR. Three patients were excluded due to major protocol deviations between 12 and 24 months post-DMR. One patient who was excluded from the 12-month PP analysis due to medication adherence was included here.**

this first year. Since this did not interfere with end points during the second year, this patient was included in the 24-month PP analysis (Supplementary Fig. 3).

Most patients in the PP population were male (64.7%) with a mean ± SD age of 56.2 ± 7.6 years, a mean T2D duration of 6.5 ± 2.4 years, and a mean BMI of 30.4 ± 3.7 kg/m^2 (Table 1). At baseline in the PP population, HbA1c was 8.5 ± 0.7% (69.1 ± 7.1 mmol/mol), FPG was 198.4 ± 41.2 mg/dL (11.0 ± 2.3 mmol/L), FPI was 16.7 ± 9.9 mU/L (116.1 ± 68.6 pmol/L), fasting C-peptide was 3.1 ± 1.3 ng/mL (1.0 ± 0.4 nmol/L), and HOMA-IR was 8.6 ± 5.9. Mean baseline liver parameters were within the normal range with ALT and AST reported as 38.1 ± 21.1 U/L and 26.7 ± 9.6 U/L, respectively. Baseline SBP and DBP were 136.2 ± 17.1 mmHg and 84.6 ± 9.9 mmHg, respectively. Mean TG levels were 193.9 ± 122.1 mg/dL (2.2 ± 1.4 mmol/L) and the mean TG/HDL ratio was 5.0 ± 3.9 mg/dL (2.2 ± 1.7 mmol/L).

4.2. *Safety*

The long-term safety findings from the REVITA-1 trial indicate that the DMR procedure was safe and well-tolerated. In the safety population (N = 46), between 6 and 24 months post-DMR, two patients (4.3%) reported treatment-emergent adverse events that were deemed possibly related to the study procedure (one patient reported constipation, and one patient reported general malaise and vitamin B_{12} deficiency), all of which were deemed mild in severity **(Supplementary Table 2)**. No device- or procedure-related SAEs or UADEs or hypoglycemic events were observed between 6 and 24 months (**Supplementary Table 3**). There were 6 patients who had a total of 7 non-device- and procedure-related SAEs between 6 and 24 months (dyspnea, lung adenocarcinoma, arteriosclerosis, severe back pain pilonidal cyst, bradycardia and joint dislocation).

4.3. *Efficacy*

4.3.1. *Treatment efficacy*

Following a single DMR procedure, HbA1c was significantly reduced at 6 months post-DMR (mean ± SD raw change from baseline; –0.9 ± 0.9 % [–10 ± 10 mmol/mol], $P < 0.001$) (Fig. 2**A**). Approximately 53% of patients in the PP population had no change or a decrease in oral glucose-lowering medication from 6 to 24 months post-DMR (Fig. 3) and only 11.8% (4/34) were using insulin at 24 months post-DMR, despite the fact that more than 40% had an indication for insulin at study entry. Taking these medication changes into account, significant reductions in HbA1c were sustained at 12 months ($P = 0.001$) and 24 months ($P = 0.034$) post-DMR, with mean ± SD raw change from baseline of –0.8 ± 1.2% (–9 ± 13 mmol/mol) and –0.8 ± 1.3% (–9 ± 14 mmol/mol), respectively (Fig. 2**A**). There were 27.3% (9/33) who reached a target HbA1c of less than or equal to 7% at the 6-month primary endpoint, 40.6% (13 of 32) who reached a target HbA1c of less than or equal to 7% at 12 month follow up and 33.3% (9 of 27) who

Table 1 – Demographics and baseline characteristics (PP population).

Characteristic	DMR (N = 34)
Age, years	56.2 (7.6)
Sex, *n* (%)	
Female	12 (35.3)
Male	22 (64.7)
Duration of type 2 diabetes, 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 plasma insulin, IU/mL (*n* = 30)	16.7 (9.9)
Fasting C-peptide, ng/mL (*n* = 12)	3.1 (1.3)
HOMA-IR (*n* = 30)	8.6 (5.9)
ALT, U/L	38.1 (21.1)
AST, U/L (*n* = 33)	26.7 (9.6)
Glucose-lowering medications, *n* (%)	
1	
2	26 (76.5)
3	7 (20.6)
	1 (2.9)
Oral glucose-lowering medication, *n* (%)	
Metformin	31 (91.0)
Meglitinide	2 (4.0)
DPP-4 inhibitor	8 (24.0)
SGLT-2 inhibitor	6 (18.0)
DTSQs	27.5 (6.6)
SBP at screening, mmHg	136.2 (17.1)
DBP at screening, mmHg	84.6 (9.9)
TG, mg/dL	193.9 (122.1)
HDL, mg/dL	42.4 (9.2)
LDL, mg/dL	95.8 (28.9)
TG/HDL	5.0 (3.9)
TC, mg/dL	169.8 (37.0)

Data are presented as mean (SD), unless otherwise noted.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; DBP = diastolic blood pressure; DMR = duodenal mucosal resurfacing; DPP-4 = dipeptidyl peptidase-4; DTSQ = diabetes treatment satisfaction questionnaire; HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment of insulin resistance; PP = per-protocol; SBP = systolic blood pressure; SGLT-2 = sodium-glucose cotransporter-2; TC = total cholesterol; TG = triglycerides.

reached a target HbA1c of less than or equal to 7% at 24 month follow up. At 6 months, 84.8% (28/33) of patients were responders with a mean (±SD) reduction in HbA1c of –1.2 ± 0.8% (–12.9 ± 8.3 mmol/mol) and at 24 months, 86.4% (19/22, 6 patients had missing data) of these patients had treatment durability in glycemic improvement with a mean (±SD) HbA1c reduction of –1.4 ± 0.8% (–15.8 ± 8.5 mmol/mol) ($P < 0.001$) (Table 2). At 24 months, 77.8% of the overall PP population (21/27) were responders with a mean (±SD) HbA1c reduction of 1.4 ± 0.8% (–14.9 ± 8.6 mmol/mol).

FPG was durably reduced over 24 months post-DMR. Significant reductions in FPG were sustained at 6 ($P < 0.001$), 12 ($P < 0.001$), and 24 ($P < 0.001$) months post-DMR; mean ± SD raw change from baseline was –37.3 ± 47.8 mg/dL (–2.1 ± 2.7 mmol/mol), –43.8 ± 44.5 mg/dL (–2.4 ± 2.5 mmol/mol), and –34.7 ± 36.0 mg/dL (–1.9 ± 2.0 mmol/mol), respectively (Fig. 2**B; Supplementary Table 5**).

HOMA-IR was significantly decreased at 6 ($P = 0.012$) and 12 ($P < 0.001$) months post-DMR, with mean ± SD raw change from baseline of –2.9 ± 6.5 and –3.7 ± 5.4, respectively, but was not significant at 24 months (mean ± SD raw change from baseline of 0.1 ± 8.8 ($P = 0.386$) (Fig. 2**C**). Of those that were responders at 6 months, 66.7% of these patients (16/24) had treatment durability at 24 months with a mean (±SD) HOMA-IR reduction of 4.5 ± 4.9.

C-peptide levels were significantly reduced from baseline at 6, 12, and 24 months post-DMR ($P = <0.001$, $P = 0.04$, $P = 0.011$, respectively). Mean ± SD raw change from baseline in C-peptide was –0.8 ± 1.1 ng/mL at 6 months, –0.5 ± 1.2 ng/mL at 12 months, and –0.7 ± 1.0 ng/mL at 24 months (Fig. 2**D; Supplementary Table 5**).

FPI levels did not change significantly from baseline at 24 months post-DMR **(Supplementary Table 5)**.

4.3.2. *Treatment satisfaction*

Mean ± SD DTSQs scores increased from 27.5 ± 6.6 at baseline to 31.1 ± 5.3 ($P = 0.0039$) at 12 months and to 30.1 ± 6.1 ($P = 0.0699$ vs. baseline) at 24 months post-DMR, indicative of an overall improvement in patient-perceived treatment satisfaction post-DMR.

4.3.3. *Weight*

Mean ± SD weight was significantly changed from 88.9 ± 11.8 kg at baseline to 88.1 ± 12.4 kg at 12 months and to 89.3 ± 12.6 kg at 24 months post-DMR (mean ± SD raw change from baseline, –2.6 ± 3.7 kg, $p < 0.001$ and –3.1 ± 6.0 kg, $p = 0.010$, 12 months and 24 months, respectively).

4.3.4. *Hepatic parameters*

ALT levels in the overall population were significantly reduced from baseline at 12 months ($P < 0.005$) and 24 months ($P = 0.048$) post-DMR (mean ± SD raw change from baseline, –10.2 ± 15.8 U/L and –8.5 ± 16.8 U/L, respectively). These reductions in ALT levels from baseline were more evident and significant at all timepoints post-DMR ($p < 0.001$) in those patients that had elevated ALT at baseline (ALT $\geq$ 40 U/L) (Fig. 2**E**). Treatment durability was seen at 24 months in 71.4% (20/28) of the patients who responded at 6 months with a mean (±SD) ALT decrease of 15.6 ± 13.7 U/L from baseline (Table 2).

Following a similar pattern to those observed with ALT, the AST mean ± SD raw change from baseline, was – 3.7 ± 8.0 U/L at 6 months ($P = 0.033$), to – 5.7 ± 6.7 U/L at 12 months ($P < 0.001$), and to – 3.5 ± 9.9 U/L at 24 months post-DMR ($P = 0.914$). Treatment durability was seen at 24 months in 73.7% (14/19) of the patients who responded at 6 months with a mean (±SD) AST decrease of 9.6 ± 5.1 U/L from baseline (Table 2).

4.3.5. *Markers of CVD risk*

Mean HDL levels were significantly increased at all timepoints. HDL mean ± SD raw change from baseline to 24 months post-DMR was 6.4 ± 14.4 mg/dL, $P = 0.037$ (**Supplementary Table 5**). Mean TG/HDL ratios changed accordingly, but mean change in LDL, total cholesterol, and TG levels at 24 months post-DMR were not statistically altered. No signif-

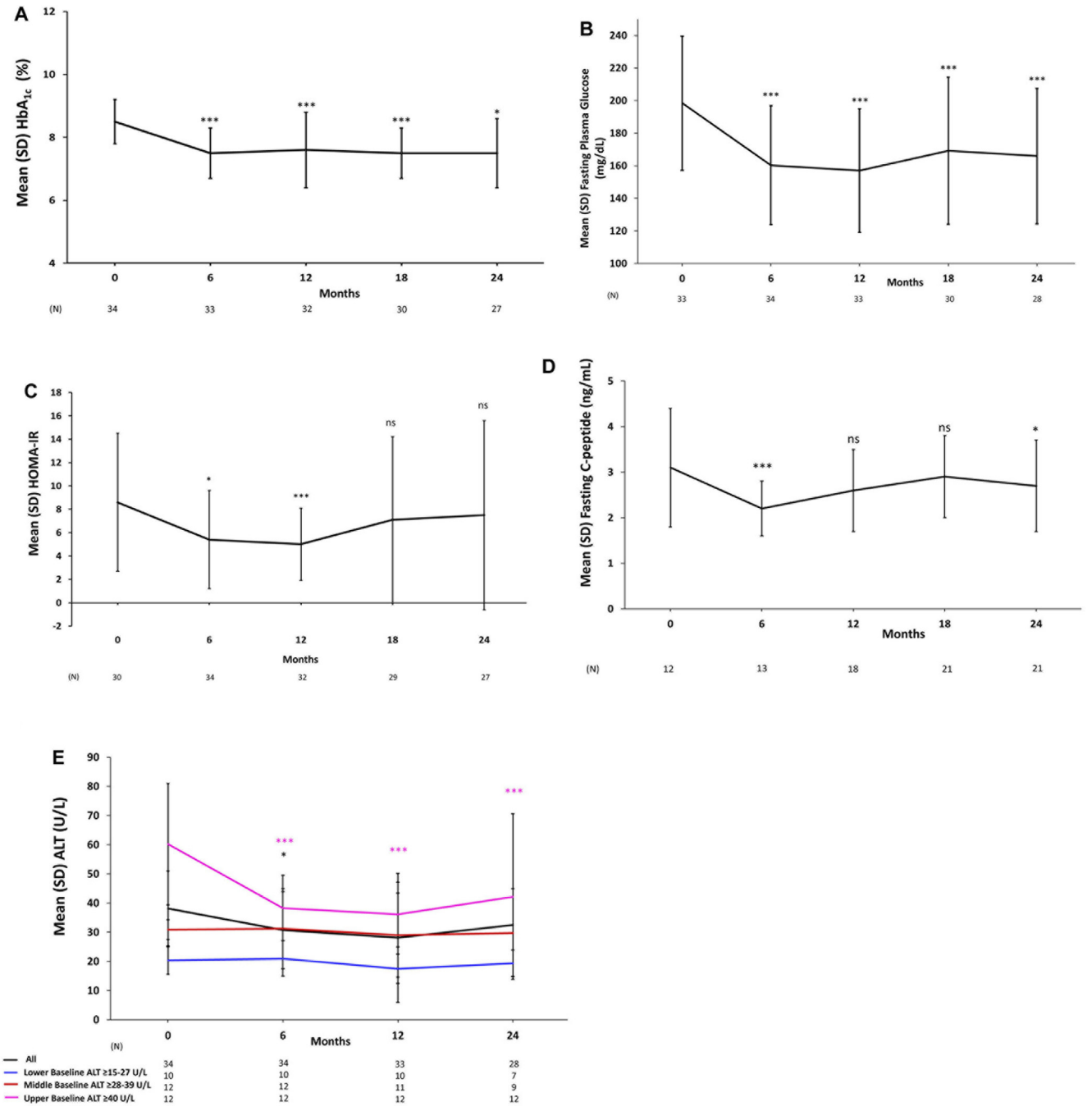

Fig. 2 – Durability of reductions in metabolic biomarkers through 24 months post-DMR. A: HbA1c (%). B: Fasting plasma glucose (mg/dL). C: HOMA-IR. D: C-peptide (ng/mL). E: ALT (U/L). All values represent the complete DMR cohort of 34 patients. Upper baseline ALT *n* = 10; Middle baseline ALT *n* = 12; Lower baseline ALT *n* = 12. *P* values are derived from Least Squares (LS) mean change from baseline from analysis of variance for repeated measures. Data presented as mean ± standard deviation. *P < 0.05, **P < 0.01; ***P < 0.001.

icant differences were observed in SBP or DBP from baseline at 24 months post-DMR.

5. Discussion

In this 24-month uncontrolled extension study we demonstrated the long-term safety and tolerability of the DMR procedure in patients with T2D. Our data suggest that over half of patients experienced long-term treatment durability with sustained improvements in metabolic parameters (glycemic, hepatic, and cardiovascular) at 12 and 24 months post-DMR without a need for additional medication. Overall, significant reductions in HbA1c were achieved at 12 and 24 months post-DMR, with mean HbA1c values of 7.5% at follow-up compared to a baseline level of 8.5%. Likewise, significant reductions in FPG were observed at 24 months post-DMR. Improvements

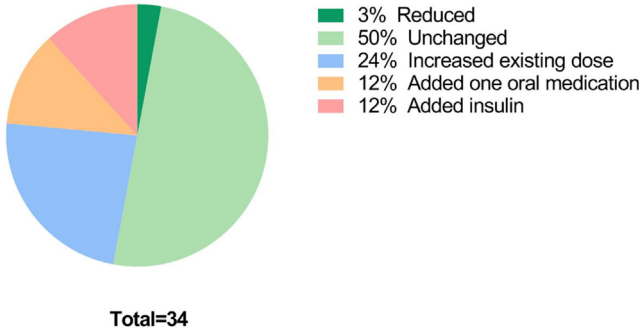

Fig. 3 – Changes in oral glucose-lowering medication from baseline at 24 months post-DMR (PP Population). Medications reduced in 1/34 patients, medications remained unchanged in 17/34 patients, 8/34 patients increased doses of an existing medication, 4/34 patients added on one oral medication, and 4/34 patients added insulin. For patients with missing 24 months visits we used last observation carried forward. DMR = duodenal mucosal resurfacing; PP = per protocol.

were also observed in patient reported DTSQ, suggesting that DMR may reduce the burden of disease in patients with T2D. The minor fluctuations in weight indicate that the effect of DMR is not driven by weight change.

DMR was followed by improved insulin sensitivity at 12 months, but the 24 months HOMA-IR results were not significantly lower compared to baseline. The improved HOMA-IR was mostly driven by the reduction in FPG, since FPI was not markedly changed throughout the study. The observed decrease in fasting C-peptide may be related to improved insulin sensitivity and may reflect a reduction in the requirement for basal insulin secretion. Both the HOMA-IR and fasting C-peptide data point to a role for improved insulin sensitivity after DMR. These findings are encouraging as insulin resistance is a known pathological driver of T2D and the multiorgan metabolic complications associated with the disease. Recent studies have shown that DMR is most effective in patients with high FPG levels, a hallmark of high insulin resistance.[22] The decline in ALT was approximately 15% from baseline measures, with a more pronounced decline in patients with high ALT levels at baseline (i.e., 30% reduction from baseline). Although liver transaminase levels might not be the best parameters for NAFLD [18] up to 70% of patients with T2D also have coexisting NAFLD even in the absence of elevated transaminase levels. Like NAFLD, dyslipidemia and its associated cardiovascular risks are frequent consequences of insulin resistance [19]. In the current study, improvements in HDL and TG/HDL ratio were observed at 24 months post-DMR. Altogether, the long-term effects on insulin resistance, liver function tests, and lipid parameters observed in REVITA-1 suggest that a single DMR-procedure has an overall beneficial effect on metabolic disturbances in T2D. However, the effect on hard end points has yet to be determined.

REVITA-1 has several limitations. This was a single-arm study with a relatively small trial size. Next, glucose- and lipid-lowering medications were tracked but not controlled after 24 weeks. Glucose lowering medications were increased in 46% of our patients. This may have contributed to the observed HbA1c improvements. Thus, the observed changes in glycemic and lipid parameters must be interpreted with caution. At this stage, there is no long term data available on duodenal histology or gut hormone response after DMR. Additional metabolic tests (e.g., oral glucose tests) and liver imaging (magnetic resonance proton density fat fraction or Fibroscan) would have added valuable information. Such assessments have been integrated into more recent DMR studies.

Overall, the safety and potential efficacy findings from the REVITA-1 study are encouraging and suggest that DMR has lasting effects on insulin resistance and related metabolic derangements in patients with T2D. Research to confirm these results and further elucidate the mechanism of action of DMR in metabolic diseases is warranted. Additional randomized, prospective, double-blind, sham-controlled, multicenter, international studies of DMR safety and efficacy in patients with sub-optimally controlled T2D are currently underway.

Declaration of Competing Interest

This study was supported by Fractyl Laboratories Inc. A.C. G.V.B., P.B., C.M., and P.V. have nothing to disclose. J.D. has received research support from Fractyl Laboratories Inc for IRB-approved studies. D.H. has received honorarium for con-

Table 2 – Treatment Durability DMR 24 months Post-Treatment (PP population).

	Magnitude of improvement		
	n/*n* † (%)	Mean (SD) raw change from baseline	
HbA1c change from baseline at		%	mmol/mol
6 months	28/33 (84.8)	−1.2 (0.8)	−12.9 (8.3)
Durability at 24 months	19/22 (86.4)	−1.4 (0.8)	−15.8 (8.5)
ALT change from baseline at		U/L	
6 months	23/34 (67.6)	−15.4 (18.2)	
Durability at 24 months	18/22 (81.8)	−16.6 (14.2)	
AST change from baseline at		U/L	
6 months	22/33 (66.7)	−7.7 (6.1)	
Durability at 24 months	14/19 (73.7)	−9.6 (5.1)	

DMR = duodenal mucosal resurfacing; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HbA1c = hemoglobin A1c; PP = per protocol.

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Author Contributions

A.C.G.V.B. contributed to study design, data acquisition, statistical analysis, and data interpretation. J.D., L.C., G.C., C.G., R.H., P.V., G.M., and C.M. contributed to data acquisition. F. H., M.N. contributed to study design and data interpretation. P.B., H.R., and J.J.G.H.M.B. contributed to study design, data acquisition, and data interpretation. P.R. contributed to study design and data acquisition. D.H., M.N., J.C.L.T. and K.W. contributed to data acquisition and data interpretation. V.B. contributed to data acquisition, statistical analysis, and data interpretation. E.C. contributed to data interpretation. All authors contributed to the critical review, editing, and final approval of the manuscript. A.C.G.V.B. and J.J.G.H.M.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.109194.

REFERENCES

[1] Chung WK, Erion K, Florez JC, Hattersley AT, Hivert M-F, Lee CG, et al. Precision Medicine in Diabetes: A Consensus Report From the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43(7):1617–35. https://doi.org/10.2337/dci20-0022.

[2] World Health Organization. Global Report on Diabetes 2016. https://www.who.int/diabetes/global-report/en/ (accessed July 13, 2020).

[3] Kasuga M. Insulin resistance and pancreatic β cell failure. J Clin Invest 2006;116:1756–60. https://doi.org/10.1172/JCI29189.

[4] Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care 2009;32(Suppl 2):S151. https://doi.org/10.2337/dc09-s301.

[5] Diabetes UK. Facts and Stats 2019. https://www.diabetes.org.uk/professionals/position-statements-reports/statistics (accessed July 13, 2020).

[6] de Pablos-Velasco P, Parhofer KG, Bradley C, Eschwège E, Gönder-Frederick L, Maheux P, et al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: Data from the PANORAMA study. Clin Endocrinol (Oxf) 2014;80(1):47–56. https://doi.org/10.1111/cen.12119.

[7] Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999–2002: The National Health and Nutrition Examination Survey. Diabetes Care 2006;29:531–7. https://doi.org/10.2337/diacare.29.03.06.dc05-1254.

[8] Galvao Neto M, Rodriguez L, Becerra P, Mani S, Rothstein R. Hydrothermal duodenal mucosal resurfacing: a novel procedural therapy for metabolic disease. VideoGIE 2016;1(1):10–1. https://doi.org/10.1016/j.vgie.2016.07.011.

[9] Hadefi A, Huberty V, Lemmers A, Arvanitakis M, Maggs D, Costamagna G, et al. Endoscopic Duodenal Mucosal Resurfacing for the Treatment of Type 2 Diabetes. Dig Dis 2018;36(4):322–4. https://doi.org/10.1159/000487078.

[10] Cherrington AD, Rajagopalan H, Maggs D, Devière J. Hydrothermal Duodenal Mucosal Resurfacing: Role in the Treatment of Metabolic Disease. Gastrointest Endosc Clin N Am 2017;27(2):299–311. https://doi.org/10.1016/j.giec.2016.12.002.

[11] van Baar ACG, Nieuwdorp M, Holleman F, Soeters MR, Groen AK, Bergman JJGHM. The Duodenum harbors a Broad Untapped Therapeutic Potential. Gastroenterology 2018;154(4):773–7. https://doi.org/10.1053/j.gastro.2018.02.010.

[12] Haluzík M, Kratochvílová H, Haluzíková D, Mráz M. Gut as an emerging organ for the treatment of diabetes: Focus on mechanism of action of bariatric and endoscopic interventions. J Endocrinol 2018;237:R1–R17. https://doi.org/10.1530/JOE-17-0438.

[13] Sullivan S, Edmundowicz SA, Thompson CC. Endoscopic Bariatric and Metabolic Therapies: New and Emerging Technologies. Gastroenterology 2017;152(7):1791–801. https://doi.org/10.1053/j.gastro.2017.01.044.

[14] Haidry RJ, van Baar AC, Galvao Neto MP, Rajagopalan H, Caplan J, Levin PS, et al. Duodenal mucosal resurfacing:

proof-of-concept, procedural development, and initial implementation in the clinical setting. Gastrointest Endosc 2019;90(4):673–681.e2. https://doi.org/10.1016/j.gie.2019.03.024.

[15] Rajagopalan H, Cherrington AD, Thompson CC, Kaplan LM, Rubino F, Mingrone G, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes: 6-month interim analysis from the first-in-human proof-of-concept study. Diabetes Care 2016;39(12):2254–61. https://doi.org/10.2337/dc16-0383.

[16] van Baar ACG, Holleman F, Crenier L, Haidry R, Magee C, Hopkins D, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: One year results from the first international, open-label, prospective, multicentre study. Gut 2020;69(2):295–303. https://doi.org/10.1136/gutjnl-2019-318349.

[17] Bradley C. Diabetes treatment satisfaction questionnaire [8]. Diabetes Care 1999;22:530–2. https://doi.org/10.2337/diacare.22.3.530.

[18] Younossi ZM, Corey KE, Alkhouri N, Noureddin M, Jacobson I, Lam B, et al. Clinical assessment for high-risk patients with non-alcoholic fatty liver disease in primary care and diabetology practices. Aliment Pharmacol Ther 2020;52(3):513–26. https://doi.org/10.1111/apt.15830.

[19] Laakso M. Cardiovascular disease in type 2 diabetes from population to man to mechanisms: The Kelly West award lecture 2008. Diabetes Care 2010;33:442–9. https://doi.org/10.2337/dc09-0749.