Reduction in Liver Fat in Patients with Type 2 Diabetes Following Treatment with Duodenal Mucosal Resurfacing

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Introduction

- Duodenal Mucosal Resurfacing (DMR) is currently being investigated as a treatment for insulin resistant metabolic disease including Type 2 diabetes (T2D).1-4
- Data from recent multicenter, single-arm Revita-1 study in T2D patients demonstrated sustained reductions (to 12 months) in HbA1c, fasting plasma glucose (FPG), and Homeostasis Model Assessment index (HOMA-IR) as well as a lowering of liver transaminase levels.[4]

Objective

- Revita-2 clinical trial (NCT02879383) is a blinded, sham controlled study designed to evaluate the effects of DMR on glycemic and other metabolic parameters in T2D, including measures of fat fraction in the liver through magnetic resonance (MR).
- Trial involves a training phase in which the study sites familiarize themselves with the intervention procedure before beginning the randomized phase of the protocol. Sites were required to conduct up to 5 (open-label) training cases for a maximum of 50 total cases and this created an open label case cohort distinct from the randomized cohort.
- We report here preliminary data from the open label case cohort.

Methods

- Eligible subjects participated in 4 week oral anti-diabetic medication run-in period to establish stable baseline glycemia, and medication and nutritional compliance.
- Metabolic data (e.g. HbA1c, lipid and hepatic parameters) was collected at baseline and 12 weeks.
- Liver MR was performed at selected sites at baseline and 12 weeks on the same MR scanner for each subject (three 3.0T and two 1.5T systems) using vendor-derived proton density fat fraction sequences. For each scan, nine region-of-interest (ROIs) were sited in each Coinaud liver segment with change in mean ROI liver fat fraction (%) recorded for each subject.
- All subjects enrolled in the open-label cohort were treated with the DMR procedure and were followed per protocol for 48 weeks.

Key Inclusion criteria include:

- Aged 28-75 years
- HbA1c 7.5-10.0%
- BMI 24-40 kg/m^2
- Fasting insulin >7 uIU/mL
- Sub-optimally controlled on at least 1 oral anti-diabetic medication

Key Exclusion criteria include:

- Diagnosed with Type 1 Diabetes or with a history of ketoacidosis
- Current use of Insulin or GLP-1 analogues
- Hypoglycemia unawareness or a history of severe hypoglycemia
- Known autoimmune disease, as evidenced by a positive AntiGAD test
- Active H. pylori infection
- Previous GI surgery that could affect the ability to treat the duodenum
- History of chronic or acute pancreatitis
- Known active hepatitis or active liver disease

Procedure Conduct:

- Subjects received DMR treatment under deep sedation in a left lateral position.
- Catheter (followed by an endoscope for visualization) was inserted trans-orally over a stiff guidewire into the duodenum to a location just distal to the papilla (Figure 1A and B).
- Duodenum underwent circumferential hydrothermal ablation after mucosal lifting at five sequential locations between the papilla and ligament of Treitz (Figure 1C).

Figure 1A. REVITA™ Catheter

Figure 1B. Schematic of DMR

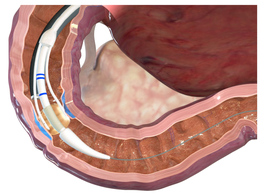
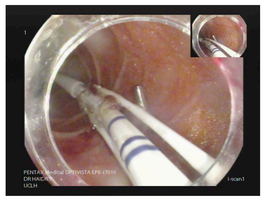
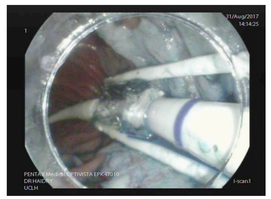


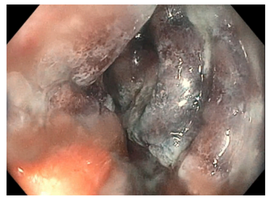
Figure 1C. DMR Images



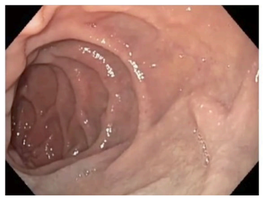
Revita Catheter in Place



Ablated Duodenum



Ablated Duodenum



One Month Follow-up

Results

- Initial data from the open-label (training case) cohort are available for 24 subjects through 3 months (12 weeks). We also report preliminary data from a subset of subjects (n=13) who underwent MR study at baseline and 12 weeks.
- Subjects enrolled had a mean age of 58 yrs with a mean duration of T2D of 8 yrs. All but one subject was receiving metformin and the majority (63%) were taking a sulfonylurea.

Table 1. Subject Demographics and Baseline Characteristics

Subject Characteristics	Baseline (n=24)
Age, years (range)	58 (43-69)
Gender, n (%)	
Female	7 (29)
Male	17 (71)
Duration of T2D, years (range)	8 (0.4 -17)
Weight (kg)	89.7 (1.9)
BMI (kg/m^2)	31.6 (3.0)
Oral antidiabetic medications	
Metformin*, n (%)	23 (96)
Sulfonylurea, n (%)	15 (63)
Meglitinide, n (%)	0
DPP-4 inhibitor*, n (%)	9 (38)
SGLT-2 inhibitor, n (%)	5 (21)

Values are mean (SD) unless otherwise noted. BMI: Body Mass Index; * includes combination agents counted in each category

Efficacy

- Key procedural metrics including procedure time, defined as catheter in to catheter out duration, and number of ablations completed vs. intended are shown in Table 2.

Table 2. Key Procedural Metrics

Metric	Data
Median procedure time (Inter-quartile range), min	45 (18)
Number of completed/intended ablations*, n (%)	116/120 (97%)

*Five intended ablations per protocol

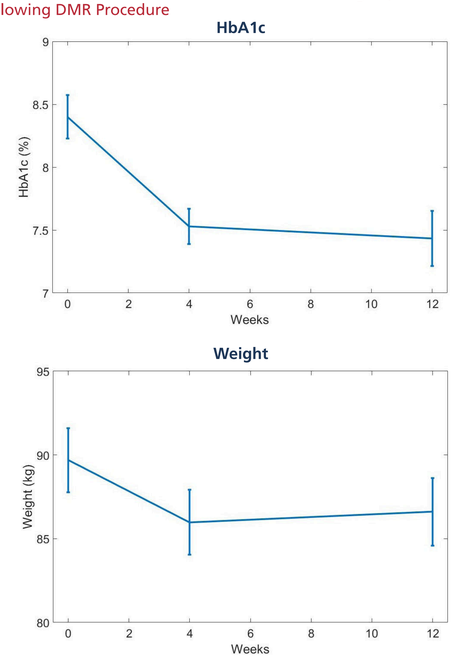
- Compared to baseline, significant improvement in all parameters of glycemia and broader metabolic parameters were observed (Table 3).
- Available MR data from a subset of 13 subjects revealed lowering of absolute (-6.3%, p = 0.008) and relative (-30.3%, p = 0.013) fat fraction in the liver (Figure 3).

Table 3. Baseline and 12 Week Metabolic Values

Indices	Baseline	12 weeks	P value
Fasting Triglycerides (mg/dl)	209 ± 32	150 ± 20	< 0.01
Fasting HDL (mg/dl)	45.7 ± 2.8	49.2 ± 3.2	< 0.05
Ferritin** (ng/ml)	98.1 ± 20.9	72.0 ± 18.7	< 0.01
Fasting Plasma Insulin* (uIU/mL)	13.6 ± 1.8	9.8 ± 1.1	< 0.05
Alanine Aminotransferase (U/L)	35.8 ± 4.1	26.8 ± 2.4	< 0.01
Fasting C-peptide (ng/ml)	3.22 ± 0.29	2.63 ± 0.17	< 0.05

Values are all mean (±SEM); n = 24 except where indicated; * n=22;** n=18

Figure 2. Changes over 12 weeks in HbA1c and Weight (mean ± SEM) following DMR Procedure



Safety

- Mild gastro-intestinal symptoms immediately post-procedure were the most commonly reported adverse event (AE), including abdominal pain, constipation, diarrhea, and dyspepsia
- No device or procedure related serious AEs were reported.
- No unanticipated adverse device effects were reported.

DISCLOSURES

S.T is a research consultant to Robarts and shareholder in Motilent; M.C, N.S, S.T are supported by the National Institute of Health Research (NIHR) University College London Hospitals Biomedical Research Centre; D.M, M.B and A.V. are employees of Fractyl Laboratories Inc and have stock/stock options

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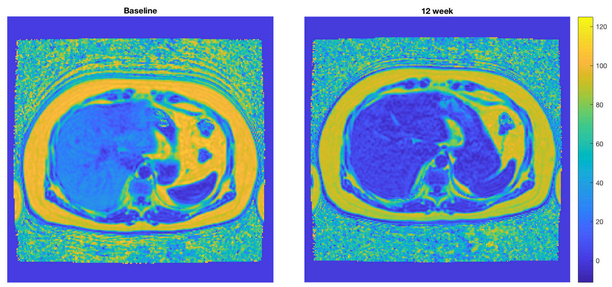
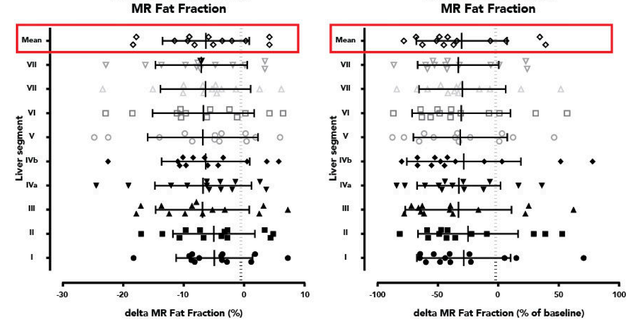
Figure 3A. Liver MR Imaging (from a single subject) following DMR Procedure

- Data was collected on Philips Ingenia 3.0T systems (three sites) and GE Discovery 3.0T/Optima 1.5T systems (two sites) in a single breath-hold (<20 seconds), with 6 mm slice thickness and 2-2.5 mm isotropic in plane resolution.
- The following acquisition parameters were used: α = 3 degrees, TR = 5-10 ms, TE = 1-2 ms, echoes = 6 and parallel imaging factor = 2. All sites used vendor-derived proton density fat fraction (PDFF) sequences (mDixon Quant, Philips; IDEAL-IQ, GE).
- Darker blue shade is indicative of a reduction in hepatic fat content as shown on pdf images below.
- Hepatic fat fraction was reduced by 30% (Relative) and 6% (Absolute).



Baseline (Left) and 12 week (Right) post treatment PDFF images from a single subject. Reduction in signal in the liver reflects a reduction in the PDFF following treatment.

Figure 3B. MR Fat Fraction (absolute and relative change at 12 Weeks) following DMR Procedure (n=13)



Conclusions

- **In this international, multi-center study, initial observations from the open-label cohort indicate that DMR was safely implemented in T2D subjects with a favorable safety and tolerability profile.**
- **Initial metabolic data also indicates that DMR exerts a favorable metabolic effect with an improvement in glycemic and other metabolic parameters.**
- **MR of the liver indicates that DMR induces a lowering of fat in the liver bed.**
- **DMR offers significant potential for the treatment of metabolic disorders that target the substantial overlap between T2D and fatty liver disease.**

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