

Duodenal Mucosal Resurfacing Reduces Liver Fat in Patients with Type 2 Diabetes

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Introduction

- Duodenal Mucosal Resurfacing (DMR) is currently being investigated as a treatment for metabolic diseases including Type 2 diabetes (T2D).¹⁻⁴
- Data from the 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

- The Revita-2 clinical trial (NCT02879383) is a blinded, sham controlled study designed to examine the effects of DMR on glycemic and other metabolic parameters in patients with T2D, including measures of fat fraction in the liver through magnetic resonance (MR).
- The trial involves a training phase in which the study sites familiarize themselves with the intervention procedure before beginning the randomized phase of the protocol. This creates an open label case cohort distinct from the randomized cohort. All subjects enrolled in the open-label cohort are treated with the DMR procedure and are followed per protocol for 48 weeks.

Methods

- Eligible patients participate in a 4 week oral anti-diabetic medication run-in period to establish stable baseline glycemia in conjunction with medication compliance and nutritional counseling. Oral diabetic medications are to be held constant from start of run-in period through the 24 week endpoint following a predefined rescue algorithm for hypo- and hyperglycemia.

Key Inclusion criteria include:

- Aged 28-75 years
- HbA1c 7.5-10.0%
- BMI 24-40 kg/m²
- Fasting insulin >7 µU/ mL
- And who are 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 Anti-GAD 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

- Subjects under deep sedation undergo the DMR procedure while in a left lateral position.
 - The catheter (followed by an endoscope for visualization) is inserted trans-orally over a stiff guidewire into the duodenum to a location just distal to the papilla (Figure 1A and B).
 - The duodenum is treated by performing circumferential mucosal lifting followed by hydrothermal ablation at five sequential locations between the papilla and ligament of Treitz (Figure 1C).
- Prior to initiation of the randomized cohort phase, each Revita-2 study site is required to conduct up to 5 (open-label) training cases for a maximum of 50 total cases. The data from the training cases will not be included in the randomized primary efficacy analysis and is presented here as an independent, preliminary report.
- Liver MR was performed at selected sites at baseline and 12 weeks on the same MR scanner for each patient (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 recorded for each subject.

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 years with a mean duration of T2D of 8 years. All but one subject was receiving metformin and a majority (63%) were taking a sulfonylurea.

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DISCLOSURES

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Figure 1A. Second-generation REVITA™ Catheter



Figure 1B. Schematic of the DMR Procedure

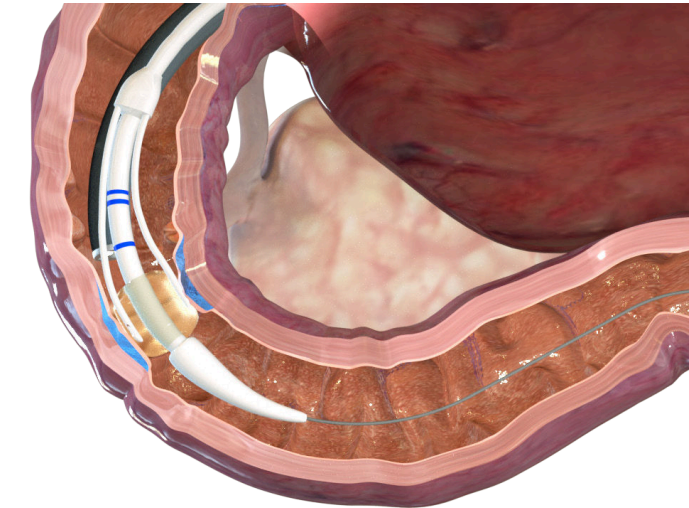
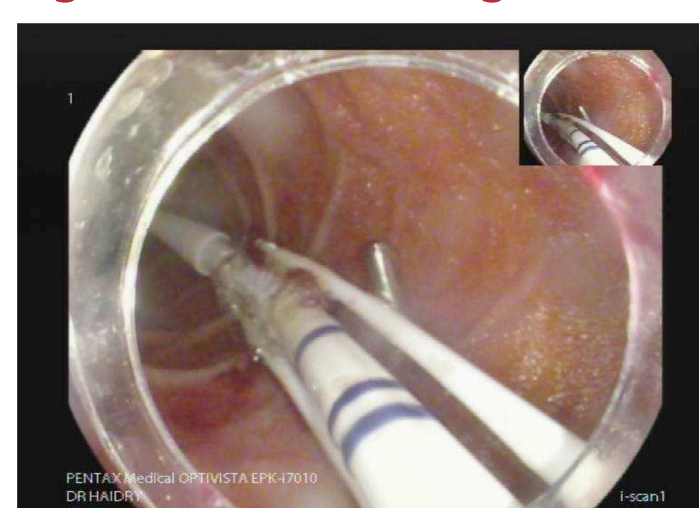


Figure 1C. DMR Images



Revita Catheter in Place



Ablated Duodenum



Ablated Duodenum



One Month Follow-up

Table 1. Patient Demographics and Baseline Characteristics

Patient Characteristics	Baseline (n=24)
Age, years (range)	58 (43-69)
Sex, 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)
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).

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.

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

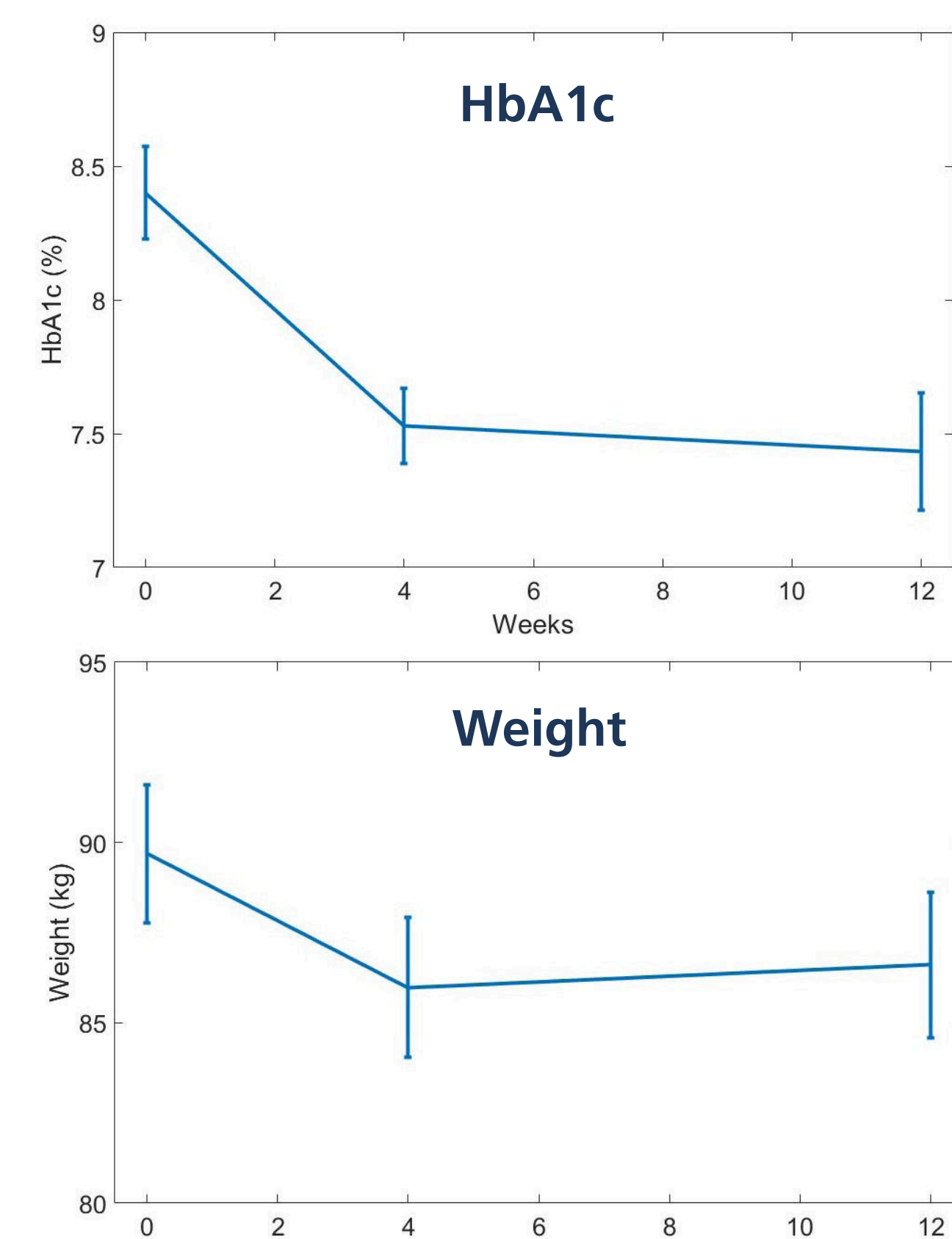
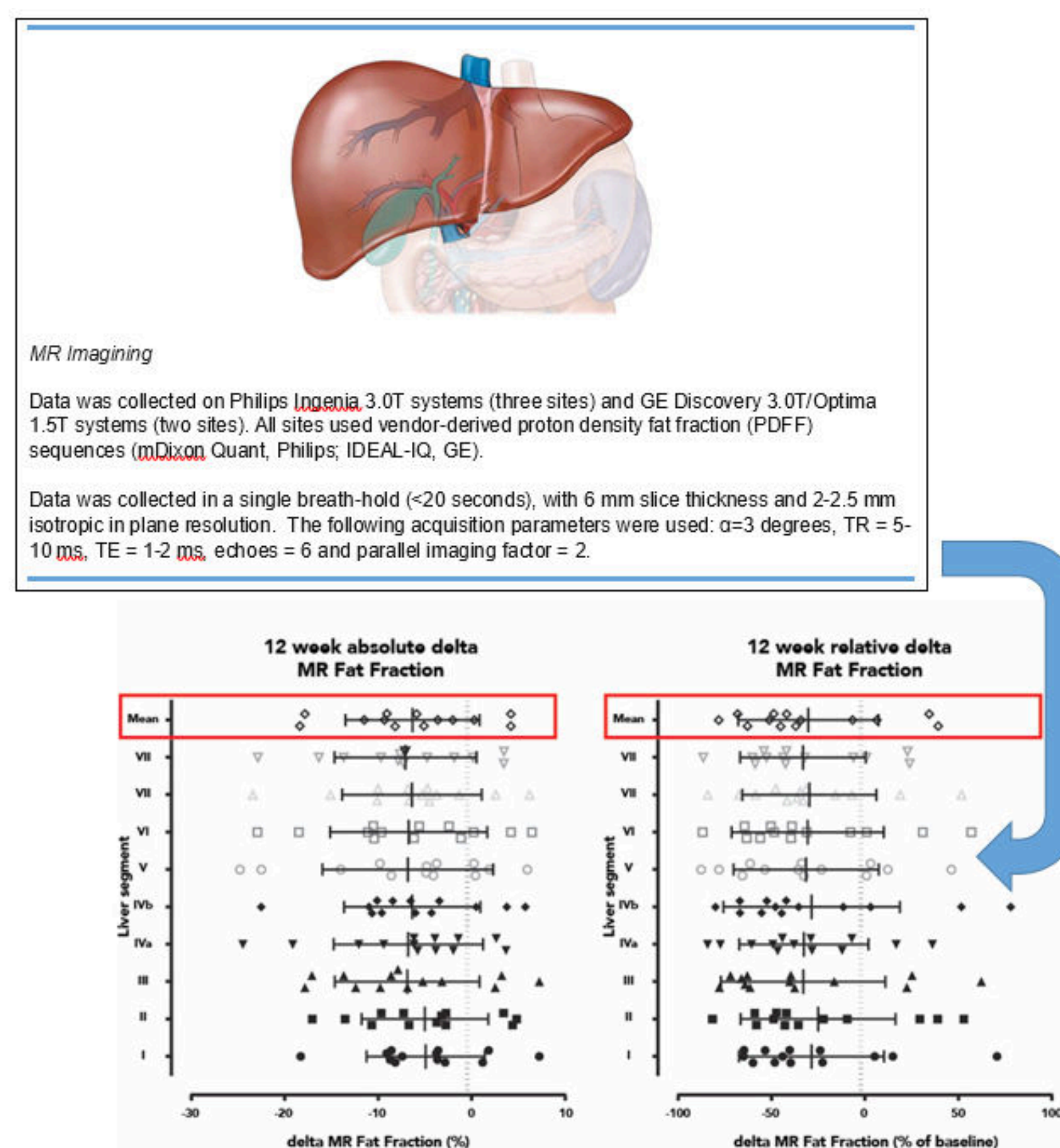


Table 3. Baseline and 12 Week Metabolic Values

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* (µU/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 3. MR Fat Fraction (absolute and relative change at 12 Weeks) following DMR Procedure



Conclusion

- 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 exerts insulin sensitizing effects in T2D, resulting in 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.