Endoscopic Duodenal Mucosal Resurfacing (DMR) Improves Glycemic and Hepatic Parameters in Patients with Type 2 Diabetes: Data from a First-in-Human Study

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Disclosures

- Harith Rajagopalan, MD, PhD
  - Employee and shareholder: Fractyl Laboratories, Inc.
  - Fractyl Laboratories provided funding for this study
Background

- Bariatric surgeries that prevent nutrient contact with the duodenum improve measures of metabolism in type 2 diabetes (T2D), including indicators of fatty liver disease.
- Revita™ duodenal mucosal resurfacing (DMR) may offer similar metabolic benefit.
Aim

- To assess procedural safety in patients with suboptimally controlled T2D
  - HbA1c > 7.5% on ≥ 1 anti-diabetic agent

- To evaluate the effect of Revita DMR on metabolic parameters
The Central Role of Insulin Resistance

"Inadequate" insulin response

Type 2 Diabetes

Retinopathy
Nephropathy
Neuropathy

End-Organ Microvascular Diseases

Insulin Resistance

CVD
HTN
Stroke

End-Organ Macrovascular Diseases

Insulin Resistance Syndrome

Fatty liver
PCOS

End-Organ Metabolic Diseases

Compensatory Hyperinsulinemia

Adapted from AACE position statement
Revita DMR: Pathophysiologic Principle

- Bypass of upper GI tract (surgery, sleeve) exerts potent effects on metabolism through insulin sensitizing pathways
- Nutrient re-exposure to the ‘Roux’ elicits return to hyperglycemia
- Abnormal hypertrophy of mucosa noted in diabetics’ upper GI tract
- Abnormal entero-endocrine cell sub-population in upper GI mucosa of diabetic patients

Revita DMR Procedure

- Minimally invasive upper endoscopic therapy using an innovative balloon catheter
- Targets duodenal mucosa between Ampulla of Vater and Ligament of Treitz
- Procedural Steps
  - Size duodenum and lift sub-mucosal space with saline injection to create protective barrier
  - Circumferentially ablate superficial mucosa using a hydrothermal approach to stimulate regeneration
  - Procedure duration ~60 minutes
- No implant, sutures or surgery
First-in-Human Study: Methods

- Single center, single arm study performed in Santiago, Chile, in patients with suboptimally controlled T2D
- Thermal ablation performed on either a short (n=11; mean 3.4 cm) or long (n=28; mean: 9.3 cm) segment of duodenum
- Procedures performed by trained endoscopists with patients under anesthesia
- 2-week, low calorie, graduated diet for all patients post-procedure (liquids → soft → puree)
- No specific recommendation on post-procedure management of anti-diabetic medication
- Post-procedure endoscopies performed at 1 and 3 months
Study Details

- **Inclusion criteria**
  - Age 28-75
  - BMI 24-40
  - HbA1c 7.5-12%
  - Disease diagnosed <10 years
  - Fasting c-peptide >1 ng/ml
  - ≥ 1 oral anti-diabetes medicine (Rx)

- **Exclusion criteria**
  - Prior GI surgery that would preclude procedure
  - Anatomical abnormalities
  - Anti-GAD Ab+
  - Injectable anti-diabetes Rx

### Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Value (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (range)</td>
<td>53.4 +/- 7.5 (38-65)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (36)</td>
</tr>
<tr>
<td>Male</td>
<td>28 (64)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.4 +/- 11.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.3 +/- 8.4</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.8 +/- 3.5</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.0 +/- 14.2</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>77.0 +/- 8.1</td>
</tr>
<tr>
<td>Duration T2D, yrs (range)</td>
<td>5.7 +/- 2.2 (0.2-9.7)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>9.6 +/-1.4</td>
</tr>
<tr>
<td>FPG, mg/dL %</td>
<td>187 +/-58</td>
</tr>
<tr>
<td>Oral anti-diabetic Rx</td>
<td></td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>42 (98)</td>
</tr>
<tr>
<td>Sulfonylurea, n(%)</td>
<td>16 (37)</td>
</tr>
</tbody>
</table>

*Data are mean ± SD or n (%), unless otherwise indicated.*
44 Patients enrolled between August 2013 and December 2014

39 Treated patients (Efficacy cohort)

5 patients excluded:
• 4 did not receive DMR
  • 2 failed screening endoscopy
  • 1 tortuous anatomy
  • 1 anticipated prolonged anesthesia duration
• 1 patient anti-GAD+ (treated & followed for safety, not efficacy)

18 Long segment ablation
8 Short segment ablation
10 Long segment ablation
3 Short segment ablation

Baseline HbA1c
- 7.5-10%
- >10-12%

26 Treated patients with Baseline HbA1c 7.5-10%
13 Treated patients with Baseline HbA1c >10-12%
Safety & Tolerability

- Procedure well tolerated with minimal GI symptoms
- No difficulty tolerating oral diet in the days after the procedure
- AEs generally mild in severity & tended to occur in immediate post-procedure period
- Most common AE was transient abdominal pain due to air insufflation/endotracheal intubation (8/40 patients)
- Most significant AE was duodenal stenosis (3/40 patients)
  - All cases occurred within the first 6 weeks post-procedure
  - Non-emergent and resolved with endoscopic balloon dilation
  - No new cases after procedure and device improvements
- No GI bleeds, perforation, pancreatitis, malabsorption
- No severe hypoglycemia
Follow up endoscopies at 1 & 3 months showed intact mucosa with unremarkable mucosal plicae, indicating full mucosal healing.
Efficacy

- DMR procedure elicited improvements in glycemia (meal challenge plasma glucose, HbA1c)
  - HbA1c reduction of 1.2% at 6 months in efficacy cohort (n=39)

- More robust glycemic effect observed among long segment cohort (n=28)
  - 2.5% reduction in baseline mean HbA1c at 3 months post-procedure vs 1.2% with short segment DMR (p<0.05)

- Modest weight reduction, but no correlation between weight loss and glycemic improvement

- Robust reduction in hepatic transaminase levels (AST, ALT)
### Overview: Changes in Metabolic Parameters in LS Cohort

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>1 Month</th>
<th>3 Month</th>
<th>6 Month</th>
<th>Normal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c - %</td>
<td>9.6±1.4</td>
<td>7.9±1.1</td>
<td>7.1±0.9</td>
<td>8.2±1.6</td>
<td>4.0-6.0</td>
</tr>
<tr>
<td>Weight - kg</td>
<td>86±11</td>
<td>82±11</td>
<td>83±12</td>
<td>85±11</td>
<td>--</td>
</tr>
<tr>
<td>ALT - IU/L</td>
<td>40±23</td>
<td>32±17</td>
<td>27±14</td>
<td>27±12</td>
<td>≤ 38</td>
</tr>
<tr>
<td>AST - IU/L</td>
<td>32±17</td>
<td>27±11</td>
<td>23±8</td>
<td>22±6</td>
<td>≤ 40</td>
</tr>
</tbody>
</table>

*Normal range based on ranges reported by lab that processed the samples. All numbers reported as mean ± SD.
DMR Improves Glycemic Measures: Long Segment Cohort (n=28)

- HbA1c reduction of 1.4% at 6 months (p<0.001 for change from screening)
- 14/28 patients had reduction in concomitant anti-diabetic medications post-procedure
Hepatic Transaminase Changes by Tertile

- Lowering of ALT and AST more pronounced in subjects with elevated pre-treatment levels

**ALT Tertiles**

- LS Cohort (n=28)

**AST Tertiles**

- LS Cohort (n=28)
DMR Reduced ALT and AST in Patients with Radiological Evidence of NAFLD

Metabolic benefits seen in 22 patients with incidental finding of fatty liver on ultrasound.
Conclusions

- DMR improves metabolic control in T2D patients, including a robust and sustained lowering of hepatic transaminase levels.

- DMR offers the potential for a single-point intervention that improves both glycemia and fatty liver.

- Further study in patients with fatty liver disease is warranted.