Endoscopic Duodenal Mucosal Resurfacing (DMR) Improves Metabolic Measures, Including Hepatic Transaminase Levels, in Patients with Type 2 Diabetes: Data from a First-in-Human Study
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Disclosures

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Study funding:

- Fractyl Laboratories, Inc.
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 evaluate the effect of Revita DMR on metabolic parameters

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

Rohde et al. BMJ. 2013 Sep 13;3(9): 2013
Dirksen et al. Diabetes Care. 33(2):0–2. 2010
Verdam et al. JCEM. 96(2):E379–83; 2011
Revita DMR Procedure

- Minimally invasive endoscopic therapy using an innovative balloon catheter
  - Targets duodenal mucosa between Ampulla of Vater and Ligament of Treitz

- Procedural Steps
  - Size duodenum
  - 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
Methods

- Single center, single arm study (Santiago, Chile) using the Revita™ DMR System (Fractyl Laboratories, Waltham, MA, USA) 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
First-in-Human Study Enrollment

- **Patients enrolled between August 2013 and December 2014:** 44
- **Treated patients for efficacy analysis:** 39

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

- **“Long segment” ablation:** 18
  - Baseline HbA1c 7.5-10%
  - Baseline HbA1c >10-12%
- **“Short segment” ablation:** 8
- **“Long segment” ablation:** 10
- **“Short segment” ablation:** 3
Patient Characteristics

**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

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Value (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (range)</td>
<td>53.3 +/- 7.5 (38-65)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (36.4)</td>
</tr>
<tr>
<td>Male</td>
<td>28 (63.6)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.5 +/- 11.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.2 +/- 8.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.9 +/- 3.5</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.1 +/- 14.4</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>76.9 +/- 8.2</td>
</tr>
<tr>
<td>Duration T2D, yrs (range)</td>
<td>5.7 +/- 2.2 (1-9)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>9.5 +/-1.3</td>
</tr>
<tr>
<td>FPG, mg/dL %</td>
<td>184 +/-58</td>
</tr>
<tr>
<td>Oral Anti-diabetic Rx</td>
<td></td>
</tr>
<tr>
<td>Metformin, n (%)</td>
<td>44 (100)</td>
</tr>
<tr>
<td>Sulfonylurea, n(%)</td>
<td>20 (44)</td>
</tr>
</tbody>
</table>
Safety & Tolerability

- Procedure well tolerated with minimal GI symptoms

- 3 duodenal stenoses resolved with endoscopic balloon dilation

- No GI bleeds, perforation, pancreatitis, malabsorption or severe hypoglycemia

- Follow up endoscopy indicated full mucosal healing at 1 month
Post-Procedure Endoscopy

- Follow up endoscopies at 1 month document full mucosal healing
Efficacy

- More potent glycemic effect observed among long segment (LS) cohort
  - Modest weight effect noted, but no correlation between weight loss and glycemic improvement

- Robust reduction in hepatic transaminase levels also observed
## Overview of Changes in Metabolic Parameters: LS Cohort

<table>
<thead>
<tr>
<th></th>
<th>Screening</th>
<th>1 Month</th>
<th>3 Month</th>
<th>6 Month</th>
<th>Normal Range*</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>

Abbreviations: HbA1c=glycated hemoglobin; ALT=alanine transaminase; AST=aspartate transaminase.

*Normal range based on ranges reported by lab that processed the samples.
All numbers reported as mean ± SD.
DMR Improves Glycemic Measures

- Early and sustained improvement in both fasting glucose (data not shown) and HbA1c

**Average Change in HbA1c**

LS Cohort (n=28)

- Mean ± SEM shown
DMR Improves Hepatic Transaminase Levels

Average Change in ALT
LS Cohort (n=28)

Average Change in AST
LS Cohort (n=28)

Early and sustained improvement in ALT and AST
Hepatic Transaminase Changes by Tertile

ALT Tertiles
LS Cohort (n=28)

AST Tertiles
LS Cohort (n=28)
DMR Reduced ALT and AST in Patients with Fatty Liver

22 subjects in LS DMR cohort had 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.
Thank You!

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