Endoscopic duodenal mucosal resurfacing (DMR) improves insulin sensitivity, hepatic transaminase levels and anti-inflammatory markers in subjects with type 2 diabetes

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INTRODUCTION

• Insulin resistance and type 2 diabetes mellitus (T2DM) are closely linked to development of nonalcoholic fatty liver disease (NAFLD) and its more aggressive phenotype, nonalcoholic steatohepatitis (NASH)
• Currently no approved therapy for NASH → Strong need for novel NASH treatment approaches
• Hypothesis: crosstalk between the proximal small intestine and liver in response to nutrient availability may modulate metabolic homeostasis
• Hydrothermal duodenal mucosal resurfacing (Revita™ DMR, Fractyl Laboratories, Inc., Lexington, MA) is an upper endoscopic technique that denudes the proximal duodenal mucosa (~10-12 cm) allowing mucosal restitution through resurfacing with neo-epithelium
• Early clinical data from a single DMR procedure in patients with T2DM demonstrate:
  – Glycemic improvement¹
  – Lowering of hepatic transaminase levels²

¹Rajagopalan et al. Diabetes Care 2016; ²Galvao Neto et al. DDW 2016

AIM

• To investigate the impact of hydrothermal DMR on markers of insulin resistance and hepatic indices in subjects with T2DM using a metabolomic approach

METHODS

• First-in-human DMR pilot study was conducted in subjects with T2DM (n=44; HbA1c ≥ 7.5%) on ≥1 oral anti-diabetic agent to evaluate procedure safety and metabolic indices
  – Same day, minimally invasive procedure performed in <1 hr utilizing techniques familiar to endoscopists with single-use, disposable catheter system
  – Standard mixed meal tolerance test (MMTT) conducted pre- and 3-months post-procedure
  – Metabolomic analysis performed from plasma samples in subcohort of patients (n=14) (Metabolon, Durham, NC)
  – Fasting → 120 min postprandial meal challenge at screening and 3 months
  – Global metabolic screen allows ~1600 analyte display
• Effects of DMR were compared pre-/post-procedure using paired t-tests

RESULTS

A subset of 14 subjects from the original 44 who underwent a single DMR procedure were included in this metabolomic analysis
• DMR was performed successfully in all subjects and the procedure was well tolerated

Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Screening Characteristics</th>
<th>Mean (SEM)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>50.9 (2.19)</td>
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<tr>
<td>Female (%)</td>
<td>14</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>88.6 (2.7)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>31.4 (0.86)</td>
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<tr>
<td>HbA1c (%)</td>
<td>10.2 (0.3)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>39.9 (3.5)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>30.9 (3.4)</td>
</tr>
</tbody>
</table>

Table 1. Screening characteristics (n=14).

Figure 2. At 3 months post-procedure, HbA1c was significantly reduced (-2.7±0.3 %), while HOMA-IR (-1.61±0.7) and body weight (-2.4±0.9 kg) were moderately reduced. Data are mean±SEM.

HbA1c, HOMA-IR and Body Weight

Fasting and Meal Challenge Glycemia

Figure 3. Both fasting plasma glucose and MMTT area under the curve (AUC) were significantly reduced 3 months post-DMR. Data are mean±SEM.

Metabolic Changes

• Improved glucose handling (↑pyruvate, ↑1,5-AG)
• Insulin sensitized (↓4-hydroxybutyrate)
• Improved mitochondrial function (↓β oxidation metabolites, ↓ dicarboxylic FAs)
• Reduced fatty liver-lipotoxic markers (↓DAGs)
• Reduced pro-inflammatory markers (↓eicosanoids)
• Reduced lipid peroxidation markers (↓HODE, ↓13-HODE)
• Increased anti-oxidant capacity (glutathione signature)
• Potentially altered microbiome (2° bile acids)

CONCLUSIONS

• A single endoscopic DMR procedure performed in subjects with T2DM produced significant improvements in glycemic indices along with improved markers of insulin resistance, systemic inflammation and oxidative stress
• These results provide evidence that DMR could become a potential method for correction of hyperglycemia and key pathophysiological drivers of fatty liver disease in T2DM