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 improvement[1]
  - Lowering of hepatic transaminase levels[2]

[1]Rajagopalan et al. *Diabetes Care* 2016; [2]Galvao 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

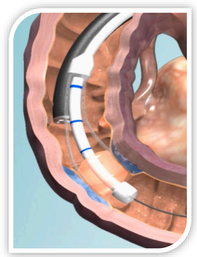

Fig. 1. Mucosal lift using Revita DMR balloon catheter.

RESULTS

Baseline Patient Characteristics

- 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

Table 1. Screening characteristics (n=14).

Screening Characteristics	Mean (SEM)
Age (yr)	50.9 (2.19)
Female (%)	14
Weight (kg)	88.6 (2.7)
BMI (kg/m^2)	31.4 (0.86)
HbA1c (%)	10.2 (0.3)
ALT (IU/L)	39.9 (3.5)
AST (IU/L)	30.9 (3.4)

HbA1c, HOMA-IR and Body Weight

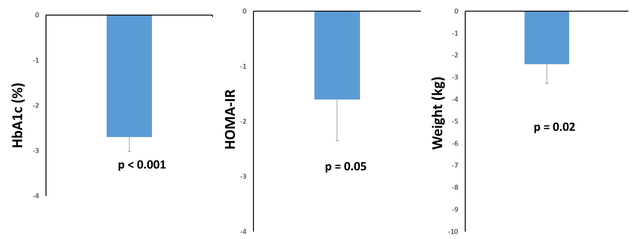

Figure 2. At 3 months post-procedure, HbA1c was significantly reduced (-2.7±0.3%), while HOMA-IR (-1.6±0.7) and body weight (-2.4±0.9 kg) were moderately reduced. Data are mean±SEM.

Fasting and Meal Challenge Glycemia

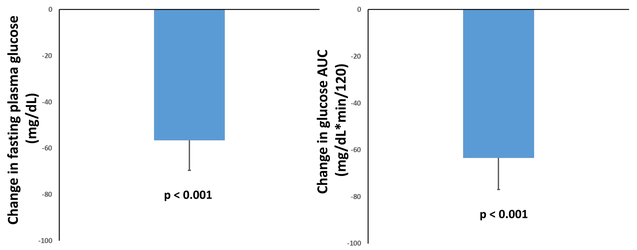

Figure 3. Both fasting plasma glucose and MMTT area under the curve (AUC) were significantly reduced 3 months post-DMR. Data are mean±SEM.

Table 2. Changes in liver enzymes and fat metabolism analytes 3 months post-DMR. Data are mean±SEM.

Hepatic & Lipid Parameters	Screening	Δ 3 Months	p-value
ALT (IU/L)	39.9 (3.5)	-9.6 (4.8)	0.06
AST (IU/L)	30.9 (3.4)	-5.7 (3.6)	NS
Diacylglycerol (uM)	80.5 (9.6)	-32.3 (6.7)	<0.05
Triacylglycerol (uM)	1356.5 (183.7)	-284 (128.3)	<0.05
FFA (uM)	500.5 (38.5)	-43.9 (58.8)	NS

Metabolomic Changes

- Improved glucose handling (↑pyruvate, ↑1,5-AG)
- Insulin sensitized (↓α-hydroxybutyrate)
- Improved mitochondrial function (↓β oxidation metabolites, ↓ dicarboxylic FAs)
- Reduced fatty liver-lipotoxic markers (↓DAGs)
- Reduced pro-inflammatory markers (↓eicosanoids)
- Reduced lipid peroxidation markers (↓9-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

FRACTYL

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