DUODENAL MUCOSAL RESURFACING IMPROVES LIPOTOXIC STRESS, MITOCHONDRIAL FUNCTION, AEROBIC METABOLISM, AND GLUCONEOGENIC DRIVE IN TYPE 2 DIABETES

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BACKGROUND

Type II diabetes mellitus (T2DM) and obesity are closely linked disorders with significant public health impact on metabolic and cardiovascular morbidity and mortality. While modern diabetic medications have reduced microangiopathic complications, there has been minimal successful influence on the cardiometabolic outcomes of T2DM.

Recently, the duodenum has been shown to play an important role as a metabolic signaling center. Normally, lumenal contents, such as fat, stimulate K-cells and gastric inhibitory polypeptide (GIP), which then enhance insulin secretion. Following bariatric surgery, exclusion of the duodenum from the food path has been shown to improve the metabolic state and induce beta cell proliferation. Less invasive methods, such as duodenal mucosal resurfacing (DMR), have shown similar effects that can last for over 6 months.

OBJECTIVE

To evaluate the impact of duodenal mucosal resurfacing on the systemic metabolome following hydrothermal ablation of the proximal duodenum in type II diabetes mellitus.

METHODS

- Study type: a prospective uncontrolled cohort pilot study of DMR.
  - Open-label, single-center trial
- 14 patients underwent DMR
  - Baseline age 51 ±2 years
  - HbA1c 10.2 ± 0.3%
- Fasting plasma levels obtained pre-procedure and 3 month post-procedure
- Systemic metabolome interrogated using gas-chromatograpy/mass spectrometry and liquid chromatography/mass spectrometry (Metabolon[inc])
- Each metabolite concentration was measured as a normalized value using an internal standard
- All samples were measured in a batch to avoid platform effects
- Data were analyzed using Metaboanalyst software

SUMMARY

Patients who underwent DMR experienced metabolic improvements including:

- Decreased lipotoxic stress
- Decreased gluconeogenic drive
- Decreased Warburg Effect, as indicated by decreased pro-oncogenic metabolic profiles
- Increased improvement of markers indicative of mitochondrial function, including those of lipid oxidation and the Krebs cycle

RESULTS

Figure 1

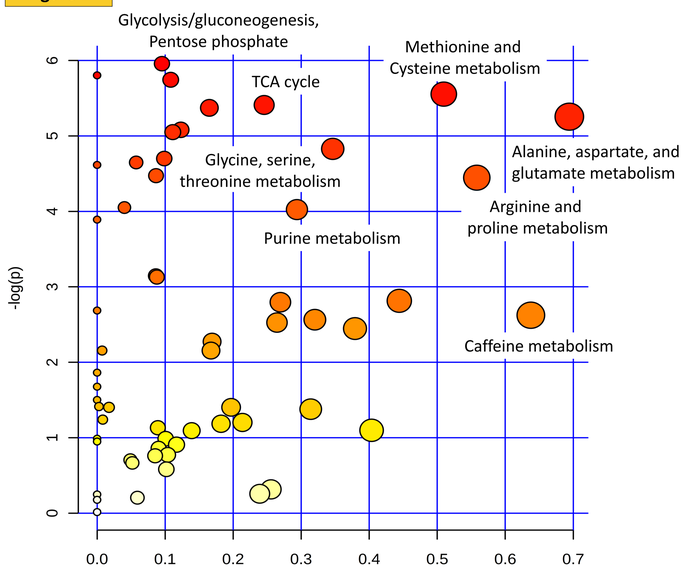

Table 1: Enrichment Analysis

Pathway	Higher Pre-Procedurally	Higher Post-Procedurally
Warburg Effect	Succinate, lactate, D-glucose, citrate, 3-phosphoglycerate, flavin adenine dinucleotide (FAD), ADP, L-glutamate	Pyruvate, glutamine, oxoglutaric acid, fumarate
Fatty Acid β-oxidation	Caproic acid, caprylic acid, FAD, AMP	L-carnitine
Fatty Acid Biosynthesis	Caproic acid, malonic acid, caprylic acid, capric acid	-
Glucose-Alanine Cycle	Glucose, glutamic acid	Pyruvate, oxoglutaric acid
Ketone and Butyrate Metabolism	succinate, FAD, AMP	-
Pyruvaldehyde Degradation	FAD	Pyruvate

Figure 1 shows pathway impact plotted against log p-value. Primary pathways affected were:

- Methionine and cysteine metabolism
- Alanine, aspartate, and glutamate metabolism
- Arginine and proline metabolism
- Glycine, serine, and threonine metabolism
- Glycolysis, gluconeogenesis, and pentose phosphate pathways

Figure 2

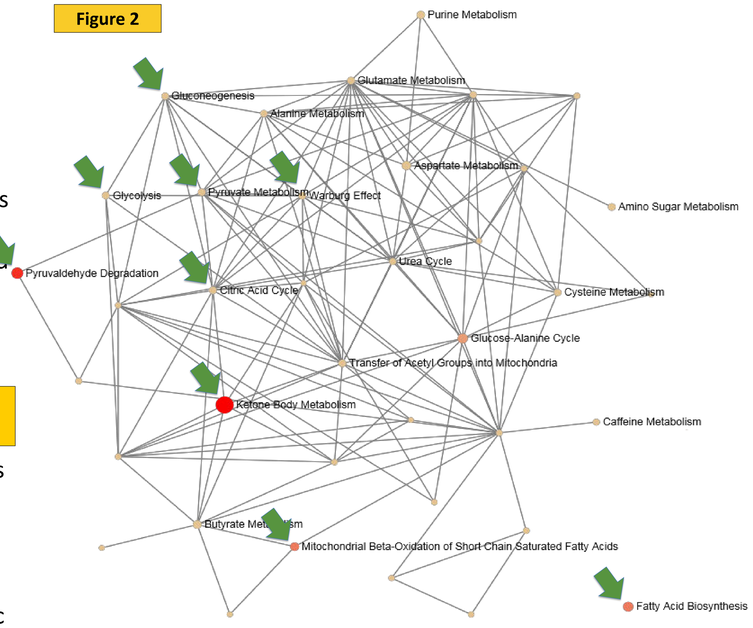

Figure 2 features enrichment analysis, which shows the pathways affected. Larger circles indicate more heavily impacted pathways. Points are interconnected to show relationships between pathways.

Table 1 displays some of the relevant affected metabolites in those pathways. In the post-procedure group, this analysis demonstrated:

- Increased concentrations of Krebs cycle metabolites such as pyruvate, oxoglutaric acid, and fumarate
- Decreased free fatty acids
- Decreased metabolites affiliated with gluconeogenesis

CONCLUSION

This study suggests that DMR is a potential non-invasive treatment option to improve overall metabolic status. Whether these metabolite concentration changes relate to long term clinical outcomes is now a subject for future research.

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