Duodenal Mucosa: A Target for Treating Metabolic Liver Disease in NASH and T2D

Harith Rajagopalan MD PhD
Fractyl Inc
Lexington, MA
Entrepreneur. Co-Founder and CEO of Fractyl Laboratories

Cardiologist. Frustrated by the real world, population-level, inability to solve the known risk factors leading to cardiovascular disease and by use of insulin as a treatment for T2D

Scientist. Enamored by what bariatric surgery can teach us about the role of the GI tract in human metabolism
Insulin resistance syndrome is an important metabolic driver of NAFLD/NASH

- Insulin sensitization can reverse fatty liver and NASH

Duodenal bypass surgery best viewed as a metabolic intervention

- Duodenal bypass has insulin sensitizing effect

Emerging evidence highlights key role of duodenal mucosa

- Adaptive changes to mucosa as a potential driver of metabolic disarray

Role for endoscopic interventions as treatments for GI root cause

- Insulin sensitizing, compliance-independent, patient friendly
The Central Role of Insulin Resistance in Metabolic Diseases

Insulin Resistance

"Inadequate" insulin response

Compensatory Hyperinsulinemia

Type 2 Diabetes

Retinopathy
Nephropathy
Neuropathy

CVD

Insulin Resistance Syndrome

Fatty liver
Hypertension
Stroke
PCOS

Adapted from AACE position statement
Insulin Sensitizing Drugs Can Resolve NASH in T2D Patients

Insulin Sensitizing Drugs (TZDs) then withdrawal after 1 year

Clinical benefit of TZDs are now well established

- Histologic resolution of NASH\(^{(1,2)}\)
- T2D
- CV disease
- Stroke
- Disease prevention (T2D)
- PCOS

(1) Cusi et al Annals Int Med 2016;
(2) Lutchman et al Hepatology 2007
Gastric Bypass Surgery Can Reverse and/or Prevent Insulin Resistant Metabolic Diseases

Improved NASH after Gastric Bypass Surgery

- NASH\(^{(4)}\)
- T2D\(^{(1)}\)
- CV disease
- Disease prevention (T2D)\(^{(5)}\)
- PCOS
- Greater patient satisfaction\(^{(6)}\)

Sources: (1) Mingrone et al. NEJM. 366(17); (2) Pories et al. Ann Surg. 222(3): 339-50; 1995; (3) Nannipieri et al. JCEM. 96(9); (4) Liu et al. Obes Surg 17(4); (5) Carlsson et al. NEJM. 367(8); (6) Mingrone et al. Lancet 386 (9997), p964-973
Duodenal Bypass Elicits Immediate Weight-Independent Insulin Sensitizing Effects

- Insulin sensitivity measured by hyperinsulinemic clamp in patients with T2D
- Similar weight loss between gastric restriction and RYGB groups
- Much greater insulin sensitization in RYGB cohort

Kashyap SR…Schauer PR IJO 2010
Exploring the Potential Role of the Duodenum: Metabolic Changes in DIO Mouse Model

**Excess weight**

- **Baseline**
- **Lean 7 weeks**
- **DIO 7 weeks**
- **Lean 13 weeks**
- **DIO 13 weeks**

**Blood glucose** (mmol/L)

Insulin (pg/ml)

**Serum insulin**

**Liver weight**

Collaboration with Gubra; unpublished data
Changes in Duodenal Mucosa Volume and Gene Expression in DIO Mouse Model

Duodenal mucosal volume expansion

Massive gene expression changes in duodenal mucosa (RNA seq)

Collaboration with Gubra; unpublished data
Changes in Duodenal Mucosa Volume and Gene Expression in DIO Mouse Model

...consistent with known increases in enteroendocrine cell numbers in human duodenal biopsies in T2D patients

...potentially due to physiologic organ adaptation to dietary fat and sugar

---

Theodorakis et al

---

O'Brien et al
Duodenal Mucosal Rejuvenation (Revita™ DMR System)

- Duodenal Mucosal Rejuvenation (DMR) procedure resurfaces the duodenal mucosa post-thermal ablation
- Designed to ‘re-set’ local abnormal signals emanating from the duodenal surface
- This approximates the duodenal exclusion in bypass surgery (as angioplasty is to CABG)
- Procedure conducted during upper GI endoscopy:
  - Minimally invasive upper endoscopic procedure conducted <1 hour
  - Techniques familiar to GI endoscopists
    - Saline expansion of submucosa
    - Hydrothermal mucosal ablation
  - Graduated diet post-procedure
Patients with T2D had pronounced and sustained improvements in liver transaminases in a weight-independent manner.

Rajagopalan H, EASL 2016 & DDW 2016,
DMR Metabolic signature (substudy n=14)

- Meal challenge samples (fasting and post-prandial) at 0 and 3 months from FIH study analyzed by Metabolon, North Carolina
- Summary of findings
  - Improved insulin sensitivity (↓αHBA)
  - ↓ FA β-oxidation
  - Improved mitochondrial function
  - ↓ inflammation (↓HETE) – marker of NAFLD→NASH

Collaboration with Sanyal and Metabolon; unpublished data

- Reductions in triglycerides
- Reductions in lipid intermediates
- Reductions in post-prandial FFAs

Collaboration with Sanyal and Metabolon; unpublished data
Revita-1 Markers of Insulin Sensitization

- Multicenter, open label, safety study in T2D patients
- ~ 50 patients; ~ 25 now at 1 year follow up
- Minimal dietary counseling
- Completed enrollment H2 2016
- Well tolerated procedure with no device or procedure related SAEs
Revita-1 Experience Suggests Sustained Improvements in Hepatic Insulin Sensitivity

- Study not actively enriched for fatty liver patients
- Future work will characterize liver in greater detail
- Expect to see synergistic benefit with focused lifestyle intervention
Sham-Controlled T2D Study Now Underway with Secondary Liver Endpoints

**Updated Revita-2 RCT**

Screening ~ 1 month from Day 0
T2D patients on >=1 oral agent (no insulin or GLP-1)
HbA1c 7.5-10%

<table>
<thead>
<tr>
<th>Sham</th>
<th>DMR</th>
</tr>
</thead>
</table>

Randomization

Week 24

- ~ 75 patients at up to 15 centers
- Primary endpoints: HbA1c; safety
- Secondary endpoints: Liver MRFF
NASH Pilot Study Initiating 2017 H2

Biopsy-proven NASH
Documented insulin resistance

DMR + Lifestyle

Follow up to 12 months

Week 24

• ~ 10-15 patients
• Primary endpoints: 6 mo MRFF
• Secondary endpoints: 12 mo biopsy
Many fascinating mechanistic questions to be explored

Apparently safe and scalable outpatient intervention performed by endoscopists/hepatologists

Early suggestion of durable disease modifying impact without enforced lifestyle intervention

Overcomes compliance challenges in real world setting

Can effectively complement & enhance effectiveness of drugs that target later stage disease

Can offer broad metabolic benefit for patients with T2D and NAFLD/NASH