Duodenal mucosal hydrothermal ablation: a new procedure designed for metabolic gain

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Disclosure

- Fractyl Laboratories employee and shareholder
Global Pandemic of Metabolic Disease

- Insulin resistance is a key pathophysiological defect at the core of T2D, fatty liver disease and cardiovascular disease.
- In 2040, 650M people around the globe will have T2D (1 in 10)\(^{(1)}\)
- Currently, 40+ different pharmacological agents available for T2D in US yet 50% of diabetics remain poorly controlled through disease progression, pharmacological failure and/or treatment non-compliance\(^{(2)}\).
- Fatty liver disease will soon be the main driver of end stage liver disease and need for organ transplant → with currently no available treatments for fatty liver disease.
- Bariatric surgery has manifested a potent effect to improve dysmetabolic conditions and has uncovered a key metabolic role of the gastro-intestinal tract.
- Yet bariatric surgery may not be a scalable solution to address population-level metabolic disease.

\(^{(1)}\) IDF 2015; \(^{(2)}\) Lipska K et al D Care 2016; \(^{(3)}\) Bazick et al D Care 2016; \(^{(4)}\) Sanofi IR deck
Gastric Bypass Surgery Epiphany

**Improved Glycemic Control Post RYGB**

- Potent glycemic improvement in T2D\(^{(1)}\)
- Anti-diabetic effect is in part weight independent\(^{(2)}\)
- Glycemic effect tied to background β cell function\(^{(3)}\)
- Disease prevention of both T2D & NAFLD\(^{(4)}\)
- Histologic resolution of NASH
- Return of ovulation in PCOS
- Reduced CV disease
- Improved patient satisfaction\(^{(5)}\)

**Clinical Benefits of RYGB**

*Bariatric surgery offering a window into the metabolic role of the GI tract*

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); \(^{(4)}\) Carlsson et al. NEJM. 367(8); \(^{(5)}\) Mingrone et al. Lancet 386 (9997), p964-973
Gastric Bypass Surgery Epiphany

Improved Glycemic Control Post RYGB

Mechanistic Explanation
- Early post-surgery hypocaloric effect
- Specific signaling from duodenum
- Hindgut incretin effect
- Bile acids
- Microbiome
- Shrinking Adipose-TG depot
- Malabsorptive contribution

Bariatric surgery offering a window into the metabolic role of the GI tract

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Metabolic Role of the Duodenum

Physiological role?
- Insulin resisting signal emanating from upper GI potentially important in early hunter gatherer

Evidence from intervention
- RYGB
- Roux re-exposure
- Endoluminal sleeve

Evidence of pathophysiology
- Hypertrophy-hyperplasia in upper GI exposed to hexose/fat
- Abnormal enteroendocrine population

Duodenal Ablation: Early Proof of Concept

**Rodent**
- GK rat POC
  - Denuding duodenum caused lowering of hyperglycemia
  - No effect seen in non-diabetic rodent

**Porcine**
- Ablation method
  - Novel balloon catheter
  - Hydrothermal heat exchange
  - Superficial mucosa re-surfacing – no deep structure damage

**Human**
- First-in-man
  - Single site (Chile)
  - T2D patients (n=48)
  - OAD treated
  - Subsequent study in multiple centers (EU)
Duodenal Mucosal Resurfacing Procedure

- Duodenal Mucosal Resurfacing (DMR) is designed to rejuvenate the duodenal mucosal surface, replicating the duodenal exclusion of RYGB

- DMR conducted during upper GI endoscopy:
  - Utilizes techniques familiar to endoscopists
  - Single-use disposable catheter system
  - Same day, minimally invasive procedure conducted <1 hour
  - Software & integrated sensors designed to minimize operator and procedural error

- DMR hydrothermal ablation resurfaces a targeted post-papillary duodenum segment of ~10-12 cm
Procedure:

- Duodenal mucosa lifted by saline to create thermal barrier protecting deeper tissues
- Circumferential ablation through thermal exchange (hot water)
- Follow up endoscopies and duodenal biopsies at 1mo and 3mo to document mucosal healing

DMR: endoscopic view
DMR Overall Safety and Tolerability

- Total ~100 cases in early FIH and ongoing multicenter study
  - Includes cases with new single catheter
- Post-procedure: patients adhere to 2 week eucaloric diet
  - liquid → puree → semi-solid
- Post-procedure: favorable tolerability profile with minimal GI symptoms
- Three duodenal stenoses in early FIH experience → each successfully treated with single non-emergent balloon dilation and no later sequelae
- No device/procedure related SAEs in last ~65 cases after implementation of improved mucosal lift procedure
- No apparent hypoglycemic risk
- No evidence of malabsorption
- No late adverse events observed (50+ patients >12 months)

Legend
FIH: first-in-human
First-in-Human Study: Patient Characteristics

- Open label, single-arm, single center feasibility study in Santiago, Chile
- Patient entry: A1C 7.5-12%, BMI 24-40, age 28-75, 1-2 OAD (no insulin)
- 44 consecutive patients enrolled
  - 4 patients were not treated (1 duodenal anatomy, 2 failed screening endoscopy, 1 procedure duration)
  - 1 patient with anti-GAD Ab (exclusion criteria) treated and followed for safety alone

<table>
<thead>
<tr>
<th>PATIENTS ENROLLED</th>
<th>(N=44)</th>
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</thead>
<tbody>
<tr>
<td>Age, mean years +/- standard deviation (“SD”)</td>
<td>53.3 +/- 7.5</td>
</tr>
<tr>
<td>Male</td>
<td>28 (63.6%)</td>
</tr>
<tr>
<td>BMI, mean kg/m2 +/- SD</td>
<td>30.9 +/- 3.5</td>
</tr>
<tr>
<td>Systolic BP, mmHg +/- SD</td>
<td>122.1 +/- 14.4</td>
</tr>
<tr>
<td>Duration T2D, mean years +/- SD</td>
<td>5.7 +/- 2.2</td>
</tr>
<tr>
<td>HbA1c, % +/- SD</td>
<td>9.5 +/- 1.3</td>
</tr>
<tr>
<td>FPG, mg/dL +/- SD</td>
<td>184 +/- 58</td>
</tr>
<tr>
<td>Hepatic Steatosis on baseline ultrasound</td>
<td>11 (25%)</td>
</tr>
</tbody>
</table>

**Oral Anti-diabetic Rx**
- Metformin, n | 44 (100%)
- Sulfonylurea, n | 20 (44%)
Ablation length was increased from short segment DMR to long segment DMR as FIH trial progressed.

Patients blinded to ablation length and managed in identical fashion.

Fasting glucose improvements observed as early as 1 week post-procedure.

Statistically significant improvement in fasting glucose versus baseline of 64 mg/dl noted in LS DMR vs 26 mg/dl in SS DMR.

Net medication reductions in LS DMR cohort post-procedure.
DMR Effects on Meal Challenge Glycemia

Meal challenge plasma glucose (PG 0-120 min) in LS-DMR subjects (n = 28)

Legend
LS-DMR: patients receiving long segment (~10cm) DMR ablation
DMR Lowered A1C (0-6 Month Data)

A1C change in LS-DMR subjects with higher (>10%) and lower (<10%) entry A1C

A1C change in LS-DMR subjects with lower entry A1C (<10%) where background OAD was either stable or reduced

Rajagopalan, H, et al., Diabetes Care, 2016
DMR Lowered Hepatic Transaminases

- Consistent lowering of hepatic transaminases (ALT and AST) in combined FIH and multi-center cohorts

- DMR is associated with a modest weight effect (2-3kg) in short term that returns to baseline by 6 months

- Graphs demonstrate change in AST and ALT by tertile starting levels
DMR Metabolomic Signature (0-3 Month Data)

- Meal challenge samples (0-3 months)
- Metabolomic analysis

- Improved glucose handling
- Improved insulin sensitivity (↓αHBA)
- ↓TAGs, DAGs
- ↓FA β-oxidation
- Improved mitochondrial function (↓dicarboxylic acids)
- ↓inflammation (↓HETE) – marker of NAFLD→NASH
- ↓lipid peroxidation – seen with insulin sensitizing
- ↑anti-oxidant capacity (↓glutathione catabolism)
- Altered 2° bile acids (microbiome-related?)
Conclusions

- Increasing evidence that the duodenum plays an important metabolic role

- Duodenal mucosal resurfacing (DMR) appears to exert an insulin sensitizing effect that impacts cardiometabolic indices
  - implications for T2D, fatty liver disease and other insulin resistant conditions
  - raising the potential for a compliance-independent approach to disease management

- Future study is necessary to understand
  - safety in larger numbers of users and patients
  - mechanism
  - efficacy and durability
  - clinical utility in the treatment of insulin resistant conditions
Metabolic Role of the Duodenum

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• DMR hydrothermal ablation

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DMR Lowers Microalbuminuria

Microalbuminuria sampling from EU multi-center trial (Revita-1)

Number of patients

- 20
- 17
- 19
- 12
Gastric Bypass Surgery Epiphany

Improved Glycemic Control Post RYGB

Clinical Benefits of RYGB

- Superior glycemic effect (T2D)(1)
- Weight independent anti-diabetic effect(2)
- Glycemic effect tied to background β cell function(3)
- Histologic resolution of NASH
- Prevent disease onset T2D/NAFLD(4)
- Return of ovulation in PCOS
- Reduced risk of CV disease
- Improved patient satisfaction(5)

Bariatric surgery offering a window into the metabolic role of the GI tract

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Procedure Animation
First-in-Human Trial

HbA1c Reductions

ALT in Subjects with Fatty Liver

Patients whose medical regimen remained stable through the 6-month follow-up period demonstrated sustained & durable drops in HbA1c.

Patients with fatty liver show significant reductions in ALT, a common marker liver inflammation, suggesting impact on NAFLD/NASH.
Glycemic Efficacy Greater with Long-Segment DMR

Effect of short segment (SS, white circles) and long segment (LS, black circles) DMR treatment on FPG plotted to 3 months (n = 39)*

FPG change from screening plotted to 3 months in individual subjects who received LS-DMR (n = 28)*

Rajagopalan, H et al., Diabetes Care, 2016; *Data are reported as mean ± SD, S = pre-procedure value.
Sugar in the duodenum appears to cause hypertrophy of mucosa

Changes lead to excess lipolysis in adipocytes and gluconeogenesis in the liver (amplified “fasting” signal)

In the absence of glucose utilization, this leads to a buildup of hepatic fuel intermediates and mitochondrial dysfunction

Hepatic and systemic insulin resistance ensues

Potentially reversible with duodenal resurfacing (akin to laser skin resurfacing)
Bariatric Surgery Provides Key Insight to Solution

RYGB exerts broad metabolic benefits

Duodenal bypass alone reduces hepatic insulin resistance\(^1,2\)

Duodenal mucosa maladapted by Western diet\(^3-5\)

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2. Cummings DE et al. IFSO 2016
DMR State of Play

- DMR as a **safe and scalable intervention**
  - Well tolerated procedure with favorable safety/tolerability profile
- DMR as a **compliance-independent approach** to disease management
  - Can overcome real world limitations of complicated drug regimens, side effects, and compliance challenges
- DMR as an **insulin sensitizing procedure**
  - Disease modification addressing root cause of insulin resistance with broad metabolic improvements relevant to T2D, NAFLD/NASH, PCOS
- Future studies will be directed at demonstrating safety/efficacy, optimizing performance, and establishing clinical utility in broader populations
Duodenal Bypass a Key Component

Before Surgery

After Surgery
Duodenal-Jejunal Bypass vs. Gastrojejunostomy

- Goto-Kakizaki rats each received one of several surgeries
- Glucose evaluated by glucose tolerance test
- Duodenal-jejunal bypass improves glucose control
- Numerous follow up studies elucidating insulin sensitization, improvement in liver fat, fibrosis post-DJB
Acute re-introduction of nutrients into the bypassed duodenum (Roux limb) via PG tube caused an immediate worsening of glycemia.
Evidence that Duodenal Mucosa is Maladapted

Small bowel abnormal in obese and diabetic genetic rodent models and fat/hexose challenged rodents

- Duodenal and proximal jejunal hypertrophy\(^{(1)}\)
- Duodenal entero-endocrine (GIP secreting) cell hyperplasia\(^{(2)(3)}\)

Abnormal enteroendocrine populations in T2D subjects

Non-diabetic (n=36) and T2D (n=17) subjects underwent duodenal biopsy and metabolic characterization.
Rodent proof of concept

- Goko-Kakizaki diabetic rodents studied
- Denudation of duodenal mucosa conducted through mechanical abrasion
- 35%↓ of hyperglycemia post oral glucose gavage
- Glucose lowering not observed in sham study or in non-diabetic Wistar rodents

OGTT before and after abrasion

OGTT before and after sham
Rodent proof of concept

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Clinical Roadmap to Date

First in Human
Single center
Open label
“Procedure Definition”

- Initial safety and feasibility for T2D
- Long segment DMR more effective (dose effect)
- Mechanistic basis of DMR as insulin sensitizing
- Diabetes Care Aug 2016, Video GIE ~ Sept 2016

Revita-1
Multicenter
Open label
“Patient Selection”

- Reproducibility of outcomes across EU centers
- Medication management more controlled
- Used to refine patient entry criteria for RCTs
- Introduced next generation catheter

Revita-2
Multicenter Ph2b equiv.
Sham RCT
“Efficacy Demonstration”

- Beginning Q4 2016 in ~ 12 EU centers
- Aim: Test efficacy in sham-controlled conditions
- Aim: Elaborate on metabolic mechanisms
- Aim: NAFLD/NASH clinical endpoints (e.g. MRFF)