# DUODENAL MUCOSA: A TARGET FOR TREATING METABOLIC DISEASE

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Targeting the Duodenal Mucosa

- Bariatric surgery epiphany
- Relevance of duodenal exclusion
- Duodenal pathophysiology
- Duodenal Mucosal Resurfacing for metabolic gain
The central role of insulin resistance in metabolic diseases

- Insulin Resistance
  - "Inadequate" insulin response
    - Type 2 Diabetes
      - Retinopathy
      - Nephropathy
      - Neuropathy
  - Compensatory Hyperinsulinemia
    - Insulin Resistance Syndrome
      - CVD
      - Fatty liver
      - Hypertension
      - Stroke
      - PCOS

AACE position statement
RYGB is the most effective treatment for T2D…but why?

“Some doctors say gastric bypass surgery appears especially beneficial…reducing the stomach to the size of a small pouch and bypassing a portion of the intestine, which potentially changes certain gastrointestinal hormones or other factors.”

- WSJ 7/1/15
Gastric Bypass Surgery experience provides key insight to a solution

**Improved Glucose Control Post Gastric Bypass Surgery**

- **Clinical Benefit of Gastric Bypass Surgery**
  - Superior glycemic effect (T2D)\(^1\)
  - Weight independent anti-diabetic effect\(^3\)
  - Can prevent disease onset (T2D/NAFLD)\(^2\)
  - Glycemic effect tied to background beta-cell function\(^4\)
  - Greater patient satisfaction\(^5\)

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**Mechanistic evidence suggests that the early metabolic improvement is ‘insulin sensitizing’**

Sources: (1) Mingrone et al. NEJM. 366(17); (2) Carlsson et al. NEJM. 367(8); (3) Pories et al. Ann Surg. 222 (3): 339-50; 1995; (4) Nannipieri et al. JCEM. 96(9); (5) Mingrone et al. Lancet 386 (9997), p964–973
Bypass of the duodenum a key component of bariatric surgery
Post RYGB: re-exposing the duodenum to nutrients immediately reproduces dysglycemia

Acute re-introduction of nutrients into the bypassed duodenum (Roux limb) via PG tube caused an immediate worsening of post-prandial glucose excursion (~50%↑)

Could the duodenum be a key driver of insulin resistance?

- Duodenal changes?
  - "Inadequate" insulin response
  - Compensatory Hyperinsulinemia

  - Type 2 Diabetes
    - Retinopathy
    - Nephropathy
    - Neuropathy
  - Insulin Resistance Syndrome
    - Fatty liver
    - Hypertension
    - Stroke
    - PCOS

- Insulin Resistance

AACE position statement
Evidence that duodenal mucosa is maladapted in obesity and diabetes

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

- duodenal and jejunal hypertrophy\(^1\)
- duodenal entero-endocrine (GIP secreting) cell hyperplasia\(^2\)

\(^2\) Bailey et al. *Acta Endocrinol (Copenh).* 1986;112(2):224-229
\(^3\) Gniuli et al. *Diabetologia.* 2010;53(10):2233-2240
Duodenal mucosa has abnormal enteroendocrine populations in T2D subjects

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

Theodorakis et al. AJP Endocrinol Metab. 2006;290(3):E550-E559.
Denuding the duodenal surface lowers hyperglycemia: 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 rodents
Mucosal resurfacing is a compelling way to target the apparent duodenal pathological defect

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<th>Approach</th>
<th>Considerations</th>
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| Pharmacological       | • No targets yet identified  
• Glucose lowering versus disease modifying  
• Drugs may not solve population level chronic disease problem |
| Duodenal resurfacing  | • Ablation is an established tool in other tissues  
• Could address root cause epithelial changes in a precise manner  
• Can potentially become a patient-friendly intervention (e.g. offering a metabolic reset and circumventing burdens of compliance) |
Duodenal Mucosal Resurfacing (DMR) procedure resurfaces the duodenal mucosa post-thermal ablation

Designed to provide a metabolic reset to approximate the duodenal exclusion in the form of bypass surgery

Procedure conducted during upper GI endoscopy:

- Control console and single-use disposable catheter
- Same day minimally invasive procedural therapy conducted <1 hour
- Techniques familiar to GI endoscopists
  - No implant, surgery, or suturing
  - Saline expansion of submucosa
  - Hydrothermal mucosal ablation
To date, 80 T2D patients have undergone DMR (S America, EU)

Procedure implemented well by endoscopists and well tolerated by patients

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 document full mucosal healing

Three stenosis observed in early use but none since procedure modification

No other major complications
Patient Case Study

43 year old male
Diabetes duration 5 years
BMI 31.3 kg/m²
Treatment Metformin, SU

Intervention: endoscopic DMR
Mild GI symptoms post-DMR for 1 day

Mixed meal tolerance test conducted pre-DMR and 6 months post-DMR

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<th>minutes</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>45</th>
<th>60</th>
<th>90</th>
<th>120</th>
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<td>Pre-DMR</td>
<td>glucose (mg/dl)</td>
<td>162</td>
<td>168</td>
<td>193</td>
<td>225</td>
<td>259</td>
<td>247</td>
</tr>
<tr>
<td>6 months</td>
<td>glucose (mg/dl)</td>
<td>132</td>
<td>141</td>
<td>172</td>
<td>185</td>
<td>198</td>
<td>215</td>
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Conclusions

- Duodenum appears to play an important gluco-regulatory role
  - Illuminated by bariatric surgical science
  - Apparent changes to duodenal mucosa may drive insulin resistance

- Duodenal mucosal resurfacing as an insulin sensitizing intervention
  - Potentially broad metabolic improvements in T2D and NAFLD/NASH
  - Compliance-independent approach to population-level disease control
  - Reduced reliance on polypharmacy is inherently attractive

- Early clinical work with favorable clinical signals
  - Future studies will be directed at demonstrating safety/efficacy, optimizing performance, and establishing clinical utility in broader populations