Metabolic Endoscopy

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Type 2 Diabetes: The Challenge

Battling the epidemic

Treatment shortcomings recognized

New solutions necessary

Images from IDF Diabetes Atlas 2014
Public Health Impact of Diabetes

- 1 in 10 people affected
- 1 in 3 born now will be affected
- 1 in every 7 healthcare $ spent annually (US)
- ~$250B spend annually (US)
- 1M+ new cases diagnosed annually (US)
- #1 cause of adult blindness, end stage kidney disease, and non-traumatic amputations
- Premature heart attack and stroke
Insulin Resistance is the Root Cause of Cardio-Metabolic Disease

The body becomes increasingly resistant to insulin
Our Management Paradigm for T2D is Failing

~ 50 Approved Drugs
> 7 Classes & Mechanisms

No improvement in outcomes over time
The evolution of Endoscopy

- Diagnostic
- Therapeutic
- Surgical
- Metabolic
Targeting the future

Each generation of gastroenterologists has had unique challenges:

- **Middle 70’**: biliary sphincterotomy
- **Middle 80’**: stents and polyps resection
- **Early 90’**: Video scopes and chromoendoscopy, metal stent
- **Early 2000**: small bowel endoscopy, ESD
- **Last years**: Third Space Endoscopy
For this generation, a major challenge (and opportunity) is to address the huge increase in the incidence of obesity and type 2 diabetes and provide endoscopic long-lasting solutions.

Small Bowel is turning from being a boring tract to a very appealing one because of its role of metabolic sensor and controller.
Key clinical observations after gastric bypass showed that weight loss and reversal of diabetes can occur and are largely caused by the **bypass of the proximal small bowel**

Several mechanisms of action for surgery of the small bowel to affect obesity and T2DM have been proposed:
- Incretin action
- Jejunal nutrient sensing
- Changes in the microbiota
Incretin Effect – Incretin Hormones

• Hormones that stimulates insulin secretion in response to meals

• The whole concept of incretin hormones comes from a decades-old observation that orally administered glucose provokes a far greater release of insulin than the same amount of glucose delivered by injection

• Here is the role of duodenal cells with adjustment of cells producing GLP-1 and GIP
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

Theodorakis et al. AJP Endocrinol Metab. 2006;290(3):E550-E559.
Changes in Duodenal Mucosa as response to dietary changes – \textit{western diet – fat and sugar excess}

...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

\begin{itemize}
  \item \textbf{A} Homeostasis
  \begin{itemize}
    \item Low local insulin (dILP3)
    \item Asymmetric division
    \item Enterocyte
    \item GLP-1(+)
    \item GLP(+)
    \item Colocalization
  \end{itemize}

  \begin{itemize}
    \item Symmetric division
    \item ISC
    \item ECL
    \item MiR-125
  \end{itemize}

  \begin{itemize}
    \item Symmetric division dominance
  \end{itemize}

\end{itemize}

\begin{itemize}
  \item \textbf{B} Feeding-Induced Growth
  \begin{itemize}
    \item High local insulin (dILP3)
    \item Symmetric division
  \end{itemize}

\end{itemize}
The expression of GIP/GLP-1-producing cells was significantly greater in individuals with T2D along the entire intestinal tract.
Central Role of Insulin Resistance

Insulin Resistance

Compensatory hyperinsulinemia

- Insulin Resistance Syndrome
  - Fatty liver
  - Hypertension
  - Stroke
  - PCOS

“Inadequate” insulin response

- Type 2 Diabetes
  - Retinopathy
  - Nephropathy
  - Neuropathy

CVD
Nutrient sensing

Bypassing the duodenum, nutrient flow is increased into the jejunum. This results in activation of jejunal nutrient-sensing mechanisms involving a series of biochemical reactions, gut-derived hormones, and neuronal circuitry that lead lower glucose production and plasma glucose levels.
Bariatric Science Illuminates the Critical Role for the Duodenum

Bariatric science has confirmed that proliferation of the duodenal mucosa, caused by excess sugar exposure, is at the root of insulin resistance.

2Salinari et al PLOS One 2013
Pitfalls of Bariatric Surgery

• Despite the well known and profound benefits, use of surgical procedures is still severely limited.

• In the United States, approximately 200,000 patients undergo bariatric procedures each year, representing approximately 0.25% of all adults with obesity and even less for those having T2D.

• Additional limitation are related to limited availability of resources and unwillingness of patients to undergo invasive procedures.
Endoscopy techniques to target duodenal changes

• **Endoscopic by-pass**
  • Stent-like device
  • Gastro-Jejunal anastomosis

• **Endoscopic Resurfacing/ablation**
  • Aiming to obtain persistent normalization of duodenal cells producing GIP/GLP-1
  • Gastric Mucosa devitalization
Duodeno Jejunal Bypass Sleeve

1) 60cm, nutrient impermeable Fluoropolymer sleeve

2) Nitinol anchoring system in duodenum
Brazil Obese Diabetes Study
Completers, n=13

HbA1c (%)

Implant time (weeks)

0 24 52

8,9

7,1

6,6

50% < 7.0

83% < 7.0
Chile Obesity Study
% Excess Weight Loss, N=24

Chile T2DM Study
(N=24)

<table>
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<tr>
<th></th>
<th>Baseline</th>
<th>52 weeks</th>
<th>p value</th>
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<tbody>
<tr>
<td>Weight (kg)</td>
<td>110.6 ± 16.5</td>
<td>88.2 ± 13.9</td>
<td>&lt;.0001</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>45.1 ± 6.2</td>
<td>36.0 ± 5.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>120.5 ± 16.7</td>
<td>96.0 ± 12.7</td>
<td>&lt;.0001</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>133.5 ± 14.5</td>
<td>124.9 ± 11.8</td>
<td>0.012</td>
</tr>
<tr>
<td>Diastolic</td>
<td>85.2 ± 6.5</td>
<td>71.2 ± 8.4</td>
<td>&lt;.0001</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL</td>
<td>196.5 ± 36.1</td>
<td>161.0 ± 38.4</td>
<td>&lt;.0001</td>
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<tr>
<td>LDL</td>
<td>44.2 ± 9.1</td>
<td>43.6 ± 8.2</td>
<td>0.70</td>
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<tr>
<td>Triglycerides</td>
<td>120.5 ± 29.5</td>
<td>94.5 ± 32.1</td>
<td>&lt;.0001</td>
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<tr>
<td>Glucose (mg/dl)</td>
<td>140.0 ± 28.4</td>
<td>94.3 ± 27.9</td>
<td>0.013</td>
</tr>
<tr>
<td>Insulin (mg/dl)</td>
<td>21.0 ± 10.7</td>
<td>15.9 ± 17.0</td>
<td>0.092</td>
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<tr>
<td>HOMA IR</td>
<td>5.7 ± 4.1</td>
<td>4.6 ± 8.6</td>
<td>0.423</td>
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<tr>
<td>HbA1c (%)</td>
<td>6.3 ± 1.4</td>
<td>6.0 ± 0.9</td>
<td>0.094</td>
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</table>
% EWL at 12 Months with EndoBarrier

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Statistics for each study</th>
<th>% EWL</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Lower limit</td>
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<tr>
<td>de Moura 2012</td>
<td>EndoBarrier</td>
<td>39.000</td>
<td>36.880</td>
</tr>
<tr>
<td>Munoz 2014</td>
<td>EndoBarrier</td>
<td>46.000</td>
<td>41.483</td>
</tr>
<tr>
<td>Koehestanie 2014</td>
<td>EndoBarrier</td>
<td>19.800</td>
<td>12.830</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>35.387</td>
<td>24.658</td>
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</tbody>
</table>

25%

Figure 5. Forest plot of studies evaluating the percentage of excess weight loss (%EWL) at 12 months after EndoBarrier implantation.

Mean difference in % EWL between EndoBarrier and control groups in RCTs

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Statistics for each study</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Difference in Mean</td>
<td>Lower limit</td>
</tr>
<tr>
<td>Tarnoff 2009</td>
<td>EndoBarrier</td>
<td>17.000</td>
<td>7.800</td>
</tr>
<tr>
<td>Gersin 2010</td>
<td>EndoBarrier</td>
<td>9.200</td>
<td>7.974</td>
</tr>
<tr>
<td>Schouten 2010</td>
<td>EndoBarrier</td>
<td>12.100</td>
<td>5.211</td>
</tr>
<tr>
<td>Koehestanie 2014</td>
<td>EndoBarrier</td>
<td>15.600</td>
<td>0.295</td>
</tr>
<tr>
<td></td>
<td>Random</td>
<td>9.457</td>
<td>8.264</td>
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</tbody>
</table>

15%

Figure 6. Forest plot of studies evaluating the mean difference in the percentage of excess weight loss (%EWL) compared with the sham or control groups after EndoBarrier implantation. RCTs, randomized, controlled trials.
### Change in HgA1c after EndoBarrier

<table>
<thead>
<tr>
<th>Group by weeks</th>
<th>Subgroup within study</th>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Mean</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P</th>
<th>Total</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>12.00</td>
<td>EndoBarrier</td>
<td>Tamoff 2009</td>
<td></td>
<td>-0.300</td>
<td>-0.922</td>
<td>0.322</td>
<td>0.345</td>
<td>3</td>
<td>-0.300</td>
</tr>
<tr>
<td>12.00</td>
<td>EndoBarrier</td>
<td>Schouten 2010</td>
<td></td>
<td>-1.100</td>
<td>-1.169</td>
<td>-1.031</td>
<td>0.000</td>
<td>8</td>
<td>-1.100</td>
</tr>
<tr>
<td>12.00</td>
<td>EndoBarrier</td>
<td>Rodriguez 2009</td>
<td></td>
<td>-0.736</td>
<td>-1.761</td>
<td>0.288</td>
<td>0.159</td>
<td></td>
<td>-0.736</td>
</tr>
<tr>
<td>24.00</td>
<td>EndoBarrier</td>
<td>de Jonge 2013</td>
<td></td>
<td>-2.400</td>
<td>-2.834</td>
<td>-1.966</td>
<td>0.000</td>
<td>10</td>
<td>-2.400</td>
</tr>
<tr>
<td>24.00</td>
<td>EndoBarrier</td>
<td>Koehstanie 2014</td>
<td></td>
<td>-1.400</td>
<td>-1.495</td>
<td>-1.305</td>
<td>0.000</td>
<td>17</td>
<td>-1.400</td>
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<tr>
<td>24.00</td>
<td>EndoBarrier</td>
<td>Escalona 2012</td>
<td></td>
<td>-1.691</td>
<td>-2.517</td>
<td>-0.865</td>
<td>0.000</td>
<td></td>
<td>-1.691</td>
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<tr>
<td>52.00</td>
<td>EndoBarrier</td>
<td>de Moura 2012</td>
<td></td>
<td>-1.400</td>
<td>-1.880</td>
<td>-0.920</td>
<td>0.000</td>
<td>6</td>
<td>-1.400</td>
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<tr>
<td>52.00</td>
<td>EndoBarrier</td>
<td>Cohen 2013.1</td>
<td></td>
<td>-2.300</td>
<td>-2.463</td>
<td>-2.137</td>
<td>0.000</td>
<td>13</td>
<td>-2.300</td>
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<tr>
<td>52.00</td>
<td>EndoBarrier</td>
<td>Cohen 2013.2</td>
<td></td>
<td>-1.100</td>
<td>-1.198</td>
<td>-1.002</td>
<td>0.000</td>
<td>16</td>
<td>-1.100</td>
</tr>
<tr>
<td>52.00</td>
<td>Random</td>
<td></td>
<td></td>
<td>-1.507</td>
<td>-2.229</td>
<td>-0.785</td>
<td>0.000</td>
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<td>-1.507</td>
</tr>
</tbody>
</table>

**Figure 7.** Forest plot depicting changes in glycosylated hemoglobin (HgA1c) after 12, 24, and 52 weeks of EndoBarrier implantation.

### Mean difference in HgA1c between EndoBarrier and control groups in RCTs

<table>
<thead>
<tr>
<th>Study name</th>
<th>Subgroup within study</th>
<th>Statistics for each study</th>
<th>Sample size</th>
<th>Difference in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez 2009</td>
<td>EndoBarrier</td>
<td>-1.790</td>
<td>10</td>
<td>-1.790 - -1.440</td>
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<tr>
<td>Schouten 2010</td>
<td>EndoBarrier</td>
<td>-0.700</td>
<td>8</td>
<td>-0.700 - -0.341</td>
</tr>
<tr>
<td>Koehstanie 2014</td>
<td>EndoBarrier</td>
<td>-0.900</td>
<td>34</td>
<td>-0.900 - -0.426</td>
</tr>
<tr>
<td>Random</td>
<td></td>
<td>-1.052</td>
<td>35</td>
<td>-1.052 - -0.426</td>
</tr>
</tbody>
</table>

**Figure 8.** Forest plot of studies reporting mean difference in glycosylated hemoglobin (HgA1c) between EndoBarrier and sham or control groups in randomized, controlled trials (RCTs). CI, confidence interval.
Tolerance and Safety Issues

• Patient tolerance of the device has been variable and early removal has necessary for symptoms in a significant percentage of patients.

• Complications related to the sleeve were reported in all the trials. The cumulative complication rate included:
  • 4.9% GI bleeding
  • 3.86% Sleeve obstruction
  • 3.4% Liver abscess
  • 0.126% Cholangitis
  • 0.126% Acute cholecystitis
  • 0.126% Esophageal perforation
USA Experience

• A pivotal multicenter randomized controlled trial was initiated in the United States in 2013

• this 21-center trial had enrollment suspended in March 2015 because of a safety issue with an increased incidence of hepatic abscesses being reported (overall 4 cases in 325 pts randomized)

• FDA has denied approval after
Scientific Advisory Board

IK+EM Study Released at EASD Shows Similar Outcomes Between Gastric Plication and EndoBarrier

LISBON, PORTUGAL — 25 September 2017 — GI Dynamics®, Inc. (ASX:GDI), a medical device company that has commercialized EndoBarrier™ in Europe, the Middle East and South America for patients with type 2 diabetes and obesity, announces that new data has been released from the Institute for Clinical and Experimental Medicine (IČU) on the comparison of 40 patients who
This 120-cm fluoropolymer sleeve is implanted with endoscopic techniques and then secured in place with a laparoscopic procedure.
GDJ BYPASS Sleeve

• Two trials, one pilot study 22pts and a second one with 13pts
• 2 implants failed in the first and 1 in the second trial
• Sleeve implanted for 12 weeks
• 7 pts required early removal within 3wks due to dysphagia/obstruction
• %WL >40% @ 3mos
• Eleven subjects in the 2 trials had T2DM and all improved with therapy (stopped medications or showed improvement in glycosylated hemoglobin).

*Sandler BJ 2011 Surg Endo, Gersin K, GIE 2010*
DUAL-PATH ENTERAL BYPASS

The goal is to create a dual-lumen proximal jejunal to distal ileal anastomosis that allows partially digested contents to pass rapidly to the distal ileum.

Ten morbidly obese subjects (mean BMI, 41 kg/m²) underwent an enteroenteral bypass under laparoscopic observation to ensure adequate anastomosis formation.
DUAL-PATH ENTERAL BYPASS

Machytka E, et al DDW 2016
Duodenal Mucosal Resurfacing Procedure – Ablation technique

- Duodenal Mucosal Resurfacing (DMR) procedure resurfaces the duodenal mucosa post-thermal ablation
- Designed to provide a metabolic reset to approximate the duodenal exclusion in bypass surgery
- Technique developed in large animal model
- Procedure conducted during upper GI endoscopy:
  - Control console and single-use disposable catheter
  - Fluoro Room and General Anesthesia
  - Same day minimally invasive procedural therapy conducted <1 hour
  - Resurfacing of ~ 10 cm of post-papillary duodenum
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 mucosal healing
Ablation length was increased from short segment DMR to long segment DMR as FIH trial progressed.

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.

<table>
<thead>
<tr>
<th></th>
<th>Month 3</th>
<th>Month 6</th>
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</thead>
<tbody>
<tr>
<td>Long segment (n=28)</td>
<td>-2.5 ± 0.2%</td>
<td>-1.4 ± 0.3%</td>
</tr>
<tr>
<td>Short segment (n=11)</td>
<td>-1.2 ± 0.5%</td>
<td>-0.7 ± 0.5%</td>
</tr>
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</table>
Revita-1: Study Characteristics

- Multi-center study in Europe and Chile
- Patients receiving Long Segment DMR with two catheter system
- Baseline beta cell function assessed by fasting insulin

### Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (n=22)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>56 ± 8</td>
</tr>
<tr>
<td>Male (n (%))</td>
<td>10 (45)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.8 ± 4.4</td>
</tr>
<tr>
<td>Duration T2D (yrs)</td>
<td>6.4 ± 2.4</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.4 ± 0.7</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>187 ± 40</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation

- Entry: HbA1c 7.5-10% on oral drugs
  - Stop sulfonylureas at - 4 weeks
  - Concomitant meds constant through 24 weeks (M6)

- Run-in 4 weeks
- Meds held constant
- Treat to Target HbA1c
DMR Safety and Tolerability

• Total ~100 cases in early First-in-Human (“FIH”) and ongoing multicenter Revita-1 study

• Three duodenal stenoses in early FIH experience → each successfully treated with single balloon dilation

• One small bowel perforation SAE in recent use but with older catheter design

• No apparent hypoglycemic risk, or evidence of malabsorption
Revita-1a: Shows Sustained Reductions in Hepatic Insulin Resistance Markers

Patients in Revita-1a (n=28) exhibit sustained reductions in HOMA-IR and ALT through 12 months follow up.
Revita-1a: Shows Sustained Reductions in Systemic Insulin Resistance Markers

Broader Markers of Systemic Insulin Resistance FPG and Urinary Albumin also Show Potent and Sustained Reductions
Revita-1a Key Findings: Blood Sugar Reductions are Sustained in Absence of Lifestyle Intervention

- 12 month data show durable improvements in HbA1c
- Weight loss of 2kg’s (in the absence of a lifestyle intervention)
## Clinical Program Overview

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Details</th>
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<tbody>
<tr>
<td>2016</td>
<td>FIH</td>
<td>Chile single-arm uncontrolled study T2D 1&lt;sup&gt;o&lt;/sup&gt; endpoint, procedure feasibility</td>
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<td></td>
<td>completed</td>
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<td></td>
<td>Revita 1</td>
<td>EU single-arm uncontrolled study, T2D 1&lt;sup&gt;o&lt;/sup&gt; endpoint 2-catheter → 1-catheter</td>
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<td></td>
<td>Revita 2</td>
<td>EU Multi-Center Randomized Study T2D 1&lt;sup&gt;o&lt;/sup&gt; endpoint, NASH 2&lt;sup&gt;o&lt;/sup&gt; endpoints</td>
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<tr>
<td></td>
<td>US Pilot</td>
<td>US Randomized Studies T2D 1&lt;sup&gt;o&lt;/sup&gt; endpoint, NASH 2&lt;sup&gt;o&lt;/sup&gt; endpoints</td>
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<td>US Pivotal</td>
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<td></td>
<td>NASH Pilot</td>
<td>NASH 1&lt;sup&gt;o&lt;/sup&gt; endpoints T2D 2&lt;sup&gt;o&lt;/sup&gt; endpoints</td>
</tr>
</tbody>
</table>
• Gastric mucosa devitalization (GMD) of 70% of the stomach was achieved by APC in a high-fat diet rat model and was compared with VSG and sham surgery

• GMD resulted in significant reductions in body weight, visceral and subcutaneous adipose tissue, and hepatic steatosis as well as an improvement in lipid metabolism
**Conclusions**

1. **Disease physiopathology:** Health of the duodenum impacts insulin resistance, which influences a broad spectrum of metabolic and physiologic functions.

2. **Unmet Need:** Current therapies for metabolic diseases target symptoms versus the root cause: insulin resistance.

3. **Endoscopy:** has strategic role since can target the duodenal and small bowel changes and try to provide persistent improvements.

4. **Stent and long-sleeve:** despite evidence of some clinical benefit, long-term complications have hampered their full adoption in clinical practice.

5. **DMR (Duodenal Mucosal Resurfacing):** is safe, minimally invasive, scalable, free from compliance concerns and has potential to reduce health care cost, polypharmacy, and therapies associated with higher AEs.