Duodenal mucosal resurfacing combined with GLP-1 eliminates insulin therapy and improves metabolic health in type 2 diabetes

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Disclosures

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• Frits Holleman reports speaker fees from Sanofi, Bioton, Astra Zeneca and Boehringer Ingelheim.
Target the duodenum for treatment of T2D

• Westernized diet induces:
  • Hyperplastic changes in duodenal mucosa
  • Altered local enteroendocrine function
  • An insulin resistant state

• Bariatric surgery improves T2D

• Surgery is too invasive for managing T2D

DMR + GLP-1 to eliminate insulin therapy and improve metabolic health in type 2 diabetes

Revita™ Duodenal Mucosal Resurfacing Procedure

- Submucosal saline injection through 3 ports attached to balloon
- Hydrothermal mucosal ablation through balloon
- Ablation between Ampulla of Vater and Ligament of Treitz
Earlier studies with DMR

• First-in-human study in Chile (n=39)
• Multicentre study in Europe (n=46)
  • In T2D patients on oral medication
  • HbA1c decrease of 10 mmol/mol (≈comparable to 1 oral drug)\(^1\)
  • Sustained at 24 months

• How does DMR work?
  • Improves insulin sensitivity (hallmark of T2D and metabolic syndrome)
  • Compliance free single step treatment

\(^1\)Van Baar, Gut. 2019
Can we eliminate insulin therapy in T2D?

- Improve insulin resistance by DMR
- Boost the effect of DMR by GLP-1
  - Improves β-cell function and β-cell protection
Inclusion criteria INSPIRE study

• Type 2 diabetes using once daily insulin

• HbA1c <64 mmol/mol

• Proof of adequate own insulin production (c-peptide >0.5)
  • Otherwise, improving insulin resistance by DMR will not be effective
Intervention triangle

1. DMR procedure
   • Insulin stopped at day of DMR

2. GLP-1 (Victoza®)
   • Stepwise dose increase to 1.8mg/day

3. Lifestyle counselling
   • Daily intake: According to Basal Metabolic Rate + 0-20%
   • Daily 30min low impact exercise
Study flow and follow-up

• Screening

• Baseline visit
  • Assessment metabolic health: Mixed meal test, liver MRI, DEXA scan
  • DMR procedure (start intervention)

• 3 month visit

• 6 month visit
  • Assessment metabolic health: Mixed meal test, liver MRI, DEXA scan

• Re-introduction of insulin in case of inadequate glycaemic control
Primary endpoint

• % of patients who were off insulin at 6 months with adequate glycaemic control (HbA1c ≤ 58 mmol/mol)

Secondary endpoints

• Glycaemic parameters: HbA1c, FPG, HOMA-IR, postprandial glucose
• Metabolic parameters: BMI, liver fat (MRI), body fat (DEXA)
Baseline characteristics

<table>
<thead>
<tr>
<th>Patient characteristics (N=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
</tr>
<tr>
<td>Duration of T2D [years]</td>
</tr>
<tr>
<td>Weight [kg]</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
</tr>
<tr>
<td>HbA1c [mmol/mol]</td>
</tr>
<tr>
<td>Fasting plasma glucose [mmol/l]</td>
</tr>
<tr>
<td>C-peptide [nmol/l]</td>
</tr>
<tr>
<td>HOMA-IR</td>
</tr>
</tbody>
</table>

### Antidiabetic medication

| Mean number of daily units of insulin | 31 |
Primary endpoint

• 75% (12/16) were free of insulin at 6 months with maintained (improved) glycaemic control (HbA1c ≤ 58 mmol/mol)
Despite elimination of insulin, improved glycaemic control

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>Δ Median (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c [mmol/mol]</strong></td>
<td>58</td>
<td>50</td>
<td>-6 (-9 - -2)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>8.9</td>
<td>2.5</td>
<td>-5.9 (-8.5 - -3.0)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>FPG [mmol/l]</strong></td>
<td>10.1</td>
<td>7.6</td>
<td>-2.5 (-4.5 - -3.2)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

Without daily median insulin dose of 31 units

DMR + GLP-1 to eliminate insulin therapy and improve metabolic health in type 2 diabetes
Extensive postprandial glycaemic inventory by mixed meal tolerance tests

All postprandial parameters improved significantly

DMR + GLP-1 to eliminate insulin therapy and improve metabolic health in type 2 diabetes
More physiological approach of T2D: Improvement in metabolic health

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<th>6 months</th>
<th>Δ Median (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI [kg/m²]</strong></td>
<td>29.7</td>
<td>27.2</td>
<td>-2.3 (-3.0 - -1.9)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Total body fat [%] (DEXA)</strong></td>
<td>32.6</td>
<td>31.1</td>
<td>-2.2 (-2.4 - -1.3)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Liver fat [%] (MRI)</strong></td>
<td>8.1</td>
<td>4.6</td>
<td>-3.7 (-6.6 - -0.5)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

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Loss of liverfat in T2D

DMR + GLP-1 to eliminate insulin therapy and improve metabolic health in type 2 diabetes
Conclusion

• Single endoscopic DMR, combined with GLP-1 and lifestyle counseling, can eliminate insulin therapy in the majority of T2D patients...
  • ...while improving parameters of glycaemia
  • ...while improving overall metabolic health

• Maybe especially suited in T2D patients with fatty livers

• May be a game changing approach in the treatment of metabolic syndrome
Limitations

• Uncontrolled pilot study with limited sample size

• Contribution of each of the individual treatment components unknown

• Data must be confirmed by RCT with placebo for DMR and GLP-1

• Mechanism of DMR not yet completely clear