CHANGES IN INCRETINS, BILE ACIDS, AND THE MICROBIOME AFTER DUODENAL MUCOSAL RESURFACING IN PATIENTS WITH TYPE 2 DIABETES.


DDW*2021
May 21-23 | VIRTUAL®

@DDWMeeting | #DDW2021
Disclosure of Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Unrestricted grant for investigator initiated DMR studies. Participated in sponsor-initiated studies by Fractyl in the use of DMR in T2D
Target the duodenum for treatment of T2D

“Westernized” diet causes changes in entero-endocrine signalling

Insulin resistance and eventually Type 2 Diabetes

Bariatric surgery improves insulin resistance via bypassing duodenum

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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
INSPIRE study

- Single arm, single center, open-label
  - Amsterdam UMC
  - 16 patients with type 2 diabetes, basal insulin

- Intervention:
  1. DMR procedure
     - Insulin stopped at day of DMR
     - 2 weeks post-procedural diet
  2. GLP-1 RA (Victoza, liraglutide)
     - Started 2 weeks after DMR
     - Stepwise dose increase to 1.8mg/day
INSPIRE study

• Single arm, single center, open-label
  - Amsterdam UMC
  - 16 patients with type 2 diabetes, basal insulin

• Endpoints
  - % pts without insulin & HbA1c ≤ 59 mmol/mol
  - Glycaemic and metabolic parameters

• Intervention:
  1. DMR procedure
     - Insulin stopped at day of DMR
     - 2 weeks post-procedural diet
  2. GLP-1 RA (Victoza, liraglutide)
     - Started 2 weeks after DMR
     - Stepwise dose increase to 1.8mg/day

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69% off insulin while improving metabolic health

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 mo ( n=16)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c [%]</strong></td>
<td>7.5</td>
<td>7.0</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>HOMA-IR</strong></td>
<td>8.4</td>
<td>2.5</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td>10.1</td>
<td>8.0</td>
<td>0.039</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>28.8</td>
<td>26.5</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Liver fat [%]</strong></td>
<td>8.1</td>
<td>5.3</td>
<td>0.053</td>
</tr>
</tbody>
</table>
How does DMR improve metabolic health?

1. Incretins (GLP-1 + GIP)
2. Bile Acids
3. Microbiome
How did we investigate this?

1. **Post-prandial incretin response**
   - Mixed meal test at baseline vs. 6 mo.

2. **Post-prandial bile acids response**
   - Mixed meal test at baseline vs. 6 mo
How did we investigate this?

1. Post-prandial incretin response
   - Mixed meal test at baseline vs. 6 mo.

2. Post-prandial bile acids response
   - Mixed meal test at baseline vs. 6 mo

3. Fecal microbiome diversity
   - Fecal sample at baseline vs. 3 mo
How did we investigate this?

1. **Post-prandial incretin response**  
   • Mixed meal test at baseline vs. 6 mo.  
   • Incretin producing cells in biopsies

2. **Post-prandial bile acids response**  
   • Mixed meal test at baseline vs. 6 mo

3. **Fecal microbiome diversity**  
   • Fecal sample at baseline vs. 3 mo
1. Incretins: GLP-1 + GIP

GLP-1 (pmol/L) vs Time (min)

- Baseline
- 6 months

$\text{GLP-1 (pmol/L)}$

$0 \quad 5 \quad 10 \quad 15 \quad 20$

Time (min) $0 \quad 30 \quad 60 \quad 90 \quad 120 \quad 180 \quad 240$

$\text{p}<0.001$

GIP (pmol/L) vs Time (min)

- Baseline
- 6 months

$\text{GIP (pmol/L)}$

$0 \quad 50 \quad 100 \quad 150$

Time (min) $0 \quad 30 \quad 60 \quad 90 \quad 120 \quad 180 \quad 240$

$\text{p}=0.735$
1. Incretin-producing K and L cells

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-cell density [cells/mm²]</td>
<td>6.37 (2.49-10.52)</td>
<td>5.47 (3.29-11.59)</td>
<td>0.28</td>
</tr>
<tr>
<td>K-cell density [cells/mm²]</td>
<td>15.08 (6.54-24.46)</td>
<td>17.37 (14.79-22.82)</td>
<td>0.69</td>
</tr>
</tbody>
</table>
2. Postprandial bile acids response

$p=0.124$
2. Postprandial bile acids response

Unconjugated BA increased:

Secondary BA increased:
3. Fecal microbiome diversity

- Negative correlation between HbA1c and microbiome diversity
  - Decreased HbA1c ~ Higher diversity
  
- Change in liver fat was correlated to change in microbiome diversity
  - Changes liver fat ~ Changes diversity

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![Graph showing correlation between change in HbA1c and change in number of MGs with p=0.011](image1)

![Graph showing correlation between change in liver fat and MGS Bray–Curtis dissimilarity with p=0.036](image2)
Conclusions

DMR + GLP-1RA results in improved metabolic health in T2D and comes with:

1. Decreased GLP-1 and unchanged GIP, unchanged L and K cell density

2. Increased unconjugated and secondary bile acids

3. Negative correlation between microbiome diversity and HbA1c
Discussion

DMR + GLP-1RA results in improved metabolic health in T2D and comes with:

1. Decreased GLP-1 and unchanged GIP, unchanged L and K cell density
   • Might reflect a negative feedback after exogenous GLP-1RA administration

2. Increased unconjugated and secondary bile acids
   • Might reflect the changes in the gut microbiome

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Discussion

DMR + GLP-1RA results in improved metabolic health in T2D and comes with:

1. Decreased GLP-1 and unchanged GIP, unchanged L and K cell density
   • Might reflect a negative feedback after exogenous GLP-1RA administration

2. Increased unconjugated and secondary bile acids
   • Might reflect the changes in the gut microbiome

3. Negative correlation between microbiome diversity and HbA1c
   • In line with findings after bariatric surgery and EndobARRIER
Limitations

• Small sample size

• Uncontrolled study:
  Effect of DMR and GLP-1RA can not be separated.
Future:

• Larger controlled trials, investigating:

1. Incretins: GLP-1 + GIP
   • Without exogenous GLP-1

2. Bile Acids
   • Post-prandial and fecal

3. Microbiome
Questions ?