Improvements In Insulin Sensitivity Seen In Patients With Type 2 Diabetes After Revita® DMR Are Associated With A Decrease In Glucagon, Glucose, And GIP After A Mixed Meal Tolerance Test

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Disclosures/Disclaimers

Revita DMR is limited in the US to investigational use under Federal law

S. Meiring, C. Busch, A. van Baar have no disclosures to note

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The role of the proximal gut in metabolic disease

Introduction
Methodology
Results
Summary
Conclusion

Diet

Direct/Indirect Mechanisms

Duodenal mucosa

Liver

Brain

Insulin Resistance
Hyperglycemia
Inflammation

Intestines

Type 2 Diabetes

Fat

Pancreas

Bariatric Surgery as a treatment for T2D
The duodenum as a target

Glycated Hemoglobin Level (%)

Months

- Medical therapy
- Sleeve gastrectomy
- Gastric bypass

$p < 0.001$

Revita DMR®: Duodenal Mucosal Resurfacing System
Investigational Device for the potential treatment of T2D

Submucosal injection of saline
Hydrothermal ablation
From Papilla to Treitz Flexure
DMR improved glucose control

**Revita-1**, open-label multicenter (oral T2D meds), N=46

Decrease in HbA1c of 0.8 ± 1.2%, durable to 2 years
DMR improved glucose control

**Revita-1**, open-label multicenter (oral T2D meds), N=46
Decrease in HbA1c of 0.8 ± 1.2%, durable to 2 years

**Revita-2**, multicenter RCT (oral T2D meds), N=109
Significant difference in HbA1c Sham vs DMR

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**HbA1c, % (Europe)**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>DMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median change in HbA1c from baseline to 24 weeks</td>
<td>-0.28</td>
<td>-0.80</td>
</tr>
</tbody>
</table>

*p = 0.033*

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DDW2022 | May 21–24, 2022
DMR improved glucose control

**Revita-1**, T2D open-label multicenter (oral T2D meds), N=46
Decrease in HbA1c of 0.8 ± 1.2%, durable to 2 years

**Revita-2**, T2D multicenter RCT (oral T2D meds), N=109
Significant difference in HbA1c Sham vs DMR

**INSPIRE**, T2D open-label single center (basal insulin), N=16
69% discontinued insulin after DMR + GLP-1RA

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**T2D Patients off insulin (HbA1c <7.6%)**

Baseline 69%, 6 mo 56%, 12 mo 53%
The role of the proximal gut in metabolic disease

**Diet**

- **Direct/Indirect Mechanisms**
- **Duodenal mucosa**
- **Liver**
- **Brain**
- **Insulin Resistance**
- **Hyperglycemia**
- **Inflammation**
- **Pancreas**
- **Type 2 Diabetes**
- **Intestines**
- **Fat**

Methodology, Mixed meal test

Standardized liquid meal
200 ml
400 kcal
20 g protein
45 g carbohydrates
15.6 g fat

Direct/Indirect Mechanisms

Blood Draw @ T(0,15,30,45,60,90, 120,180 min)

Gut-hormones stimulating insulin production
- GLP-1
- GIP

Glucose
Insulin
C-Peptide
Glucagon

Incretins

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Methodology

**Revita-1**, subset who underwent Mixed Meal Test (MMT) (n=13)

**Revita-2**, open-label phase who underwent MMT (n=15)

Mixed Meal Test Performed
Baseline and 3 months post-DMR

n = 28

Selection Criteria
- ≥ 3 ablations
- Stable diabetes medication
- HbA1c: 7.6 – 10.0%

Endpoints
- Glucose, insulin, glucagon, c-peptide, incretins
- HOMA-IR, Matsuda Index
- Insulin secretion rate, disposition index

Analysis
- Mixed Effect Models
- AUC and iAUC

Introduction | Methodology | Results | Summary | Conclusion
## Baseline Characteristics

<table>
<thead>
<tr>
<th><strong>Number</strong></th>
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<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>55  (50 – 63)</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>86</td>
</tr>
<tr>
<td><strong>Duration of T2D (y)</strong></td>
<td>6.8  (3 – 10)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>31.4 (29 – 34)</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>8.2  (7.9 - 9.0)</td>
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Data are expressed as median (IQR) or %
Glucose control improved

<table>
<thead>
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<th>Baseline (n=28)</th>
<th>3 months (n=28)</th>
<th>p-value</th>
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<td>Body weight, kg</td>
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<td>87.4</td>
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<td><strong>Fasting glucose, mg/dL</strong></td>
<td>198</td>
<td>162</td>
<td>&lt;0.001</td>
</tr>
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<td>HOMA-IR</td>
<td>5.4</td>
<td>3.6</td>
<td>0.005</td>
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<tr>
<td>Matsuda index</td>
<td>2.64</td>
<td>3.49</td>
<td>0.005</td>
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<tr>
<td>Insulin Secretion Rate</td>
<td>4x10^5</td>
<td>5x10^5</td>
<td>0.002</td>
</tr>
<tr>
<td>Disposition Index</td>
<td>4.71</td>
<td>6.46</td>
<td>0.001</td>
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## Insulin sensitivity improved

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**HOMA-IR**

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<td>5.4</td>
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**Matsuda index**

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<td>2.64</td>
<td><strong>32% Improvement</strong></td>
<td>3.49</td>
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- **Insulin Secretion Rate**: 4x10^5 to 5x10^5, p=0.002
- **Disposition Index**: 4.71 to 6.46, p=0.001

Data are expressed as median or %

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### β-cell function improved

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**Insulin Secretion Rate**
- \( 4 \times 10^5 \) 25% Improvement \( 5 \times 10^5 \) 0.002

**Disposition Index**
- 4.71 37% Improvement 6.46 0.001

Data are expressed as median or %
**Glucagon Decreased**

**Glucagon**

- Baseline
- 3 months

*p*-value <0.001

**Time (min)**

- 15
- 30
- 45
- 60
- 90
- 120
- 150
- 180

**Mean (SD) Glucagon (pmol/L)**

**Glucagon AUC**

- Median (IQR) Glucagon AUC (pmol/L * min)

- Baseline
- 3 Months

*p*=0.032

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*Fractyl Health May 2022 | Confidential*

**Introduction**

**Methodology**

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**Conclusion**
Incretins did not change

GLP-1

GIP

\( p \)-value <0.564

\( p \)-value <0.958
Correlation glucose control and GIP

Inverse relationship between MI and GIP

Patients with improved insulin sensitivity had a decreased GIP

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Correlation ΔMI + ΔGIP

ΔGIP AUC
p-value 0.004; r-value -0.580

ΔGIP iAUC
p-value 0.031; r-value -0.451

ΔMatsuda Index (MI) at 3 months

ΔGIP (pmol/L)
Summary

Insulin sensitivity and β-cell function improved

- Further validates the duodenum as target for T2D

FPG and Glucagon decreased

- Indicates beneficial effects of DMR

Incretins did not change

- Improved insulin sensitivity was correlated to a decreased GIP
Summary

Insulin sensitivity and β-cell function improved

- Further validates the duodenum as target for T2D

FPG and Glucagon decreased

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**Summary**

**Insulin sensitivity and β-cell function improved**

- Further validates the duodenum as target for T2D

**FPG and Glucagon decreased**

- Indicates beneficial effects of DMR

**Incretins did not change**

- However, improved glucose control correlated to a decrease in GIP
Study Limitations and Conclusions

Limitations

- Post-hoc analysis small sample size
- No controls
- High variability in glucoregulatory hormones (GLP-1 and GIP)

Conclusions

- Revita® DMR improved insulin resistance and β-cell function
- Duodenum as a target for T2D
Study Limitations and Conclusions

Limitations

- Post-hoc analysis small sample size
- No controls
- High variability in glucoregulatory hormones (GLP-1 and GIP)

Conclusions

- Revita® DMR improved insulin sensitivity and β-cell function
- Confirms duodenum as a therapeutic target for T2D