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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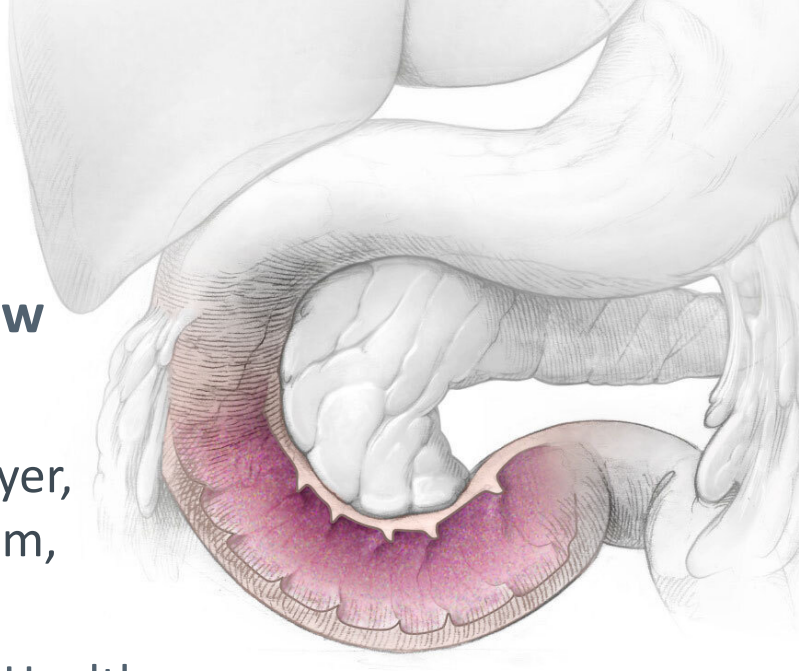
Disclosures/Disclaimers



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

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R. DeFronzo participates in advisory boards for AstraZeneca, Novo Nordisk, Bayer, Boehringer-Ingelheim, Intarcia; has research support from Boehringer-Ingelheim, AstraZeneca, Merck and is on a speaker's bureau for AstraZeneca

JC. Lopez Talavera, K. White, and **M. Hagen** are full-time employees of Fractyl Health, and may hold Fractyl stock and/or stock options

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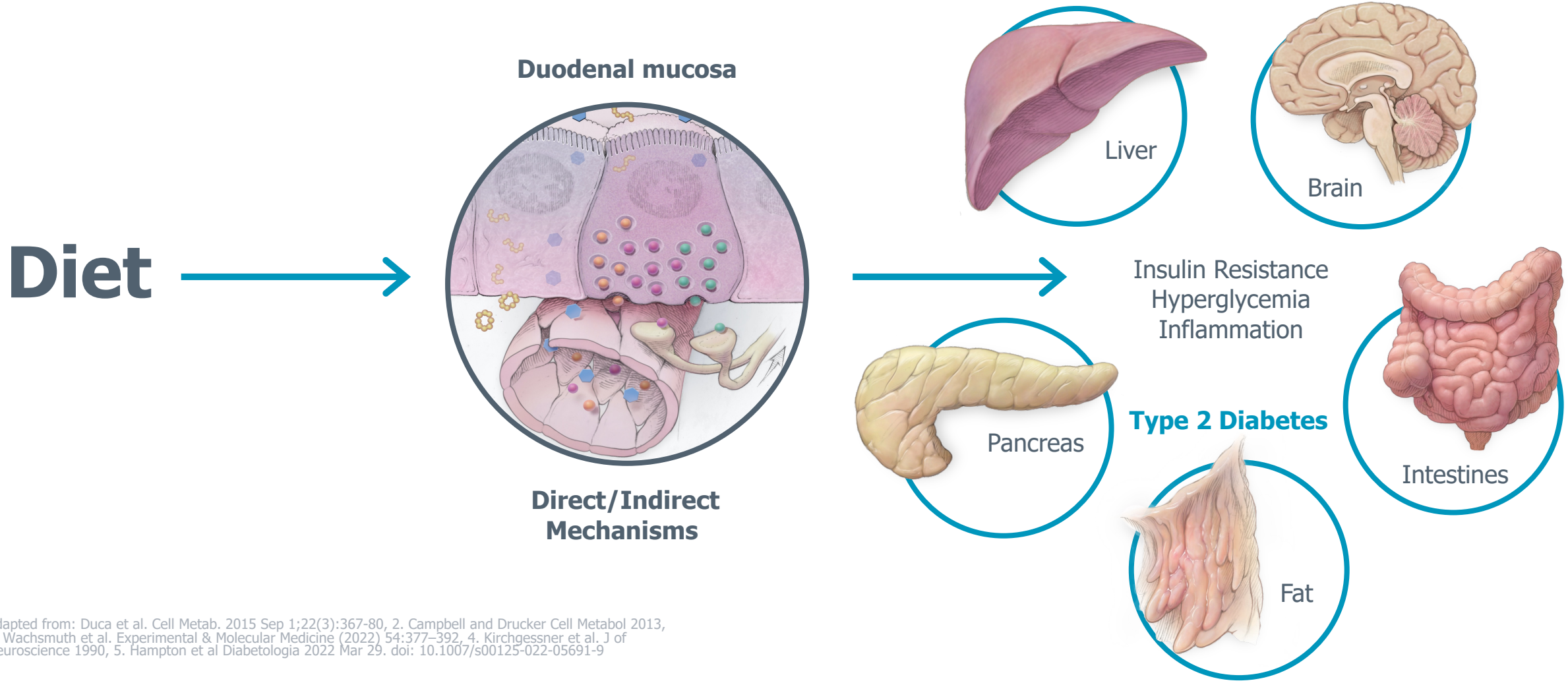
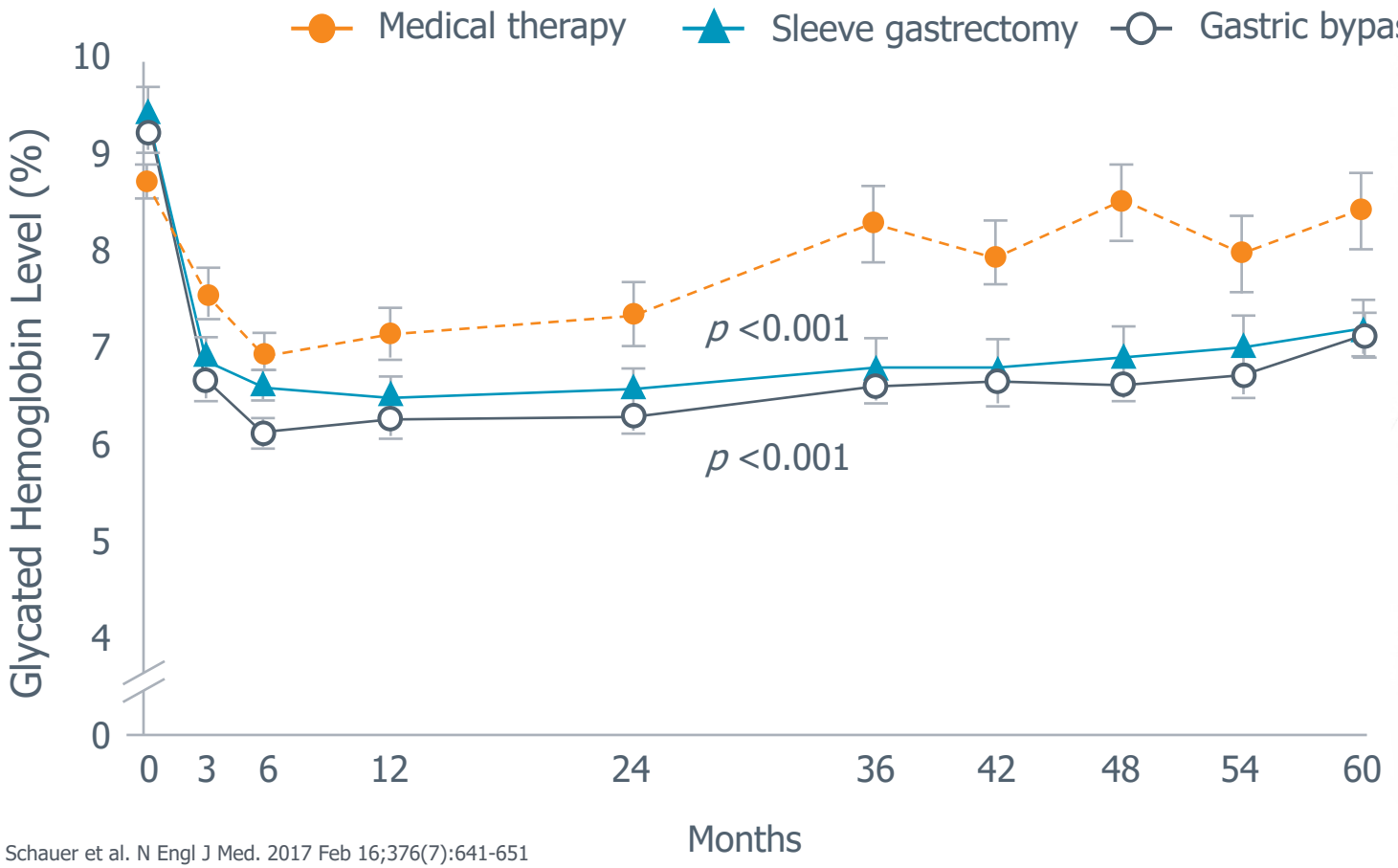
The role of the proximal gut in metabolic disease

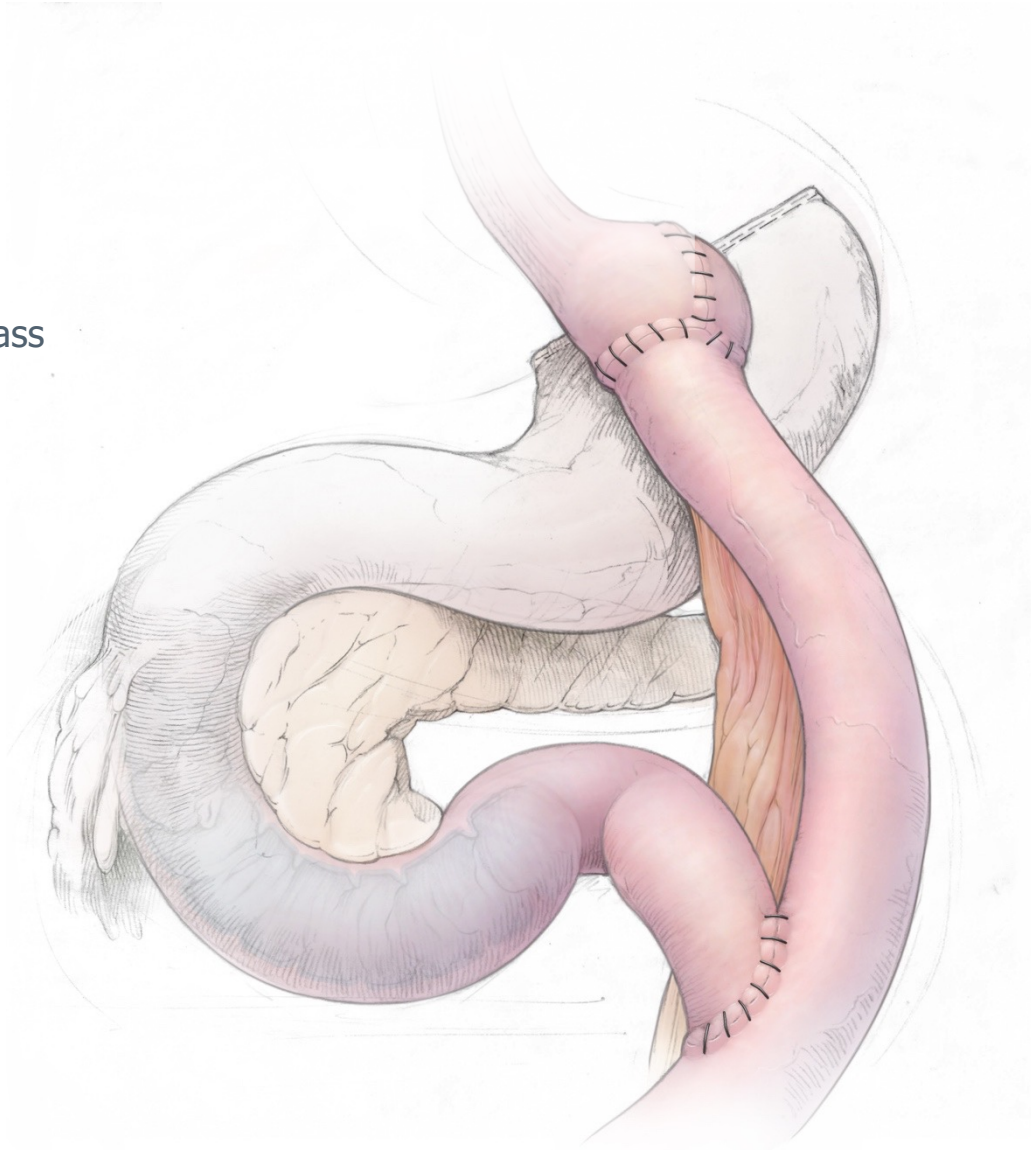


Adapted from: Duca et al. Cell Metab. 2015 Sep 1;22(3):367-80, 2. Campbell and Drucker Cell Metabol 2013, 3. Wachsmuth et al. Experimental & Molecular Medicine (2022) 54:377–392, 4. Kirchgessner et al. J of Neuroscience 1990, 5. Hampton et al Diabetologia 2022 Mar 29. doi: 10.1007/s00125-022-05691-9

Bariatric Surgery as a treatment for T2D

The duodenum as a target



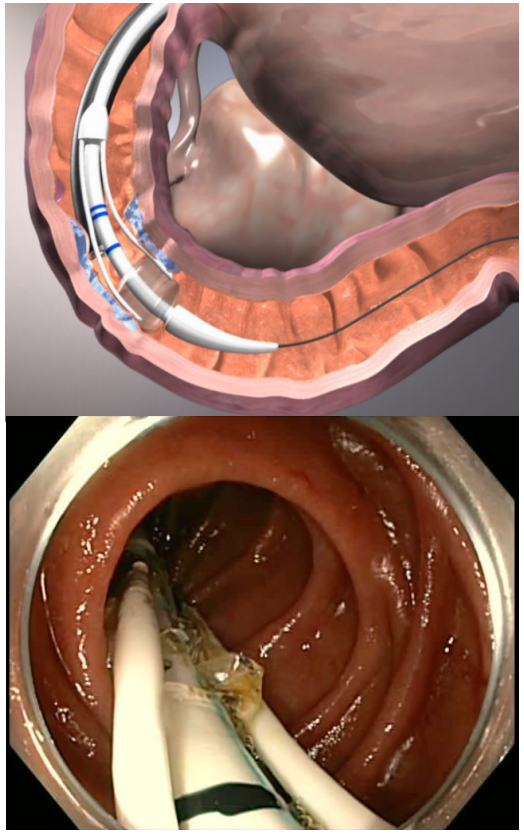


Schauer et al. N Engl J Med. 2017 Feb 16;376(7):641-651

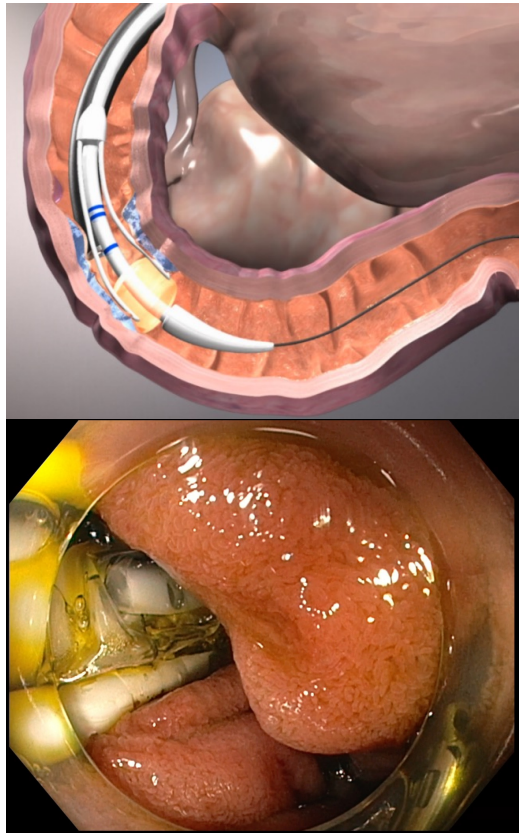
Revita DMR®: Duodenal Mucosal Resurfacing System

Investigational Device for the potential treatment of T2D

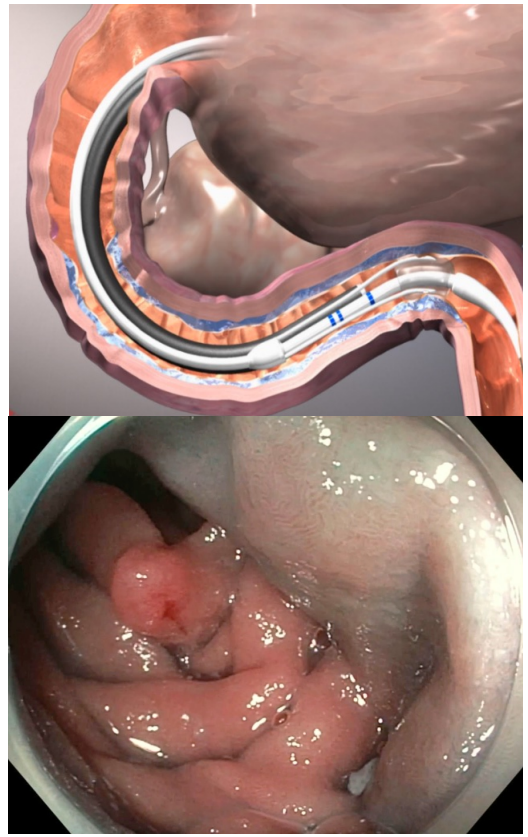
Submucosal injection of saline



Hydrothermal ablation



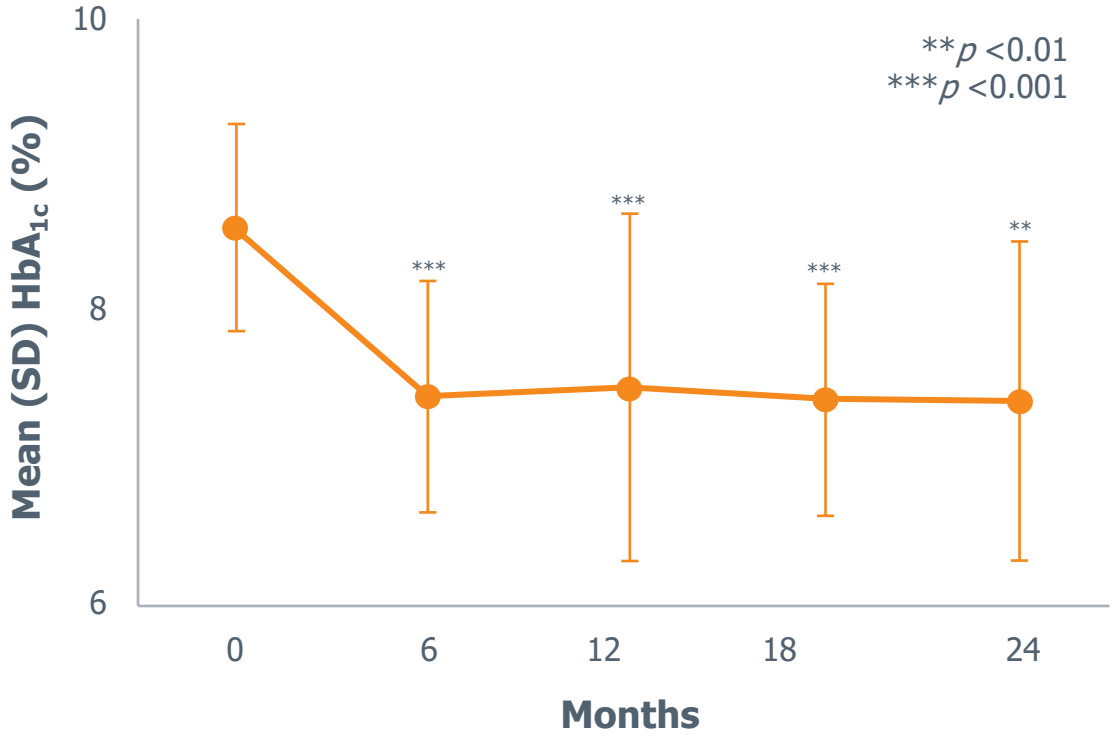
From Papilla to Treitz Flexure



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



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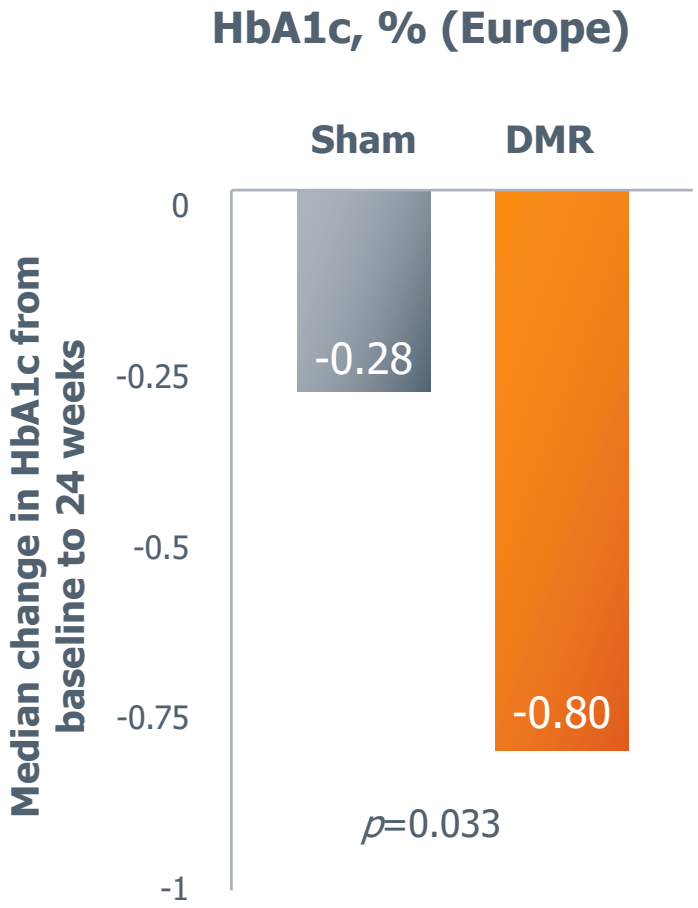
Revita-2, multicenter RCT (oral T2D meds), N=109

Significant difference in HbA1c Sham vs DMR



DMR improved glucose control

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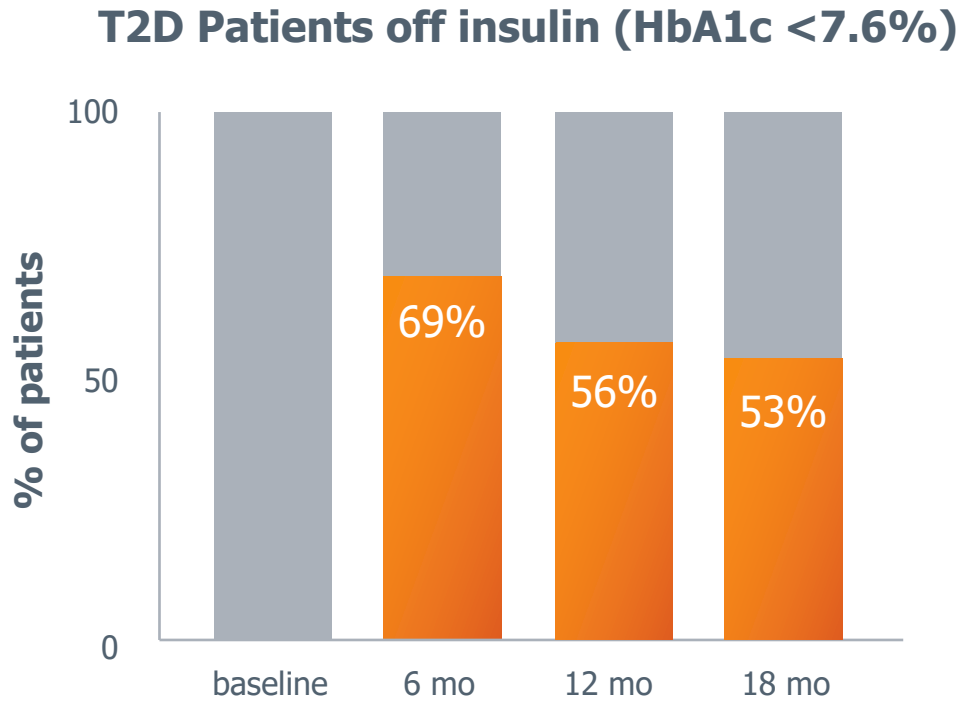
Decrease in HbA1c of 0.8 ± 1.2%, durable to 2 years

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

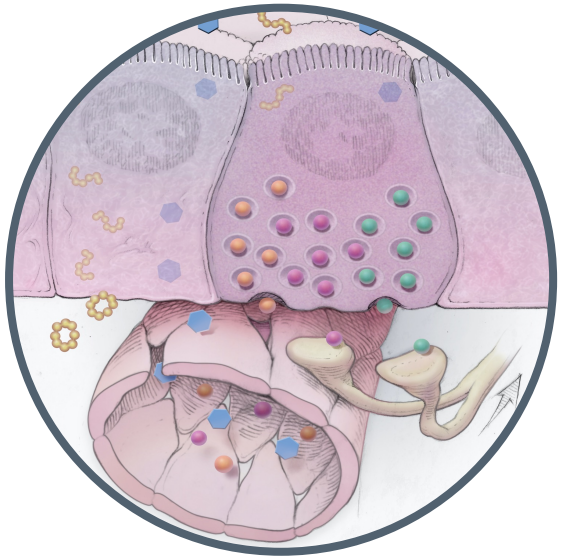
69% discontinued insulin after DMR + GLP-1RA



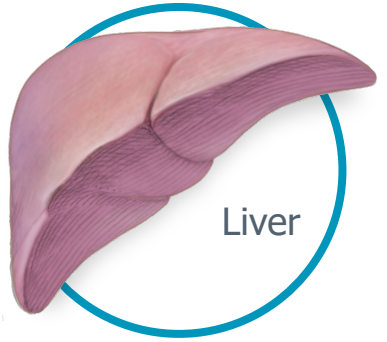
The role of the proximal gut in metabolic disease

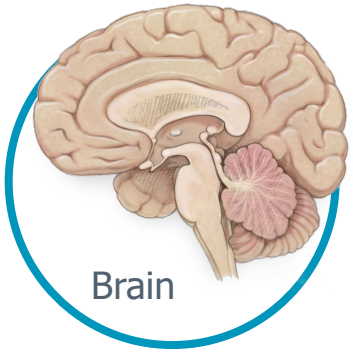
Diet

Duodenal mucosa

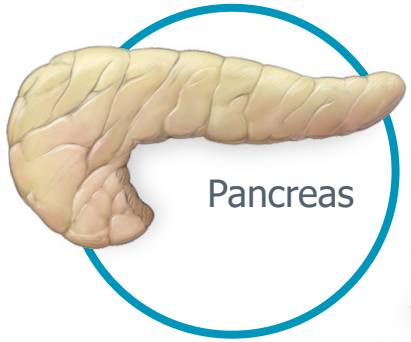


Direct/Indirect Mechanisms

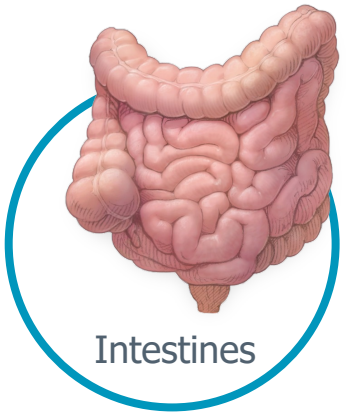


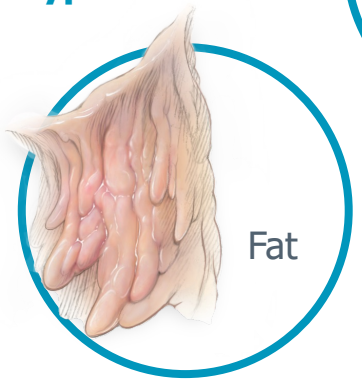


Insulin Resistance
Hyperglycemia
Inflammation



Type 2 Diabetes





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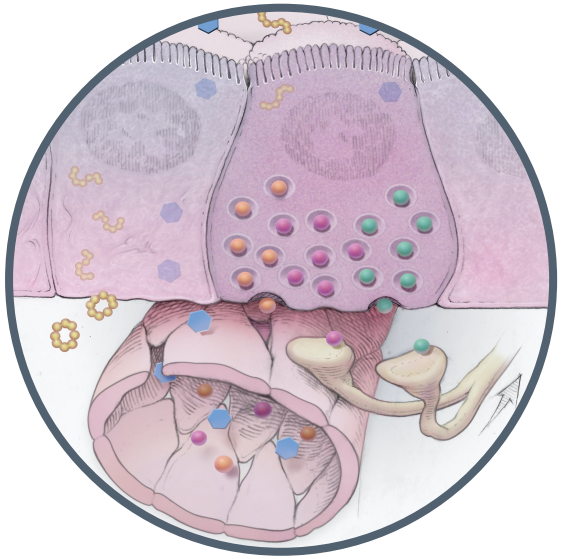
Methodology, Mixed meal test

Standardized liquid meal

200 ml
400 kcal
20g protein
45g carbohydrates
15.6g fat



Direct/Indirect Mechanisms

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

Glucose

Insulin

C-Peptide

Glucagon

Gut-hormones stimulating insulin production

Incretins
- GLP-1
- GIP

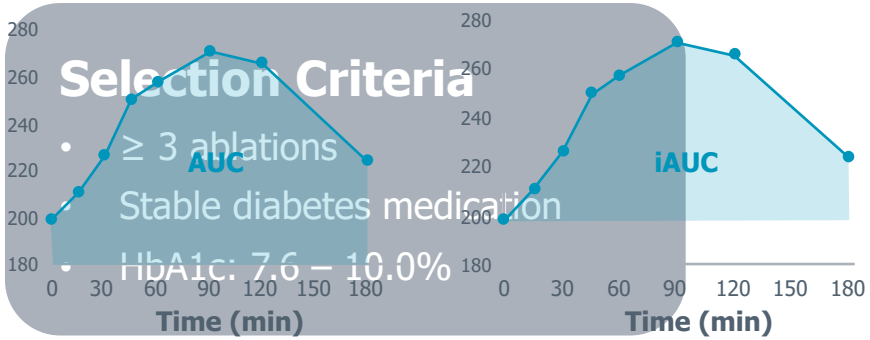
Methodology

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

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

n = 28

Mixed Meal Test Performed
Baseline and 3 months post-DMR



Selection Criteria

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

Analysis

- Mixed Effect Models
- AUC and iAUC

Endpoints

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

Baseline Characteristics

Number	**28**
Age (y)	55 (50 – 63)
Male (%)	86
Duration of T2D (y)	6.8 (3 – 10)
BMI (kg/m^2)	31.4 (29 – 34)
HbA1c (%)	8.2 (7.9 - 9.0)

Data are expressed as median (IQR) or %

Glucose control improved

	Baseline (n=28)	3 months (n=28)	*p*-value
Body weight, kg	91.7	87.4	<0.001
BMI, kg/m2	31.4	29.5	<0.001
Fasting Insulin, pmol/L	11.9	8.8	0.004
Fasting C-peptide, nmol/L	3.07	2.43	0.001
HbA1c, %	8.2	7.4	0.002
Fasting glucose, mg/dL	198	162	<0.001
HOMA-IR	5.4	3.6	0.005
Matsuda index	2.64	3.49	0.005
Insulin Secretion Rate	$4x10^5$	$5x10^5$	0.002
Disposition Index	4.71	6.46	0.001

Data are expressed as median or %

Insulin sensitivity improved

	Baseline (n=28)		3 months (n=28)	*p*-value
Body weight, kg	91.7		87.4	<0.001
BMI, kg/m2	31.4		29.5	<0.001
Fasting Insulin, pmol/L	11.9		8.8	0.004
Fasting C-peptide, nmol/L	3.07		2.43	0.001
HbA1c, %	8.2		7.4	0.002
Fasting glucose, mg/dL	198		162	<0.001
HOMA-IR	5.4	**33% Improvement**	3.6	0.005
Matsuda index	2.64	**32% Improvement**	3.49	0.005
Insulin Secretion Rate	$4x10^5$		$5x10^5$	0.002
Disposition Index	4.71		6.46	0.001

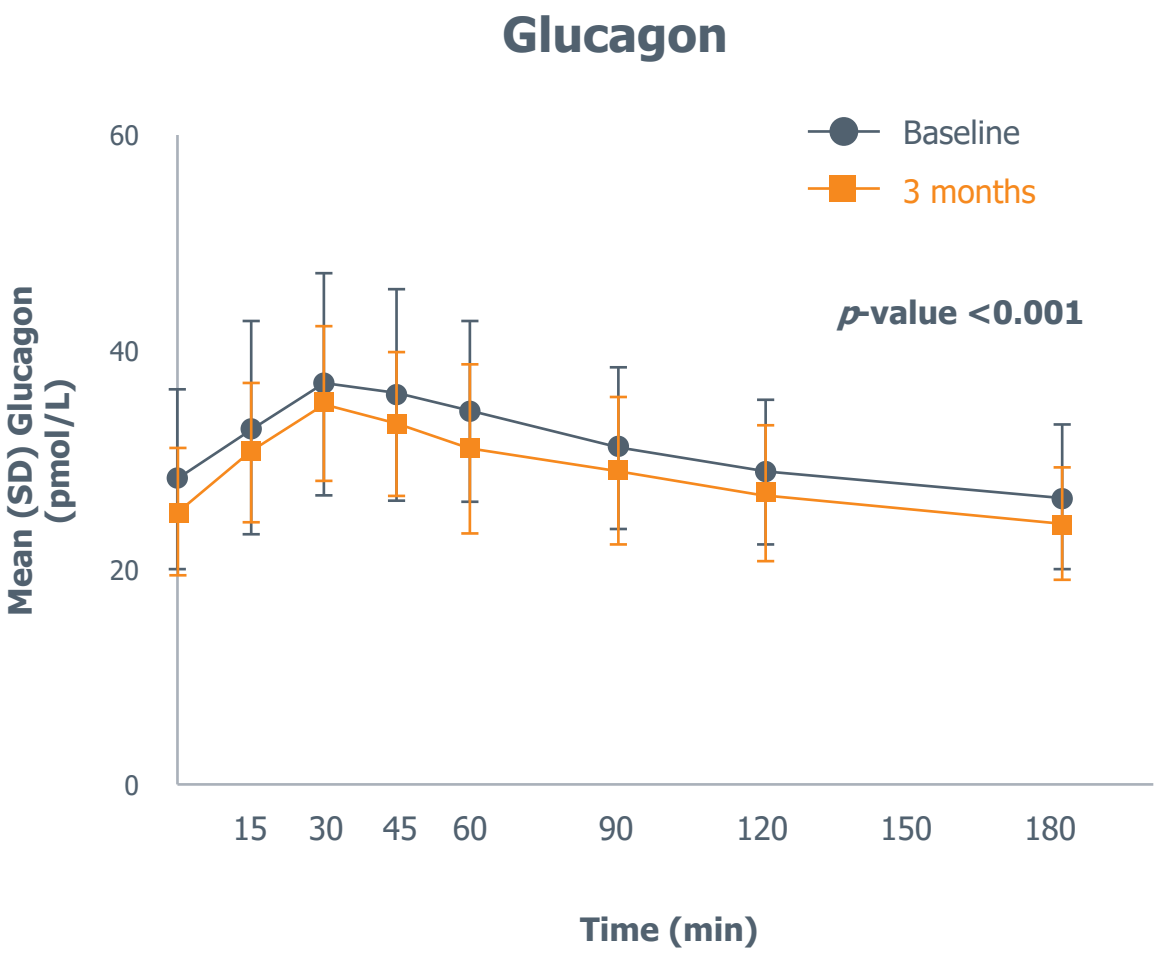
Data are expressed as median or %

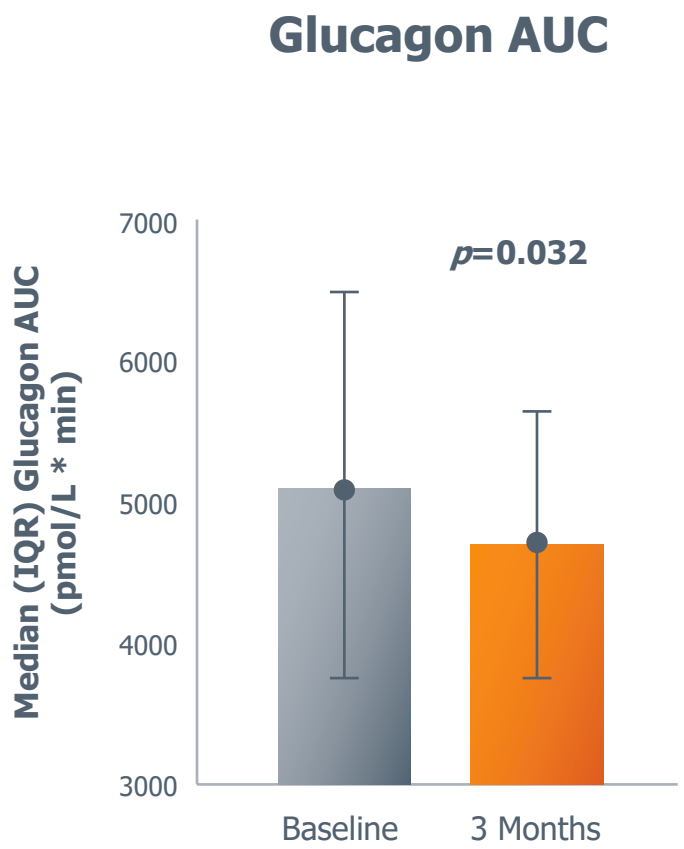
β-cell function improved

	Baseline (n=28)		3 months (n=28)	*p*-value
Body weight, kg	91.7		87.4	<0.001
BMI, kg/m2	31.4		29.5	<0.001
Fasting Insulin, pmol/L	11.9		8.8	0.004
Fasting C-peptide, nmol/L	3.07		2.43	0.001
HbA1c, %	8.2		7.4	0.002
Fasting glucose, mg/dL	198		162	<0.001
HOMA-IR	5.4		3.6	0.005
Matsuda index	2.64		3.49	0.005
Insulin Secretion Rate	$4x10^5$	**25% Improvement**	$5x10^5$	0.002
Disposition Index	4.71	**37% Improvement**	6.46	0.001

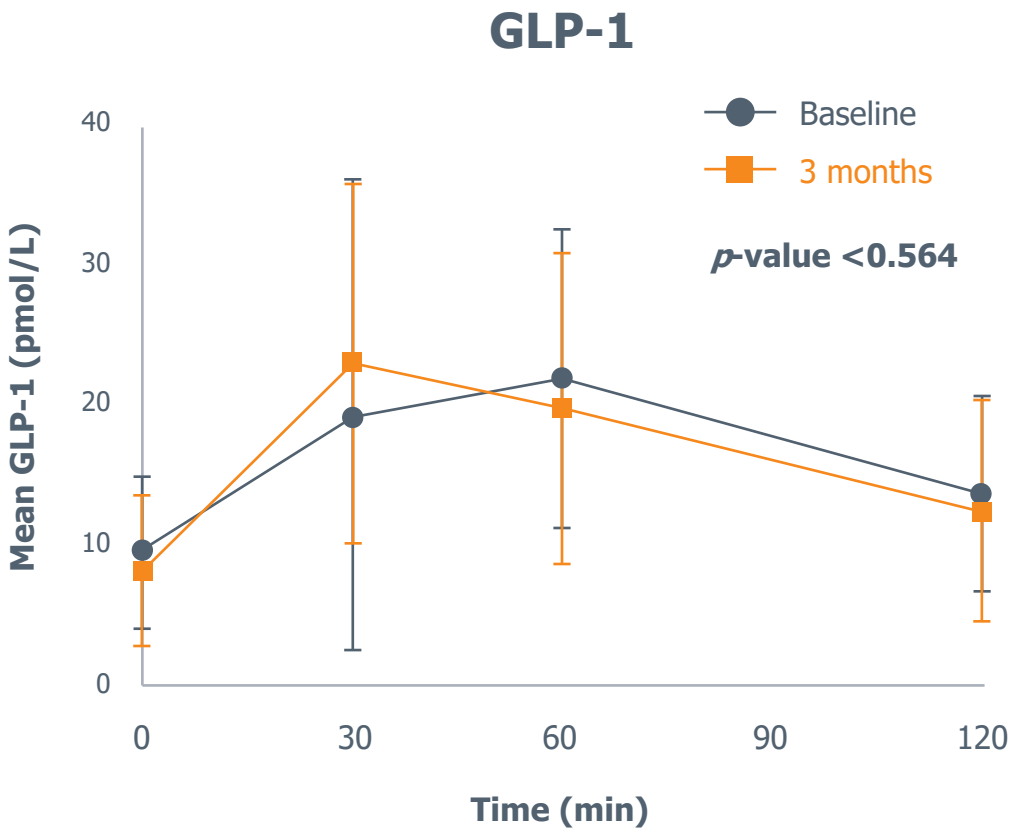
Data are expressed as median or %

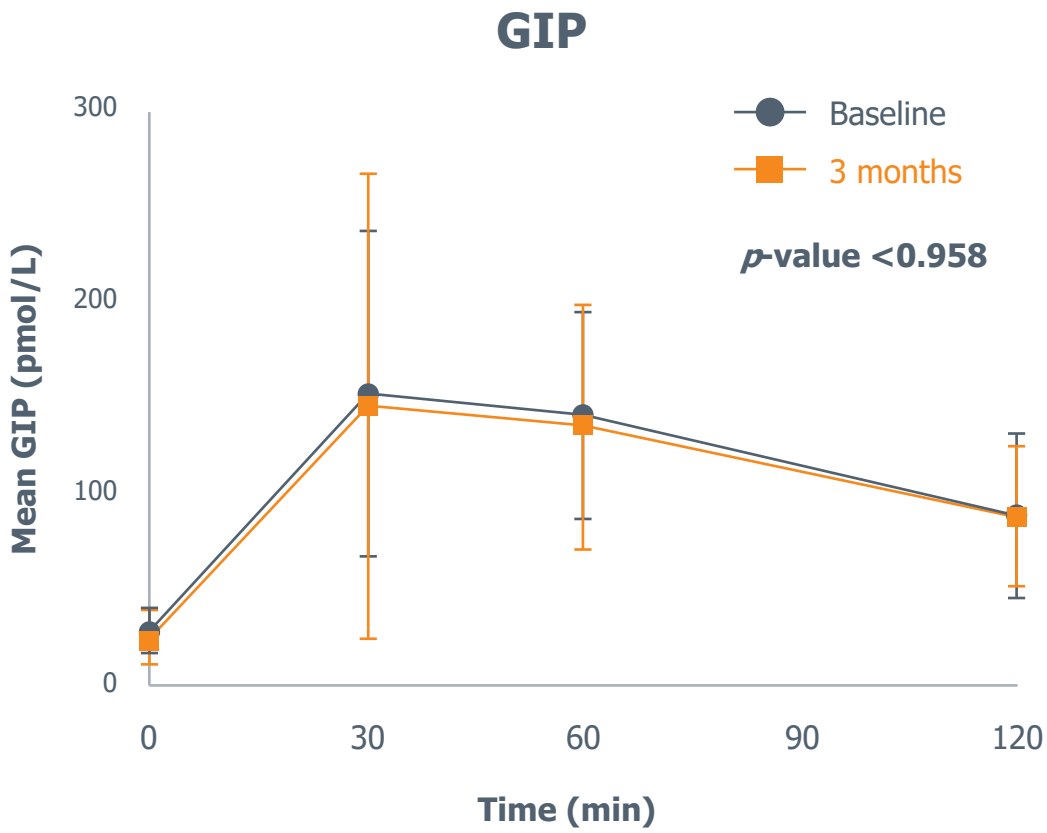
Glucagon Decreased





Incretins did not change

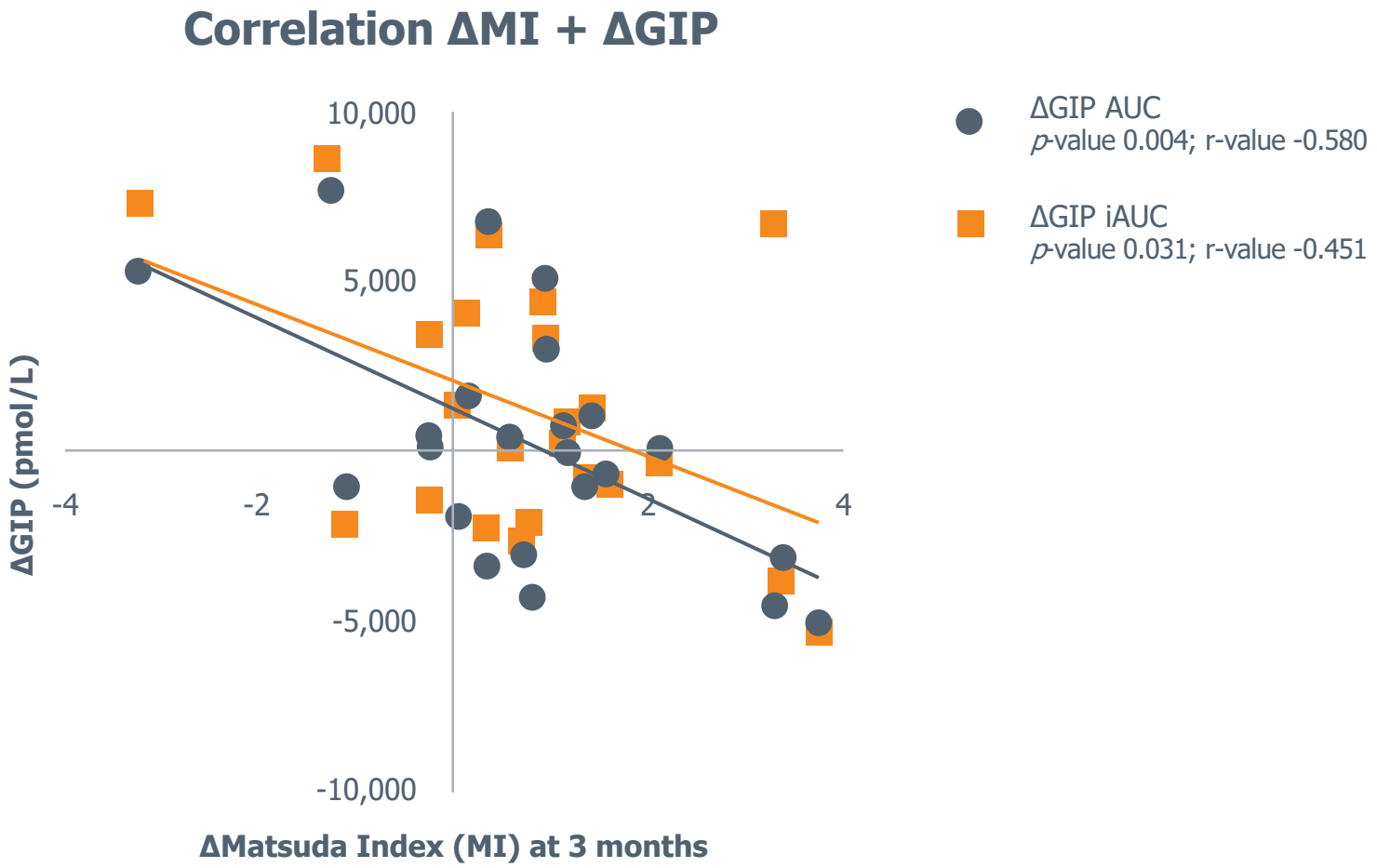




Correlation glucose control and GIP

Inverse relationship between MI and GIP

Patients with improved insulin sensitivity had a decreased GIP



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

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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

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- 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**