

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:

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Duodenal mucosal resurfacing combined with GLP-1RA may eliminate insulin treatment in type 2 diabetes while improving glycaemic control and metabolic health

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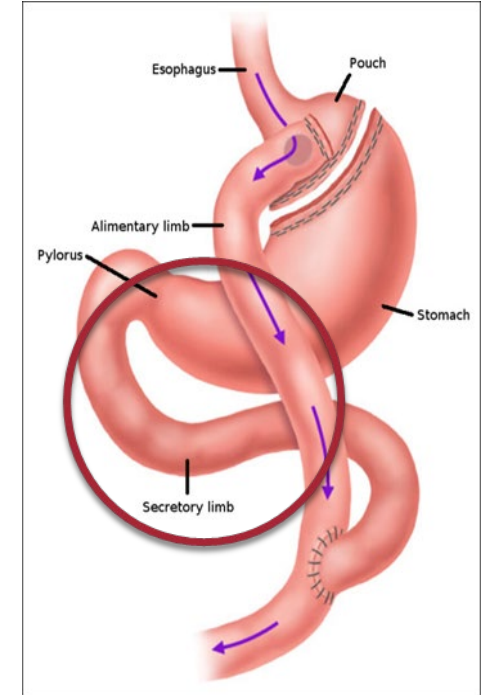
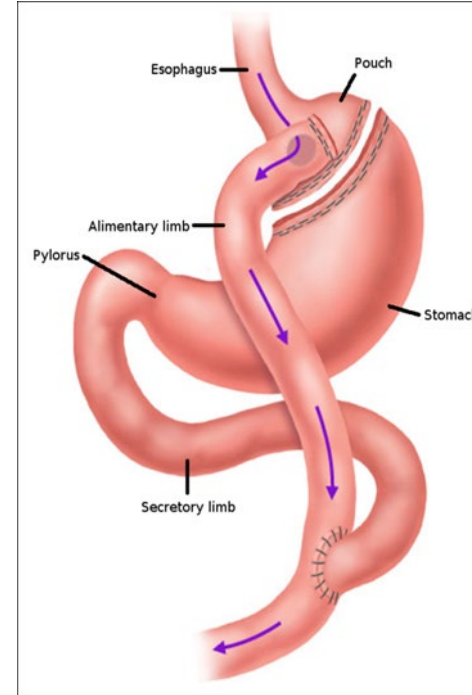
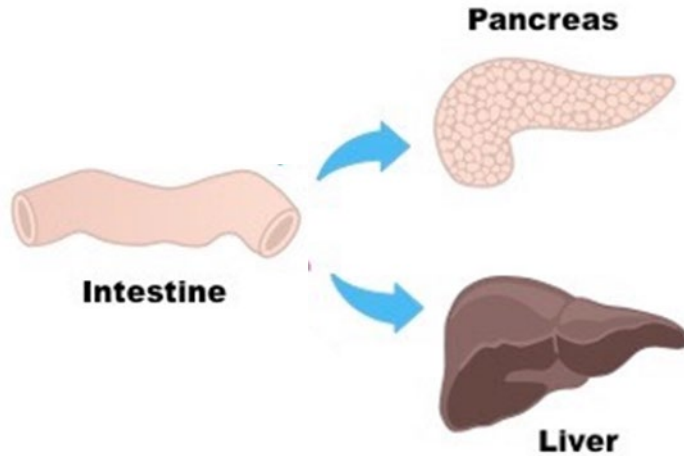
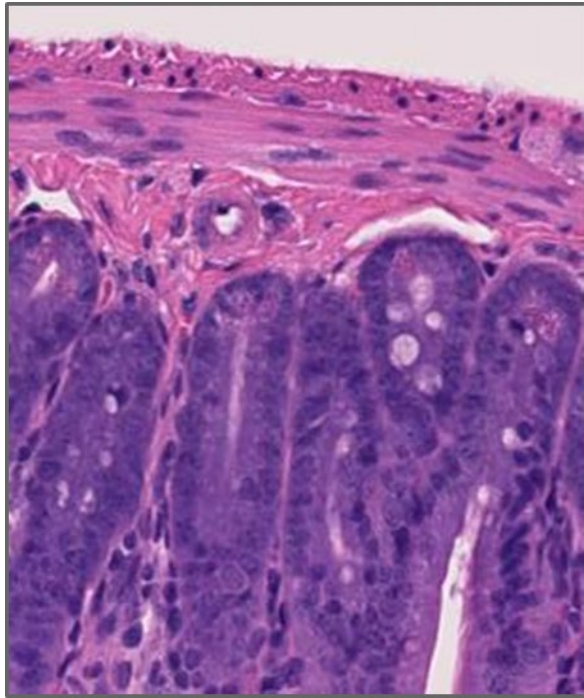
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Target the duodenum for treatment of T2D



Duodenal mucosa changes due to 'Western diet'



Changes in hormonal signaling causes insulin resistance



Bariatric Surgery effective treatment T2D



Bypassing duodenum improves insulin resistance



UEGW presentation 2020_def - PowerPoint

Bestand Start Invoegen Ontwerpen Overgangen Animaties Diavoorstelling Controleren Beeld EndNote X9 Acrobat Shakespeak Geef aan wat u wilt doen...

Meining, S. (Suzanne) Delen

Voorbeeld Geen Verschijnen Vervagen Binnenvlieg... Binnenzwev... Splitzen Wissen Vorm Draaien Willekeurig... Vergroten e... In- en uitzo... Rondraaien Stuteren Puls Pulserende... Wankelen Draaien Vergroten/v... Saturatie on... Effectoities

Animaties

Deelvenster Animatie Trigger - Animatie toevoegen - Animatie kopiëren/plakken Geavanceerde animatie

Start: Bij klikken Animatievolgde wijzen Eerder verplaatsen Later verplaatsen

Duur: Vertraging: Tijdsinstellingen

Animatiedeel... Alles afspelen

1 DMR - Lifting ... 2 DMR - Ablati... 3 DMR - Pull-b...

Trigger: DMR - Lifting cycle.mp4 1 DMR - Lifting ...

Trigger: DMR - Ablation cycle.m... 1 DMR - Ablati...

Trigger: DMR - Pull-back 1.mp4 1 DMR - Pull-b...

Seconden 0 2 99%

15:36 15-9-2020

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

How does DMR work?

Revita™ Duodenal Mucosal Resurfacing Procedure

How does DMR work?

- Improves insulin sensitivity (hallmark of T2D and metabolic syndrome)
- First-in-human study in Chile (n=39)
- Multicentre study in Europe (n=86)
 - In T2D patients on oral medication
 - HbA1c decrease of 10 mmol/mol (comparable to 1 oral drug)
 - Sustained at 24 months

INSPIRE study

- Single arm, single center, open-label
 - Amsterdam Universitair Medisch Centrum
 - 16 patients
- Inclusion criteria:
 - Type 2 diabetes
 - Long standing insulin
 - HbA1c ≥ 64 mmol/mol (8.0%)
 - C-peptide ≥ 0.3 nmol/L
- Intervention triangle:
 - DMR procedure
 - Insulin stopped at day of DMR
 - 2 weeks post-procedure rest
 - GLP-1 (Victoza, Bylgintide)
 - Start 2 weeks after DMR
 - Step-wise dose increase to 1.8mg/day
 - Lifestyle counselling
 - HLG, tobacco

The idea behind Duodenal Mucosal Resurfacing, or DMR, is to cause regeneration of the duodenal mucosa and restore the disturbed enteroendocrine signaling.

First, the duodenum is entered via gastroduodenoscopy using a paediatric colonoscope with an over-the-wire catheter. The papilla is located and a clip is placed.

At the distal tip of the catheter a balloon is inflated and saline is injected in order to protect underlying layers from thermal damage.

Then the balloon is filled with water of around 90 degrees Celsius and hydrothermal energy is applied to circumferentially. In total, the duodenum is ablated over a length of 10 cm.



How does DMR work?

- Improves insulin sensitivity (hallmark of T2D and metabolic syndrome)
- 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 (\approx comparable to 1 oral drug)¹
 - Sustained at 24 months

INSPIRE study



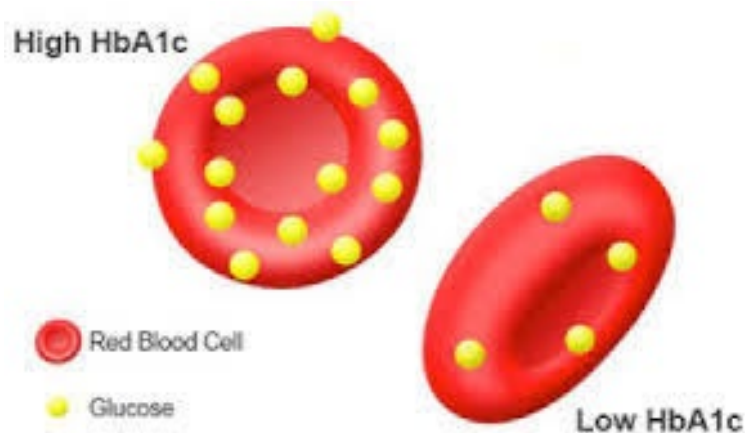
- **Single arm, single center, open-label**
 - Amsterdam Universitair Medisch Centrum
 - 16 patients
- **Inclusioncriteria:**
 - Type 2 diabetes
 - Long acting insulin
 - HbA1c \leq 64 mmol/mol (8.0%)
 - C-peptide: \geq 0.5 nmol/L
- **Intervention triangle:**
 1. **DMR procedure**
 - Insuline stopped at day of DMR
 - 2 weeks post-procedural diet
 2. **GLP-1 (Victoza, liraglutide)**
 1. Start 2 weeks after DMR
 - Stepwise dose increase to 1.8mg/day
 3. **Lifestyle counseling**
 - Mild, isocaloric

INSPIRE study



Follow-up: Every 4-12 weeks

- Lifestyle counseling
- Blood collection:
 - $\text{HbA1c} \leq 58 \text{ mmol/mol} \Rightarrow$ Continue GLP-1RA
 - $\text{HbA1c} > 58 \text{ mmol/mol} \Rightarrow$ Stop GLP-1RA and restart insulin



- **Primary endpoint:**

- % of patients off insulin at 6 months with adequate glycaemic control ($\text{HbA1c} \leq 58 \text{ mmol/mol}$)

- **Secondary endpoints:**

- Glycaemic and metabolic parameters
- % of patients off insulin at 12 months

Baseline characteristics

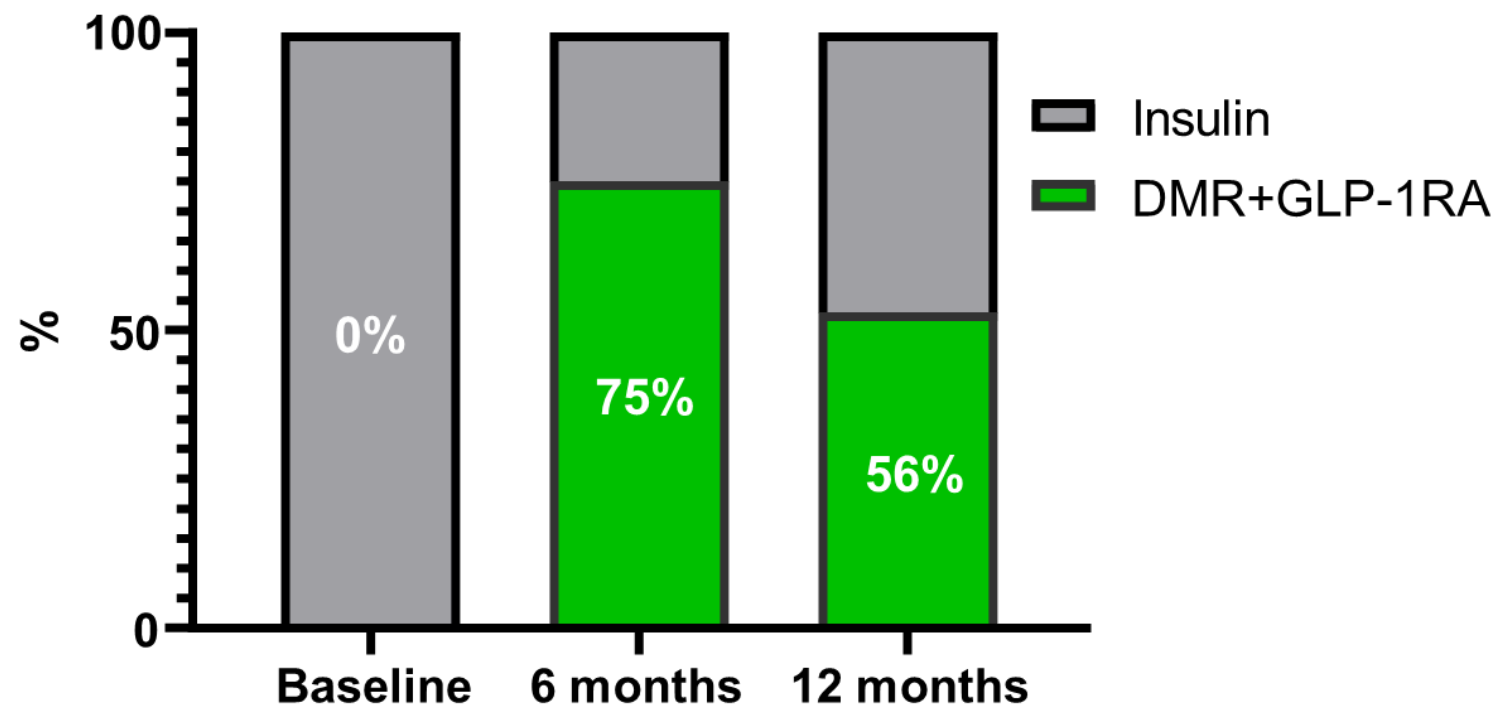
Patient characteristics (N=16)	
Age [years]	61
Male gender, n (%)	10 (63%)
Duration of T2D [years]	11
Weight [kg]	87.5
BMI [kg/m ²]	29.2
HbA1c [mmol/mol]	58
Fasting plasma glucose [mmol/l]	10.1
C-peptide [nmol/l]	0.70
HOMA-IR	8.1
Antidiabetic medication	
Mean number of daily units of insulin	31



Primary endpoint;

Responders : HbA1c < 59 mmol/mol

% of patients free of insulin





Despite elimination of insulin, improved glycaemic parameters

Responders

	Baseline	6 months (n=12)		12 months (n=9)	
		6 months	p-value	12 months	p-value
HbA1c [%]	7.4 (7.1-7.6)	6.7 (6.6-7.3)	0.009	6.7 (6.5-7.2)	0.024
HOMA-IR	8.9 (4.5-13.3)	2.6 (1.4-4.1)	0.004	7.1 (6.7-7.7)	0.008
FPG [mmol/l]	10.5 (9.2-12.0)	7.6 (6.5-8.8)	0.003	3.6 (1.6-6.7)	0.015

Without daily median insulin dose of 31 units



Improved metabolic parameters

Responders

		6 months (n=12)		12 months (n=9)	
BMI [kg/m²]	29.8 (26.5-34.2)	27.2 (23.4-31.9)	0.002	25.5 (22.1-29.5)	0.008
Liver fat [%]	8.1 (5.1-13.2)	4.6 (2.4-11.0)	0.016	6.0 (2.7-10.9)	0.208

Complete study population

		6 months(N=16)		12 months(n=16)	
BMI [kg/m²]	29.2 (26.5-32.0)	27.6 (24.3-29.8)	<0.001	26.4 (22.7-29.8)	<0.001
Liver fat [%]	8.1 (4.0-13.5)	5.3 (3.9-11.4)	0.053	5.6 (2.8-10.9)	0.030



Conclusion

- Single endoscopic DMR, combined with GLP-1 and lifestyle counseling, can eliminate insulin therapy in a subset of T2D patients...
 - ...while improving parameters of glycaemia
 - ...while improving overall metabolic health
- The effect slightly fades after 12 months, but majority is off insulin
 - Effect of multiple DMRs is unknown, but could extend/enlarge effect
- May be a game changing approach in the treatment of metabolic syndrome
 - A large international RCT has been started, based on these results



Limitations

- Uncontrolled pilot study with limited sample size
- Contribution of each of the individual treatment components unknown
 - Data must be confirmed by new multicenter RCT
- Mechanism of DMR not yet completely clear
 - Results of mechanistic studies will follow soon