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

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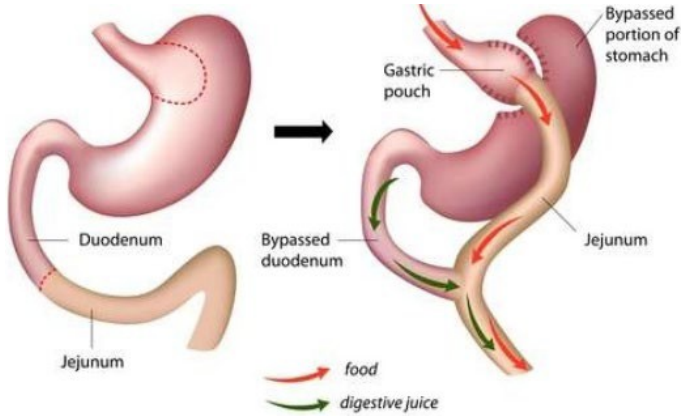
Disclosures

- Jacques Bergman received research support from Fractyl for IRB-based studies and received a consultancy fee for a single advisory board meeting of Fractyl in September 2019.

- Frits Holleman reports speaker fees from Sanofi, Bioton, Astra Zeneca and Boehringer Ingelheim.

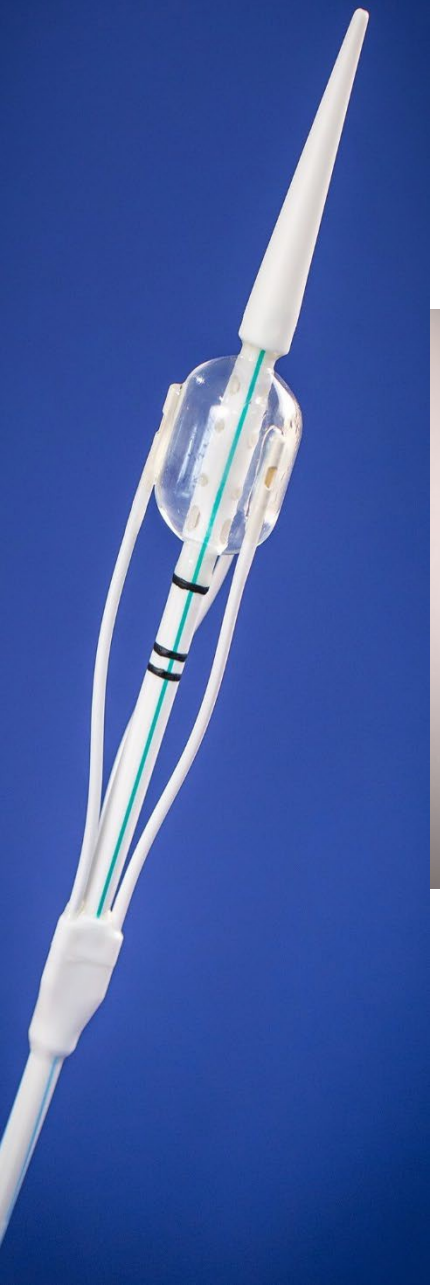
Target the duodenum for treatment of T2D

- 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

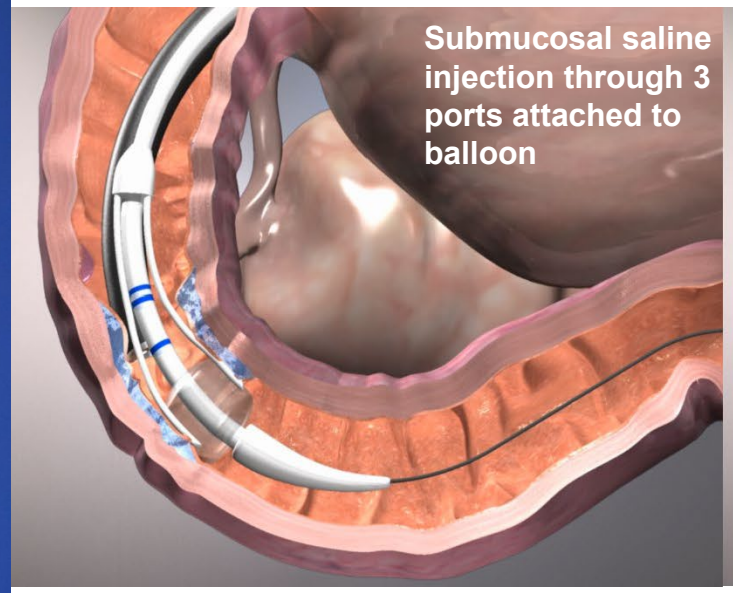


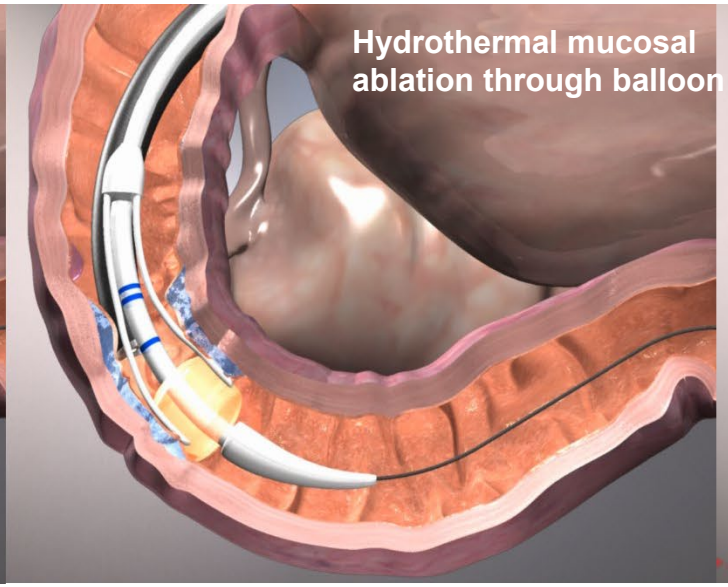
Roux-en-Y Gastric Bypass

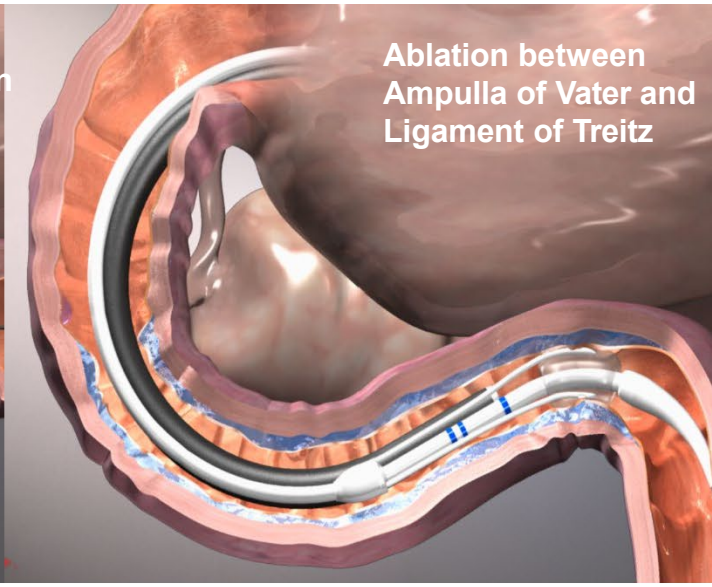
West, submitted. 2019; Van Baar, *Gastroenterology*. 2017; Mingrone, *Lancet*. 2015; Rohde, *Diabetes, Obesity & Metabolism*. 2016; Rubino, *Ann Surg*. 2006



Revita™ Duodenal Mucosal Resurfacing Procedure







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 ß-cell function and ß-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

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

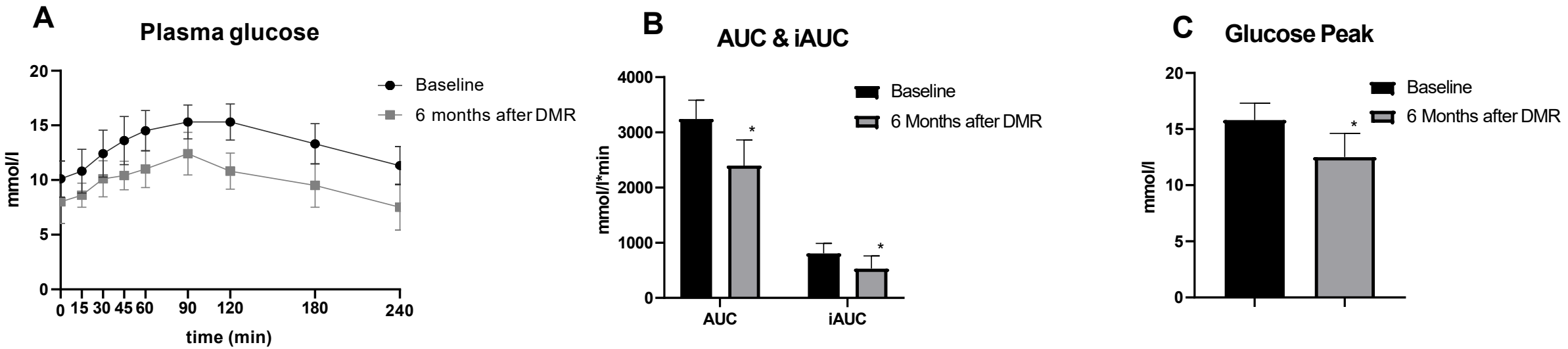
- **75% (12/16) were free of insulin** at 6 months
  with maintained (improved) glycaemic control (HbA1c ≤ 58 mmol/mol)

Despite elimination of insulin, improved glycaemic control

	Responders (n=12)			
	Baseline	6 months	Δ Median (95% CI)	p-value
HbA1c [mmol/mol]	58	50	-6 (-9 - -2)	0.009
HOMA-IR	8.9	2.5	-5.9 (-8.5 - -3.0)	0.002
FPG [mmol/l]	10.1	7.6	-2.5 (-4.5 - -3.2)	0.011

Without daily median insulin dose of 31 units

Extensive postprandial glycaemic inventory by mixed meal tolerance tests

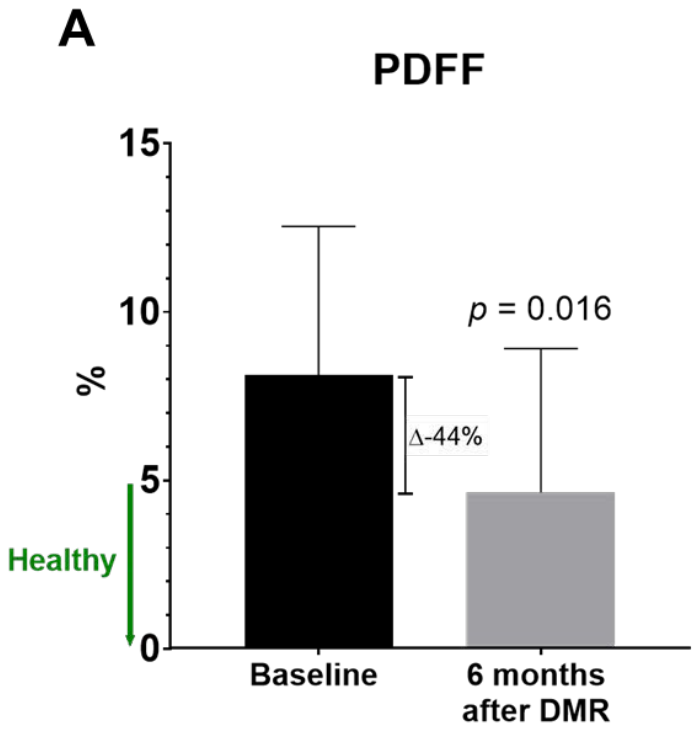


All postprandial parameters improved significantly

More physiological approach of T2D: Improvement in metabolic health

	Responders (n=12)			
	Baseline	6 months	Δ Median (95% CI)	p-value
BMI [kg/m2]	29.7	27.2	-2.3 (-3.0 - -1.9)	0.002
Total body fat [%] (DEXA)	32.6	31.1	-2.2 (-2.4 - -1.3)	0.002
Liver fat [%] (MRI)	8.1	4.6	-3.7 (-6.6 - -0.5)	0.016

Loss of liverfat in T2D



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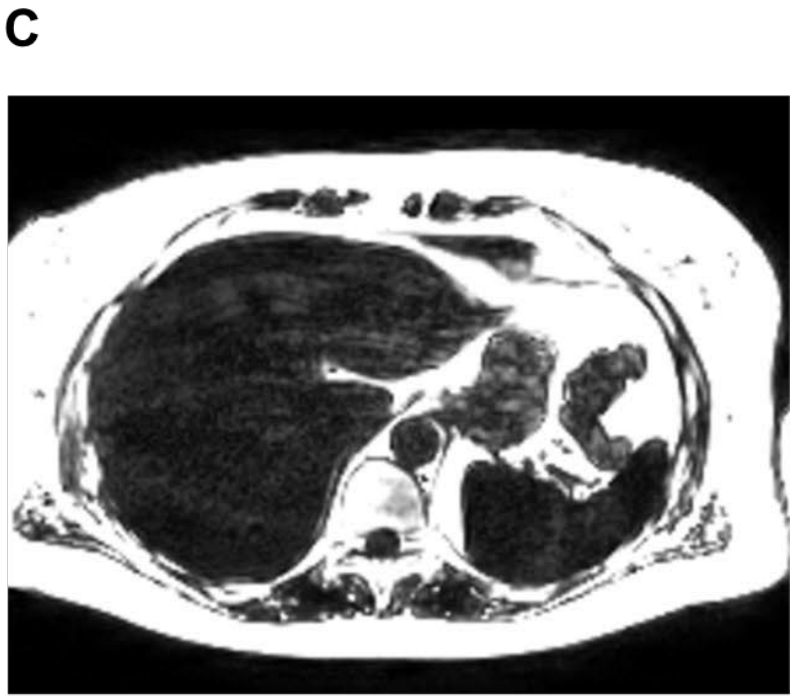

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Conclusion

- 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