



Center for Obesity
& Metabolic Therapy

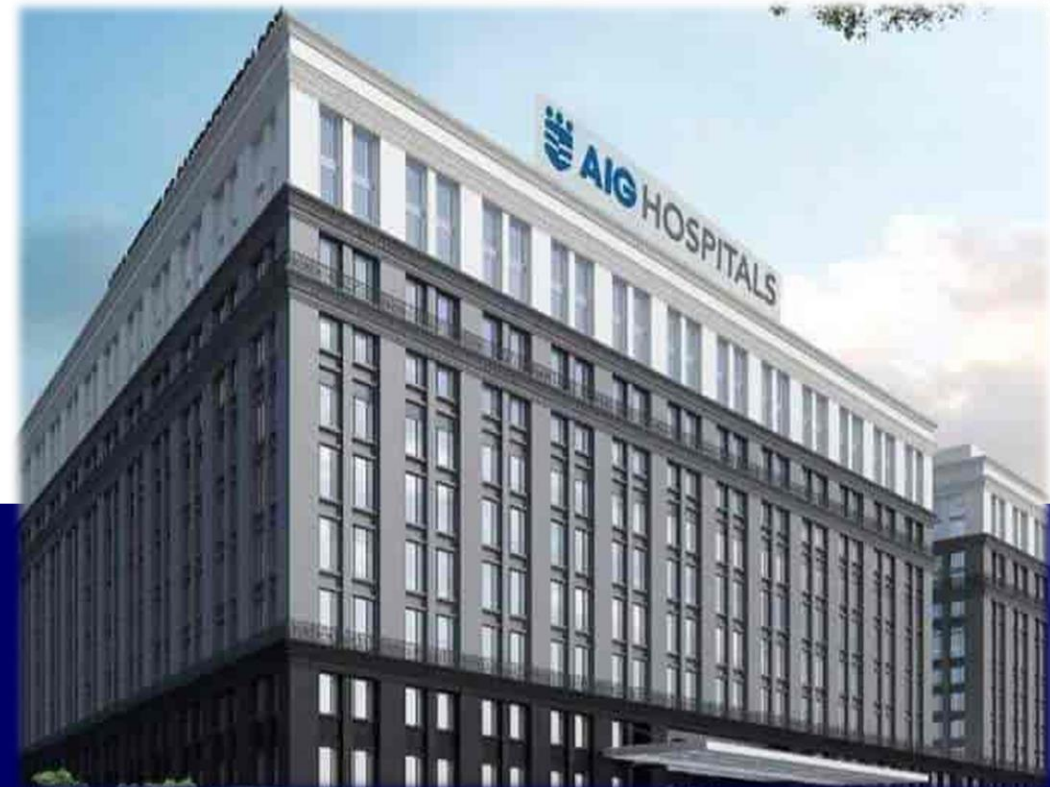
Small Bowel Liners and Ablations

Rakesh.Kalapala

M.D, D.N.B, FSGEI, FASGE, FJGES.

Director – Center for Obesity and Metabolic Therapy & Center for
Artificial Intelligence and Innovation

AIG Hospitals
Hyderabad, India.



MAYO CLINIC
CARE NETWORK
Member

Combinations of these hormones could be harnessed clinically



Suppress glucagon
Increase insulin
Weight loss



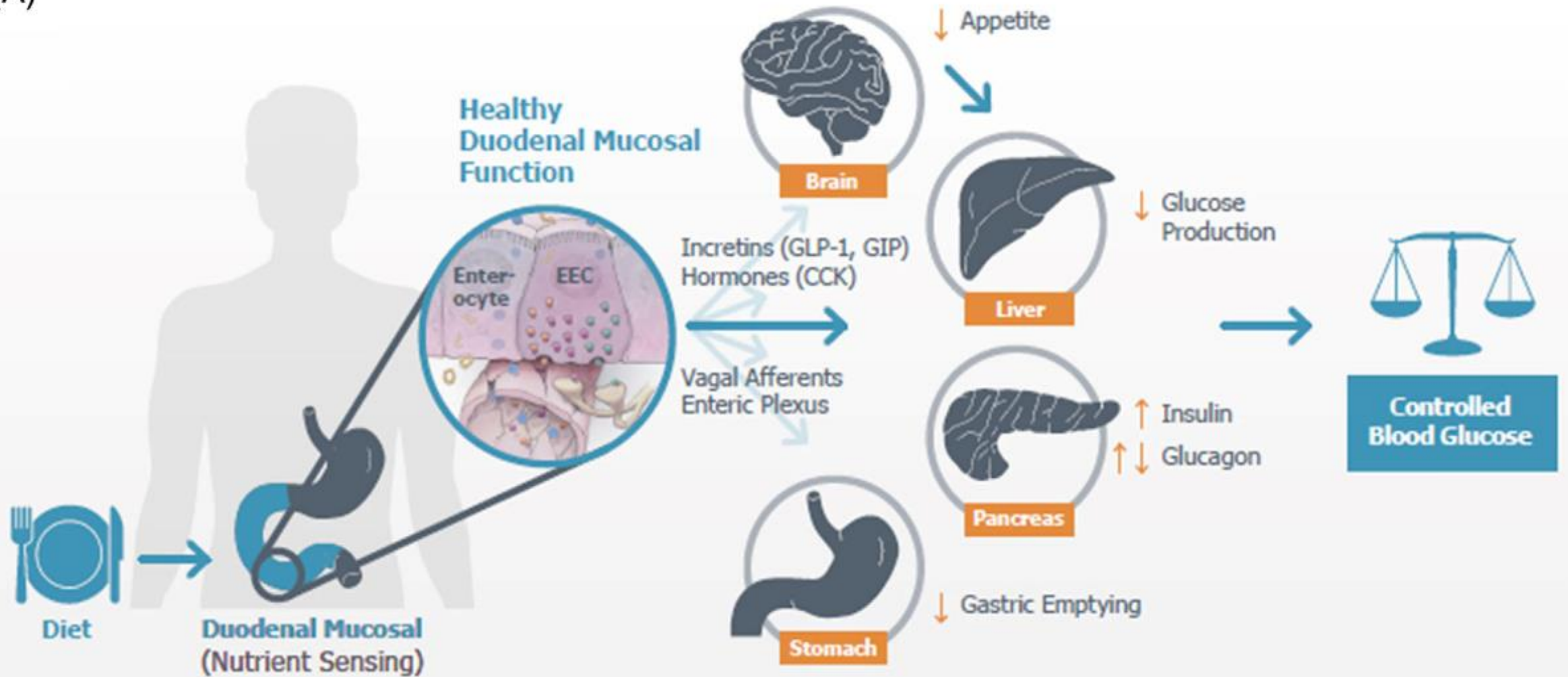
Increase glucagon
Increase insulin
But Obesogenic



Energy expenditure
Weight loss
But diabetogenic

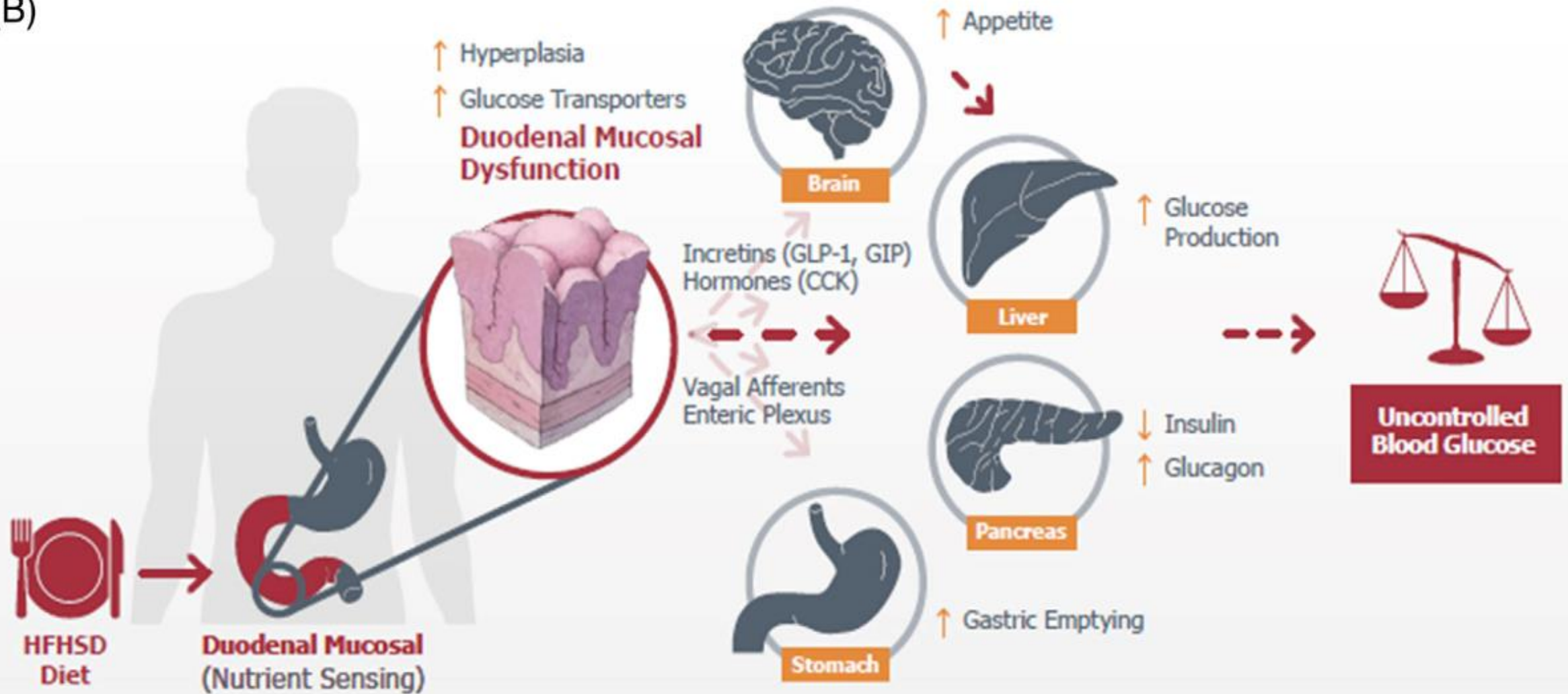
Duodenal Mucosa Nutrient Sensing Healthy

(A)



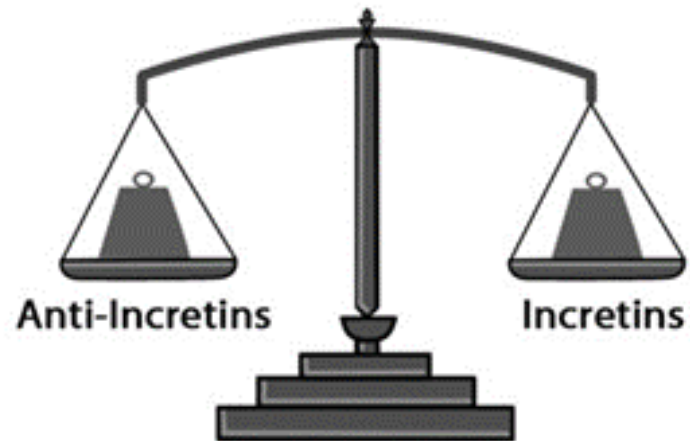
Duodenal Mucosa Nutrient Sensing - unhealthy

(B)



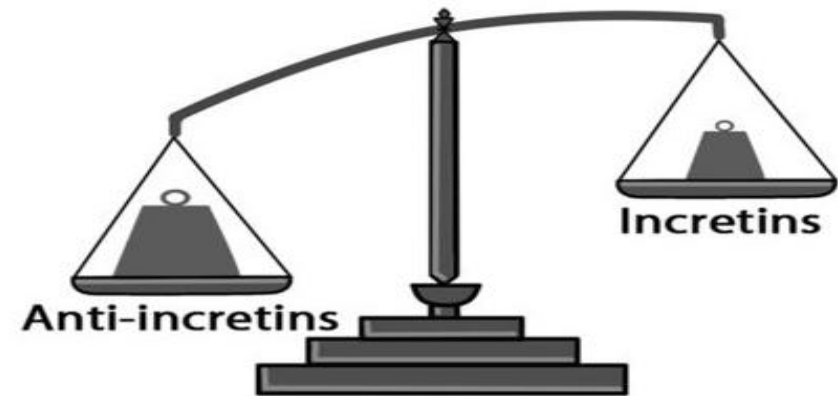
Incretin / Anti-incretin

Incretin/Anti-Incretin Balance



Normal glucose homeostasis
Maintenance of β -cell mass

Too Much Anti-Incretin



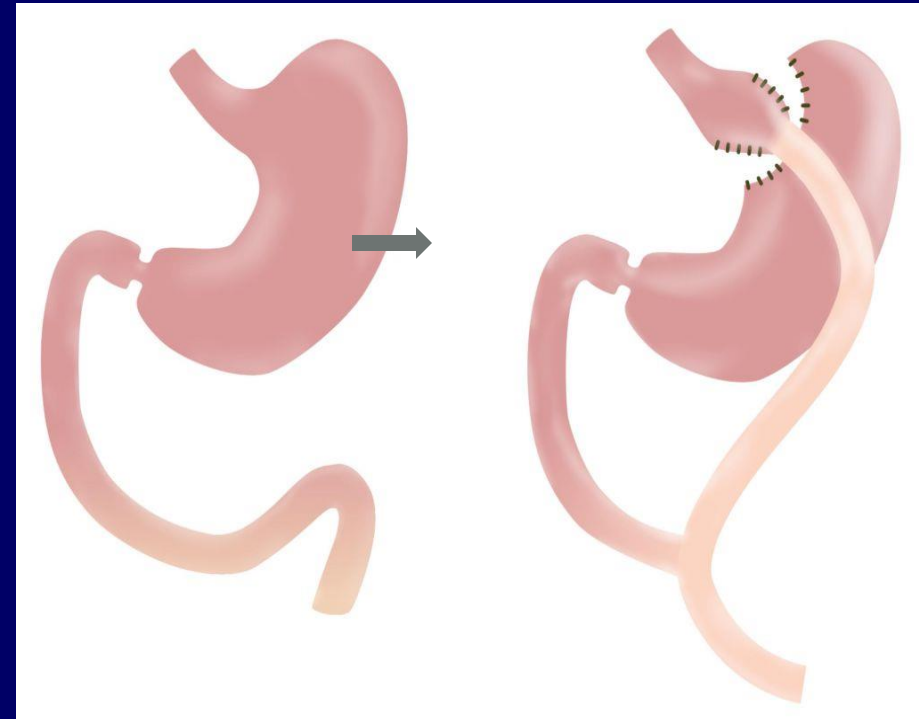
Insulin resistance
Impaired β -cell function
 β -cell depletion

(T2D)

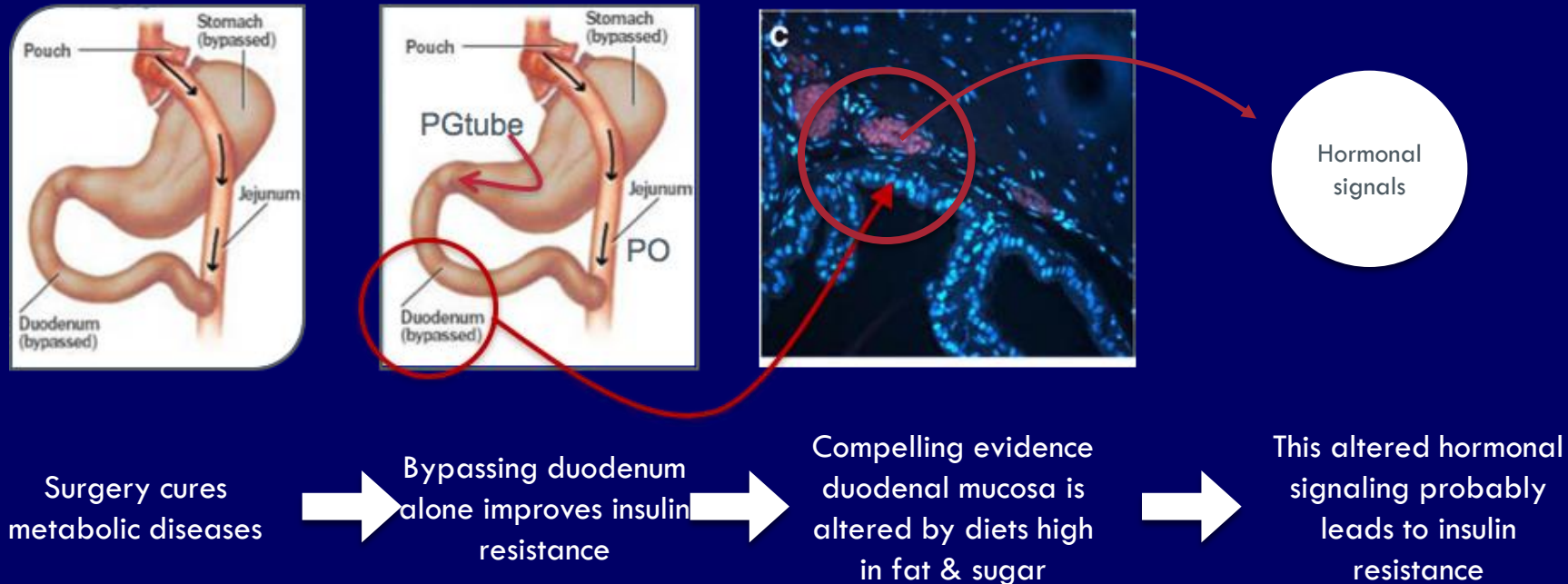
Gastric Bypass Surgery is a Proven Therapy for Metabolic Diseases

Gastric bypass surgery can effectively treat obesity and type 2 diabetes

- Landmark published studies 15 years ago (a meta-analysis and a randomized trial) have shown that T2DM was resolved in more than 75% patients undergoing gastric bypass surgery ^{1,2}
- Unfortunately the benefits of surgery are available to only a fraction patients because it is invasive, expensive, and risky



Gastric bypass surgery illustrates the critical role of the duodenum in causing insulin resistance

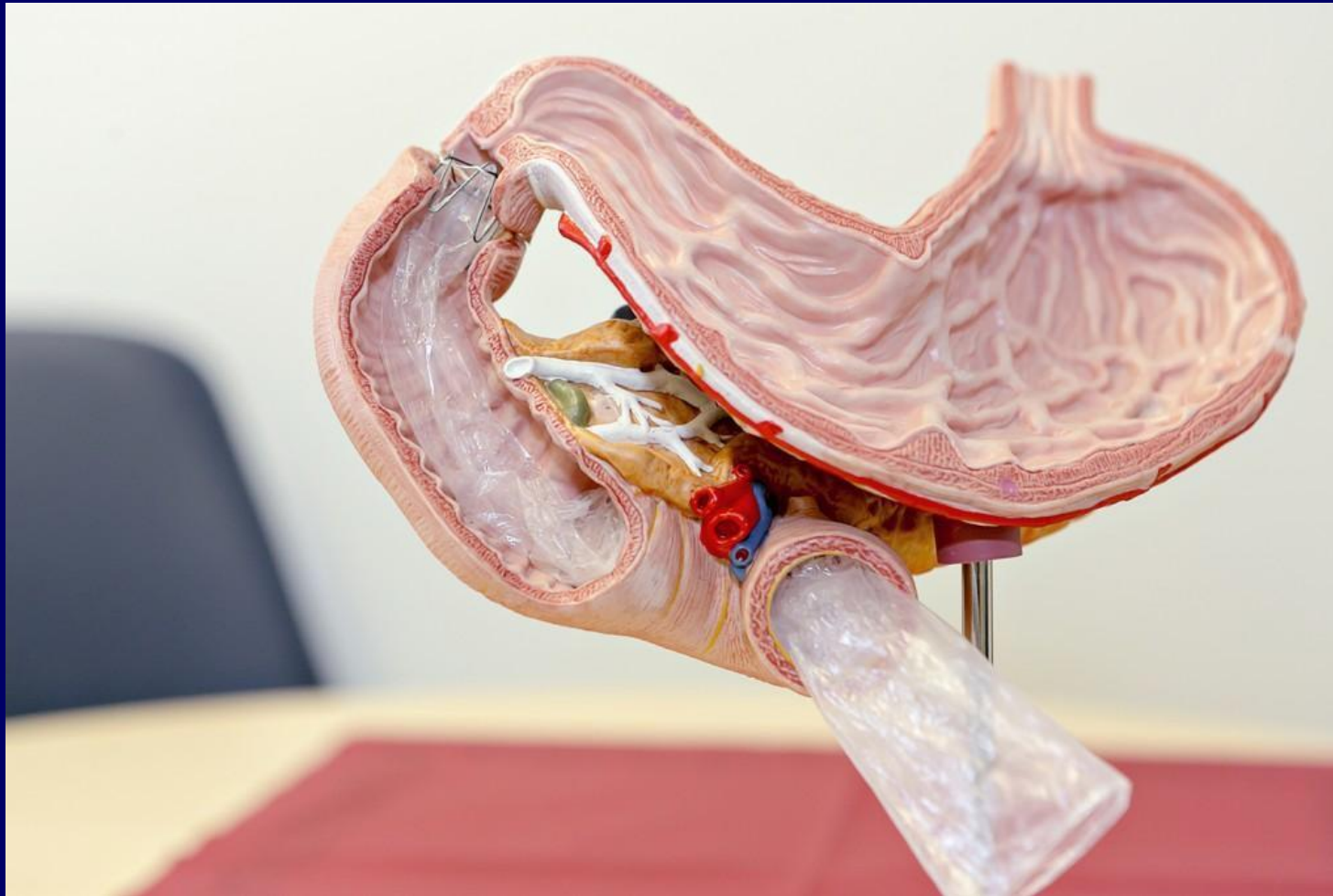


Could an anatomical defect of the duodenum, caused by excess sugar exposure, be at the root of metabolic diseases like T2D and NASH?

Small bowel Endotherapies

- Duodeno Jejunal Bypass Liners
- Duodeno Jejunal Mucosal Ablations
- Gastro Duodeno Jejunal Bypass devices

In 2012 the Endobarrier Intestinal Liner that mimics the physiological effects of gastric bypass surgery was introduced



Effect on Diabetes

- 28 patients: BMI 44.8 ± 7.4 kg/m
- 13 patients completed the 52-week study (Migration , Bleeding , Pain)
- Reduction
 1. In fasting blood glucose (-30.3 ± 10.2 mg/dL)
 2. In fasting insulin (-7.3 ± 2.6 μ U/mL)
 3. In HbA1c ($-2.1 \pm 0.3\%$)

Benefit maintained 6months after retrieval

Demoura et al S1427

Meta-Analysis Show EndoBarrier Improves Glycemic Control, Induces Weight Loss in Patients with Type 2 Diabetes and Obesity

- HbA1c: 1.3% mean reduction at explant
- HbA1c: 1.0% mean reduction 6 months post explant
- Total Body Weight: 14% mean reduction at explant

“The effect of the duodenaljejunal bypass liner on glycemic control in type2 diabetic patients with obesity: a metaanalysis with secondary analysis on weight loss and hormonal changes,”

Endobarrier Large Worldwide Registry Results

Table 1—Benefits of EndoBarrier among 1,022 patients from 33 centers in 10 countries

	<i>n</i>	Baseline	At removal	Difference	<i>P</i> value
Impact of EndoBarrier treatment on weight, systolic BP, and cholesterol					
Weight (kg)	811	120.2 ± 25.3	106.9 ± 23.8	−13.3 ± 9.7	<0.001
BMI (kg/m ²)	808	41.2 ± 10.0	36.6 ± 8.8	−4.6 ± 3.6	<0.001
Systolic BP (mmHg)	448	135.7 ± 18.0	129.5 ± 17.0	−6.3 ± 19.2	<0.001
Cholesterol (mmol/L)	467	4.8 ± 1.2	4.2 ± 1.0	−0.6 ± 1.03	<0.001
Impact of EndoBarrier treatment on HbA _{1c} ranges (%)					
All	646	8.3 ± 1.8	7.1 ± 1.3	−1.3 ± 1.5	<0.001
HbA _{1c} 7.0–7.9	141	7.5 ± 0.3	6.8 ± 0.8	−0.7 ± 0.8	<0.001
HbA _{1c} 8.0–8.9	158	8.4 ± 0.3	7.3 ± 1.0	−1.1 ± 1.0	<0.001
HbA _{1c} 9.0–9.9	96	9.4 ± 0.3	7.8 ± 1.1	−1.6 ± 1.1	<0.001
HbA _{1c} ≥10	111	11.2 ± 1.2	8.0 ± 1.5	−3.2 ± 1.7	<0.001
Impact of EndoBarrier treatment on BMI ranges (kg/m ²)					
All	808	41.2 ± 10.0	36.6 ± 8.8	−4.6 ± 3.6	<0.001
BMI 23.0–29.9	24	28.3 ± 1.9	26.0 ± 2.2	−2.2 ± 1.9	<0.001
BMI 30.0–34.9	144	32.9 ± 1.4	29.8 ± 2.6	−3.1 ± 2.4	<0.001
BMI 35.0–39.9	253	37.6 ± 1.4	33.3 ± 2.9	−4.3 ± 2.6	<0.001
BMI ≥40	387	47.5 ± 10.4	41.9 ± 9.7	−5.5 ± 4.2	<0.001

Data are from the Worldwide EndoBarrier Registry and are mean ± SD unless otherwise specified. The centers are located in Australia, Austria, Brazil, Czech Republic, England, Germany, Israel, the Netherlands, Scotland, and Slovenia. BP, blood pressure.

But the Endobarrier failed in the marketplace because of inherent design flaws

- The EndoBarrier FDA trial was halted due to liver infections resulting from their anchoring barbs that penetrate the small intestine leading to bacterial translocation and product was withdrawn globally



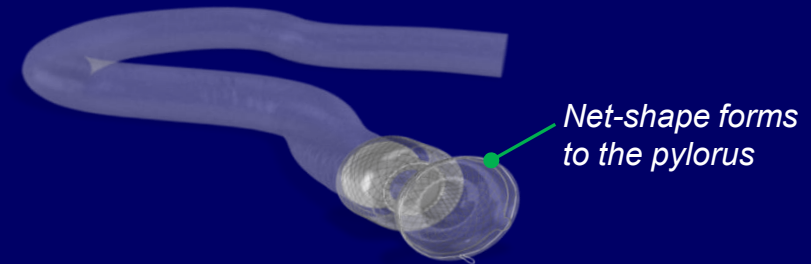
Next Generation Solution

The EndoSleeve™ has significant competitive advantages and can leverage an established path to market



EndoBarrier

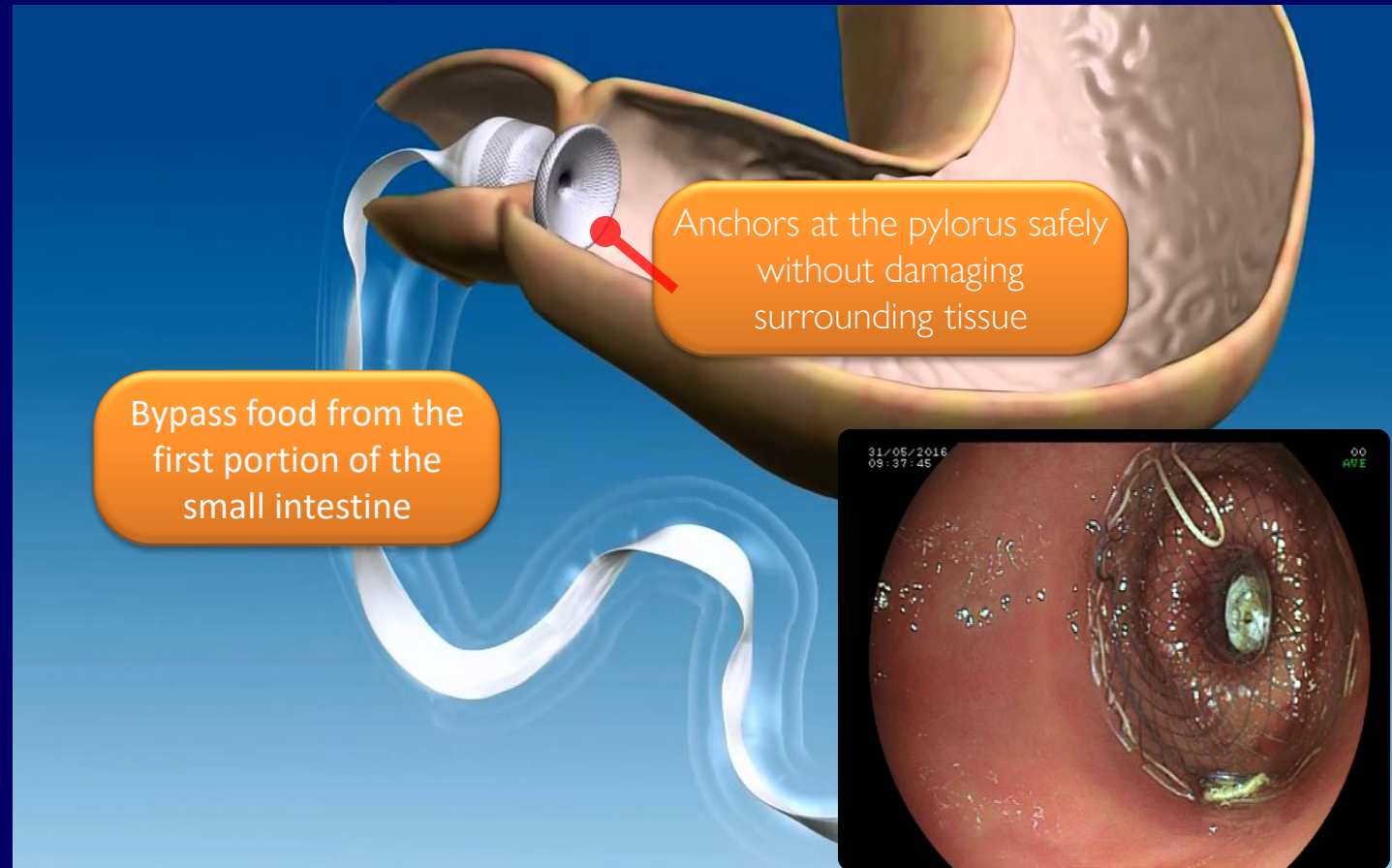
- Anchors with 8mm barbs piercing the duodenal bulb, causes complications such as liver abscess that halted FDA trial⁸
- Positive efficacy results - average 1.3% reduction in HbA1c and 15kg weight loss⁹
- Regulatory approvals in international markets, reimbursement in Germany and UK in 2018



EndoSleeve™

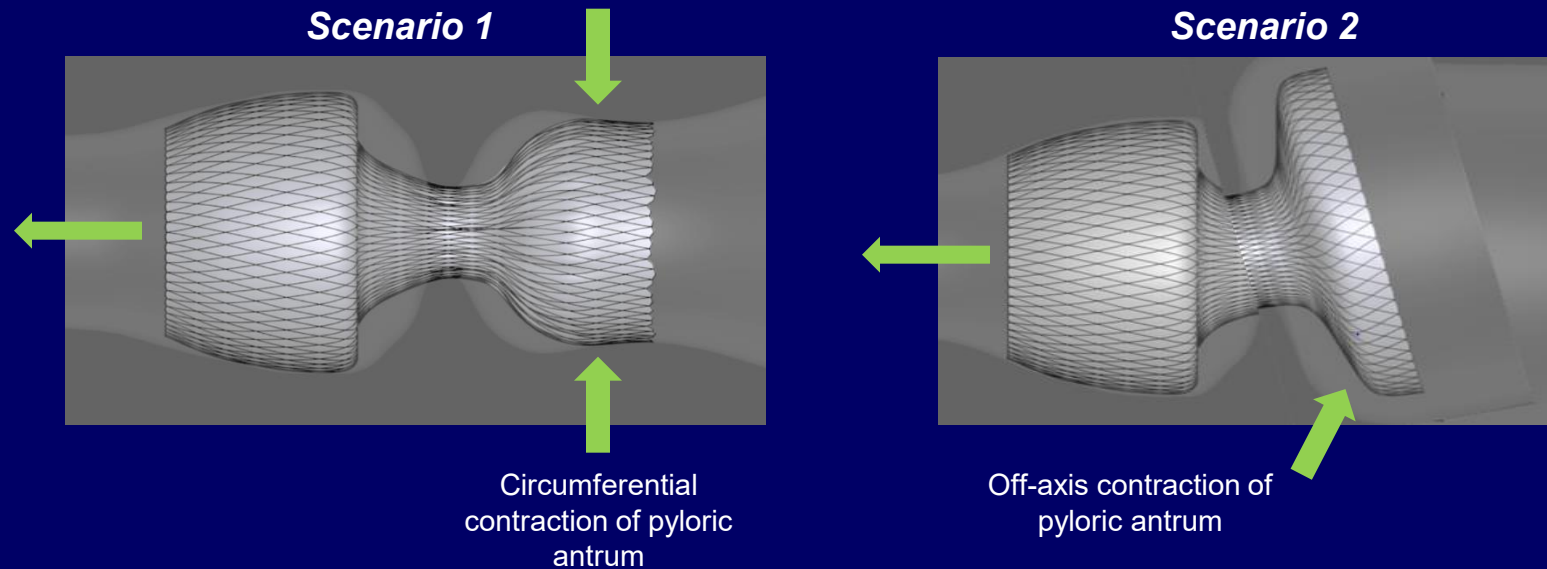
- Anchors without piercing tissue by conforming to the anatomy of the pylorus, results from first-in-man study show feasibility of anchoring with no injury¹⁰
- Consistent efficacy results from first-in-man study due to similar sleeve configuration
- Leverage existing regulatory path and reimbursement codes to speed market entry

METAMODIX ENDOSLEEVE



Distal Migration Mechanisms

- The implant is designed to resist deformation by the body and maintain position across the pylorus
- When the implant is subject to an axial force (such as during transport of chyme through the sleeve) and the stomach flange is displaced sideways, distal migration can occur





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<https://doi.org/10.5056/jnm19200>

Journal of Neurogastroenterology and Motility

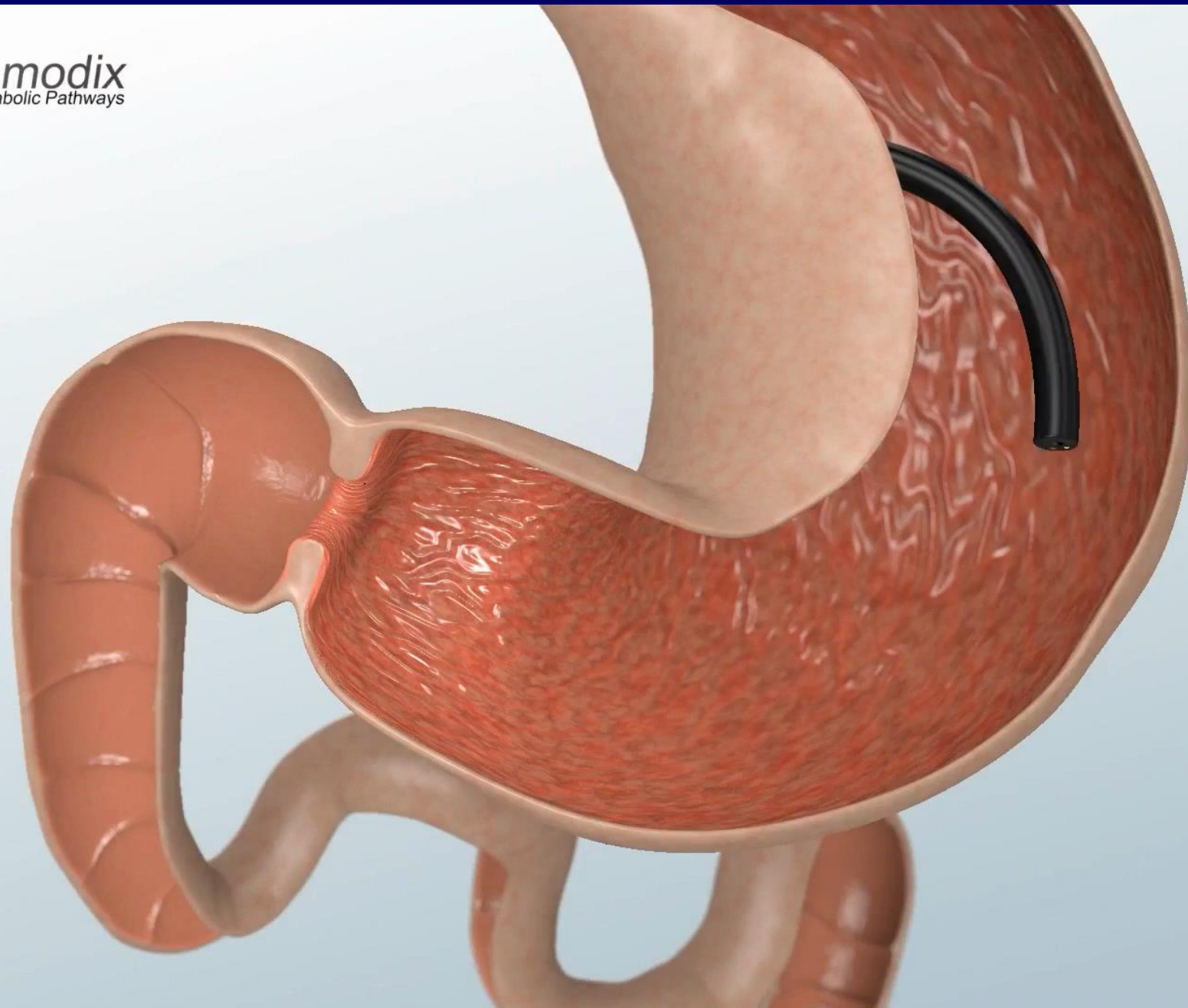


Original Article

Assessment of Pyloric Sphincter Physiology Using Functional Luminal Imaging Probe in Healthy Volunteers

Nitin Jagtap,* Rakesh Kalapala, and D Nageshwar Reddy

Department of Medical Gastroenterology, Asian Institute of Gastroenterology, Hyderabad, India



Promising EndoSleeve 3 month Efficacy Results at our institution

Endosleeve has many clinical advantages and can be safely anchored at the pylorus with supplemental anchoring with attachment to two stomach plications

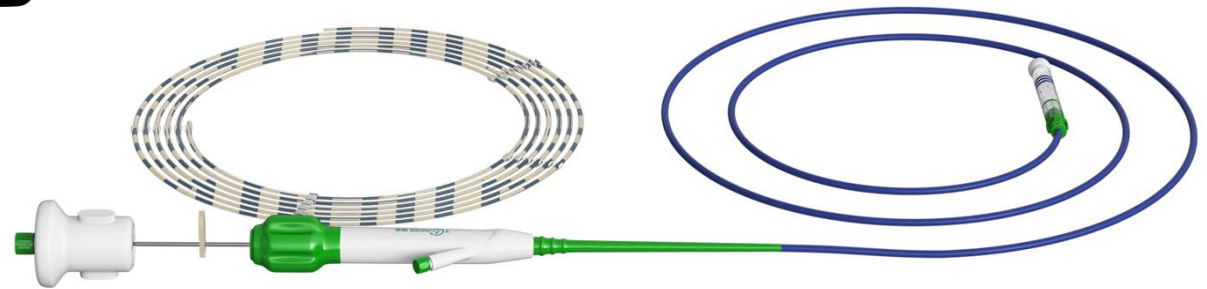
Subject ID	Weight (Kilograms)		% TBWL
	Baseline	At explant	
102-16	98	82	16.3%
102-17	107	90	15.9%
102-18	137	109	20.4%
102-19	87	69	20.7%

Tongjee Medical DJBS

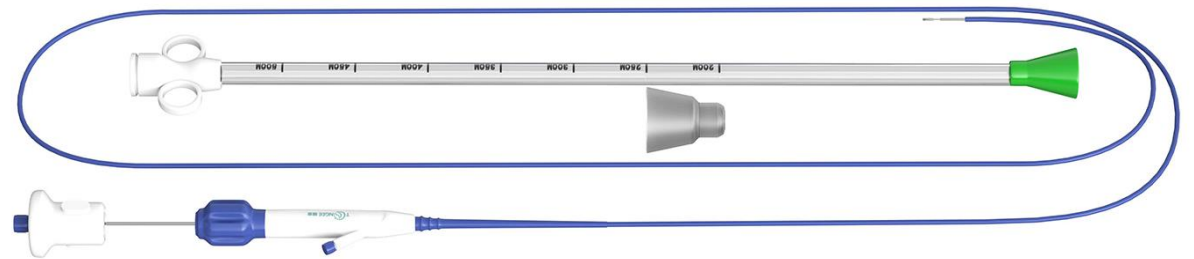
A polyethylene sleeve very similar in design to the Endobarrier was implanted
For 3 months and patients were followed up for 6 months thereafter



B



C



Tongjee DJBS effect on metabolic parameters




At 3months explantation time and 6 months after explantation

Table 2 Changes in anthropometric, liver, and metabolic parameters at DJBS explantation and 6 months post-explantation

Variables	Baseline	3 months	9 months	3 months vs. Baseline		9 months vs. Baseline	
	(n = 22)	(n = 22)	(n = 19)	Difference	P-value [†]	Difference	P-value [†]
Anthropometric parameters							
Body weight, kg	93.6 ± 15.6	85.6 ± 15.9	84.3 ± 12.3	-8.0 ± 3.6	< 0.001	-7.5 ± 10.3	0.005
BMI, kg/m ²	32.6 ± 3.9	29.8 ± 4.3	29.4 ± 3.7	-2.8 ± 1.2	< 0.001	-2.6 ± 3.3	0.003
Fat mass, kg	36.8 ± 9.0	30.3 ± 8.8	29.2 ± 7.7	-6.4 ± 3.1	< 0.001	-6.5 ± 6.9	< 0.001
Body fat percentage, %	38.8 ± 6.4	34.9 ± 7.2	34.6 ± 6.7	-3.9 ± 2.5	< 0.001	-3.8 ± 4.1	< 0.001
Waist circumference, cm	106.3 ± 11.7	99.6 ± 11.8	97.0 ± 10.2	-6.8 ± 4.0	< 0.001	-7.2 ± 7.2	< 0.001
Hip circumference, cm	112.3 ± 9.1	106.9 ± 9.8	104.2 ± 5.7	-5.4 ± 4.9	< 0.001	-6.3 ± 6.7	< 0.001
Waist-to-hip ratio	0.94 ± 0.06	0.93 ± 0.05	0.93 ± 0.06	-0.01 ± 0.04	0.175	-0.01 ± 0.06	0.443

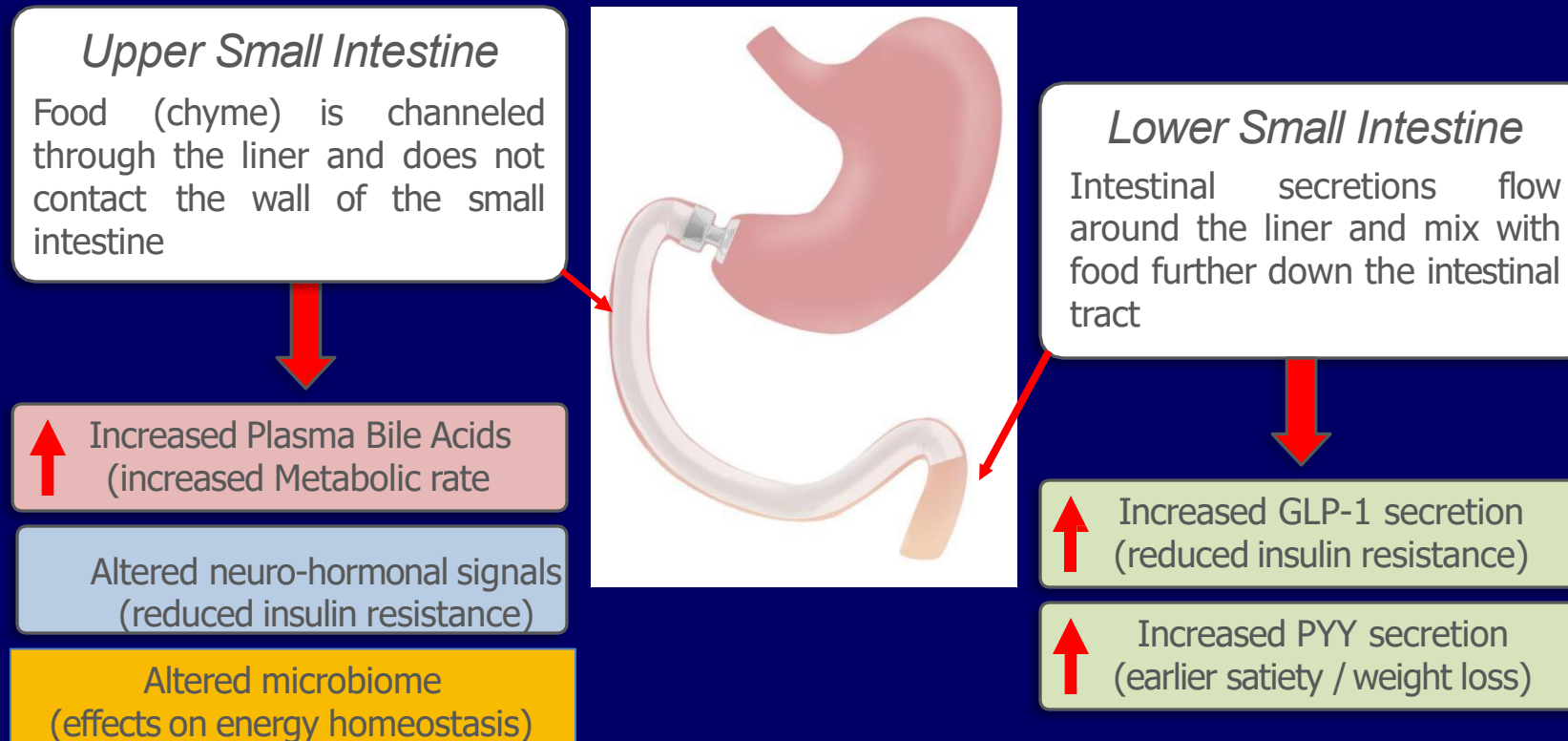
Current Sleeve Technologies

Used to mimic gastric bypass surgery with a less invasive approach – differ by anchoring method

	 <p>Endobarrier</p>	 <p>Metamodix EndoSleeve</p>	 <p>Tongee DJBS (China)</p>
Technical Characteristics	Sleeve anchored in the duodenal bulb with active fixation (barbs) extending to the proximal jejunum	Sleeve anchored at the pylorus ,additional active plication fixation extends to the proximal jejunum	Very similar to Endobarrier, anchored in the duodenal bulb with barbs and extending to the proximal jejunum
Phase of Development	Commercial, over 3500 cases WW	Human feasibility trial in India	3 month study with 6 months followup, Approved in China,
Clinical Results	-1.2% reduction in HbA1c, average 10% TBWL in 12 months	-1.5% reduction in HbA1c, 16-20% TBWL in 3 months	9% TBWL at 3 month sustained at 9 months
Advantages	Positive effect on T2DM and obesity	Positive effect on T2DM and obesity	Positive effect on obesity and on other metabolic parameters
Disadvantages	Complications due to anchoring with barbs	More data needed to validate anchoring durability	More data needed to validate effect on T2DM

In Summary How Do Intestinal Liners Work?

By modifying our metabolism and may provide durable metabolic benefits in a significant proportion of patients treated because of changes to the gut microbiome



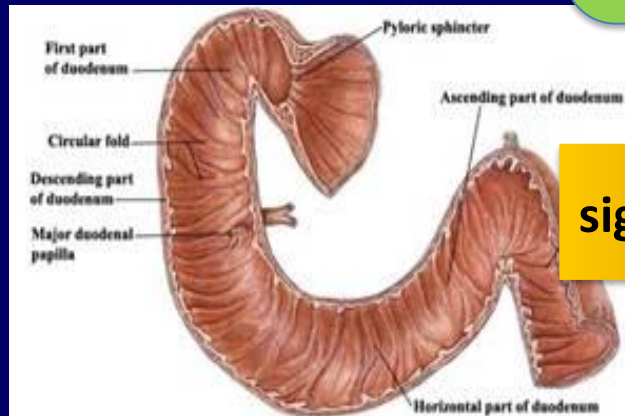
Duodenal Ablation Devices

DMR therapies

- Laser
- Thermal
- RFA
- Electroporation
- Vapour ablation

Metabolic Role of Duodenum in Causing Insulin Resistance

Duodenum



signal

Physiological role?

- Insulin resisting signal emanating from upper GI potentially important in early hunter gatherer

Evidence from intervention

- RYGB
- Endoluminal sleeve
- DMR hydrothermal ablation

Evidence of pathophysiology

- Hypertrophy-hyperplasia in upper GI exposed to hexose/fat
- Abnormal enteroendocrine population

Dirksen et al. Diabetes Care. 2010;33(2):375-377

Cummings DE et al. IFSO 2016

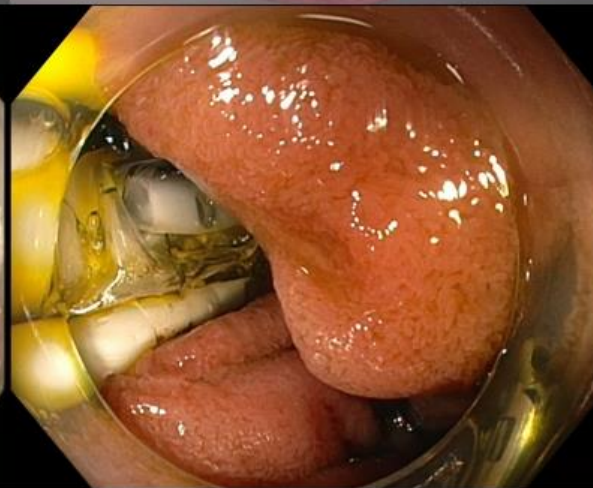
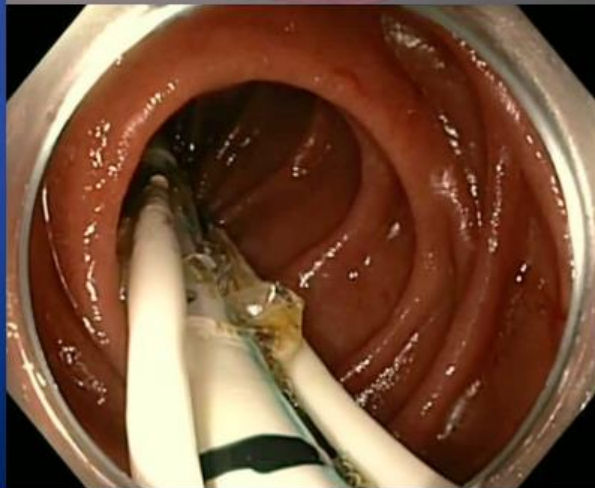
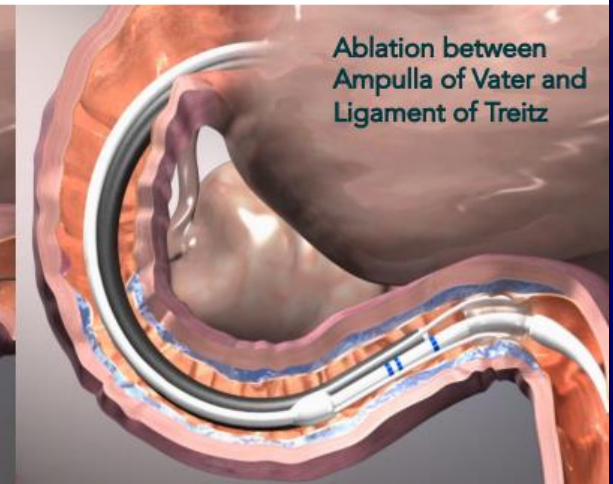
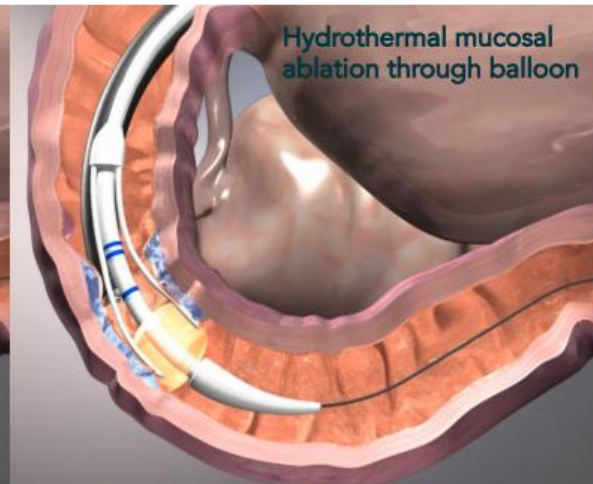
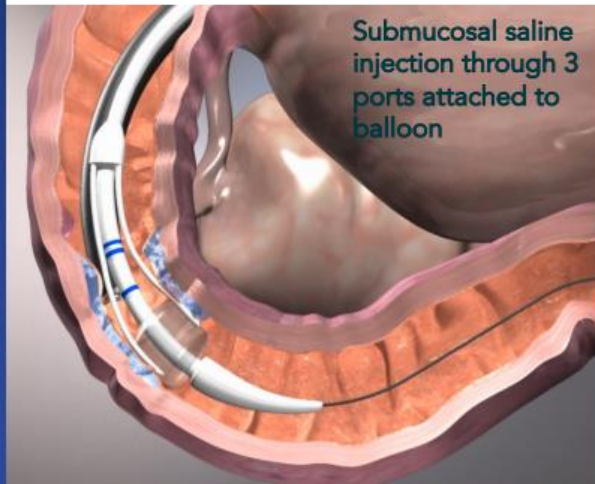
Adachi et al Endocr J. 2003;50(3):271-279

Bailey et al. Acta Endocrinol (Copenh). 1986;112(2):224-229

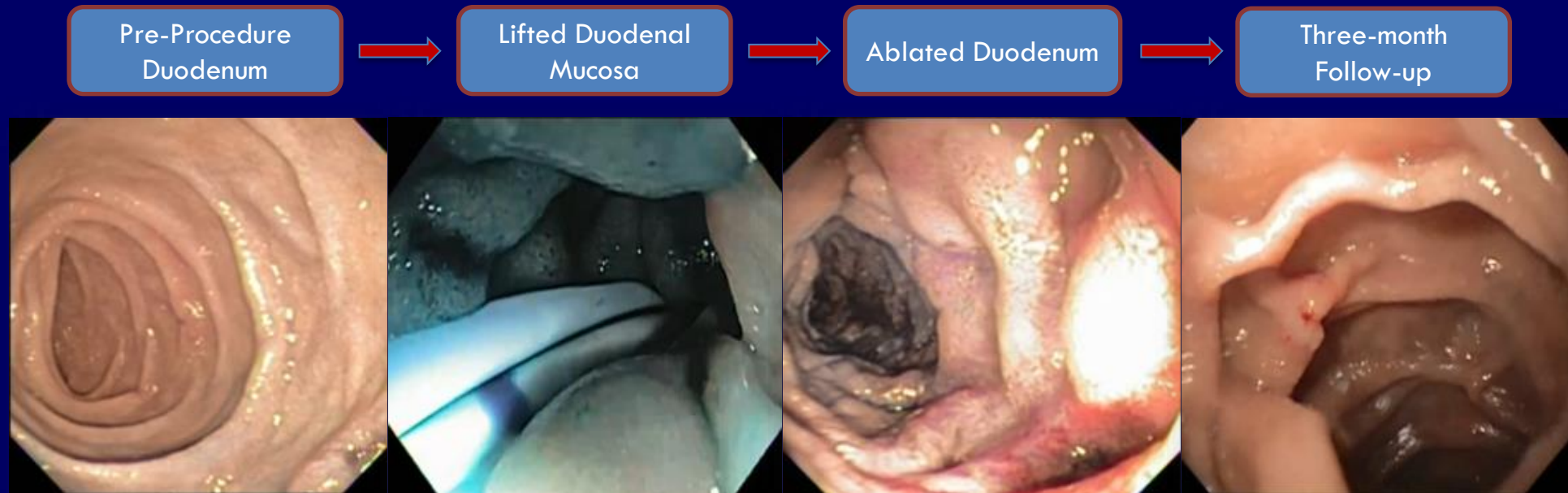
Gniuli et al. Diabetologia. 2010;53(10):2233-2240

Fractyl Health Duodenal ablation using a heated balloon

Revita™ Duodenal Mucosal Resurfacing Procedure



DMR : Endoscopic view



➤ Procedure:

- Duodenal mucosa lifted by saline to create thermal barrier protecting deeper tissues
- Circumferential ablation through thermal exchange (hot water)
- Follow up endoscopies and duodenal biopsies at 1mo and 3mo document mucosal healing

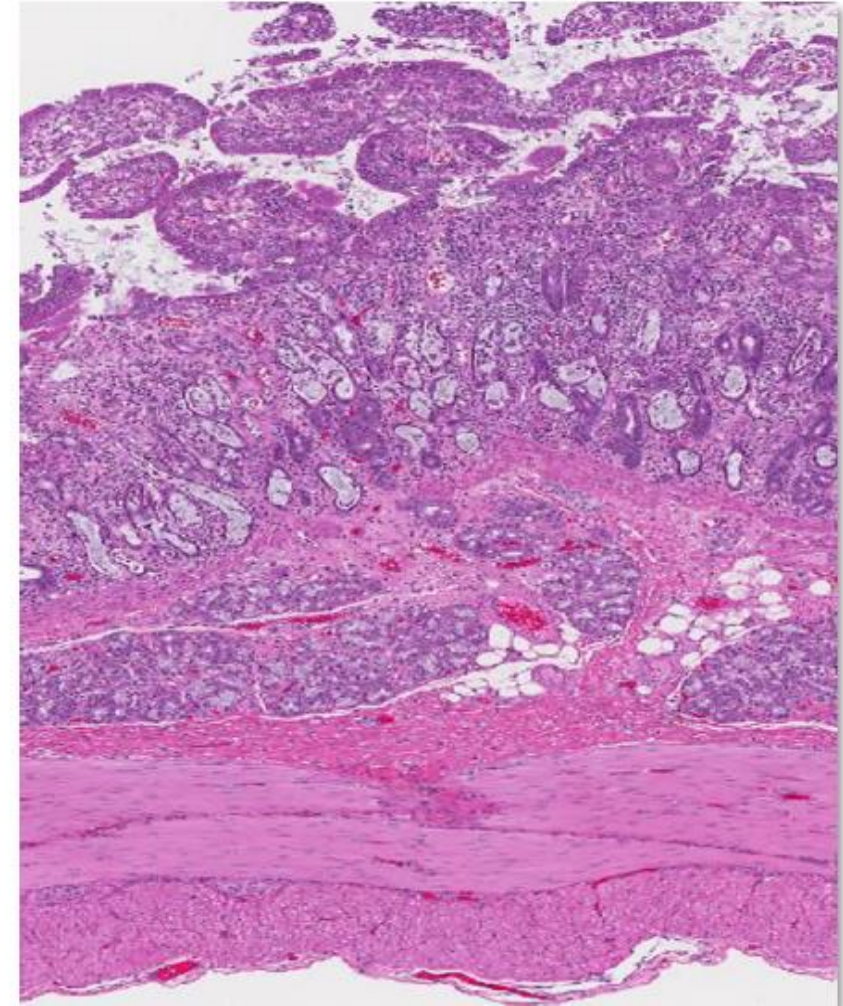
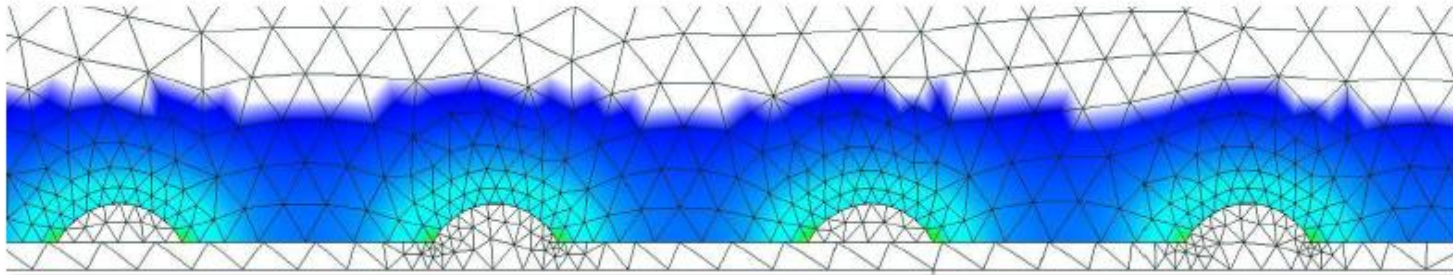
Fractyl DMR data

Author (year)	Study design	Intervention	Total (n)	Inclusion criteria	Outcome	Notes
Rajagopalan et al ¹⁷ (2016)	Single-arm Open-label	DMR	39	HbA1c 7.5%–12.0% with BMI \geq 31 kg/m ²	HbA1c was reduced by 1.2% at 6 months	Three patients experienced duodenal stenosis
Hadefti et al ¹⁸ (2018)	Case report	DMR	1	44-year-old, overweight (BMI = 28 kg/m ²) with T2D treated with OHA	HbA1c decreased by 1.2% (8.2% to 7.0%) at 3 months	Presented with a video demonstration
van Baar et al ¹⁹ (2020)	Multi-center (seven sites, internationally) Single-arm Open-label	DMR	46	HbA1c 7.5%–10.0% with BMI 24–40 kg/m ²	HbA1c was reduced by 0.9% at 24 weeks, with preservation of the effect up to 12 months HOMA-IR was reduced by 2.9 at 24 weeks, by 3.3 at 12 months	DMR was completed successfully in 80% of the enrolled patients 81% of adverse events related to DMR was classified as 'mild'
van Baar et al ²⁰ (2021)	Single-arm Open-label	DMR combined with GLP-1RA (liraglutide)	16	HbA1c < 8.0% with BMI 24–40 kg/m ² with fasting C-peptide > 0.5 nmol/L using long-acting insulin	69% patients met adequate glycaemic control at 6-month follow-up without insulin, 56% patients were still responders at the 12-month follow-up	No device-related AEs or treatment-related SAEs were reported
Mingrone et al ²¹ (2022)	Double-blind RCT	DMR Control	DMR, 56; sham, 52	HbA1c 7.5%–10.0%, BMI 24–40 kg/m ² , fasting insulin > 48.6 pmol/L with \geq 1 OHA	HbA1c change was –6.6 mmol/mol in DMR group versus –3.3 mmol/mol post-sham 12-week post-DMR liver-fat change was –5.4% in DMR group versus –2.2% post-sham	South American cohort failed to prove relative efficacy of DMR in liver fat reduction

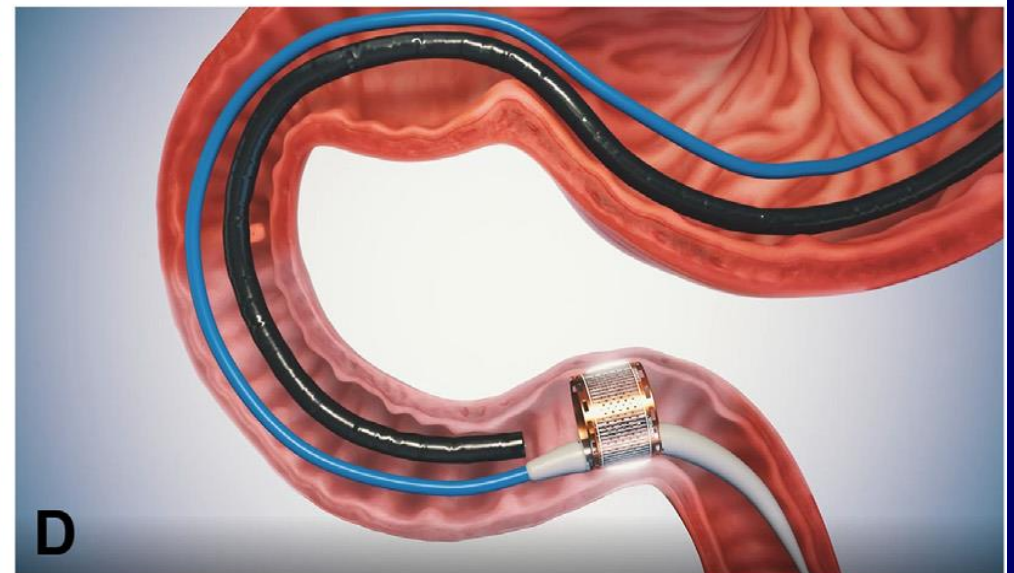
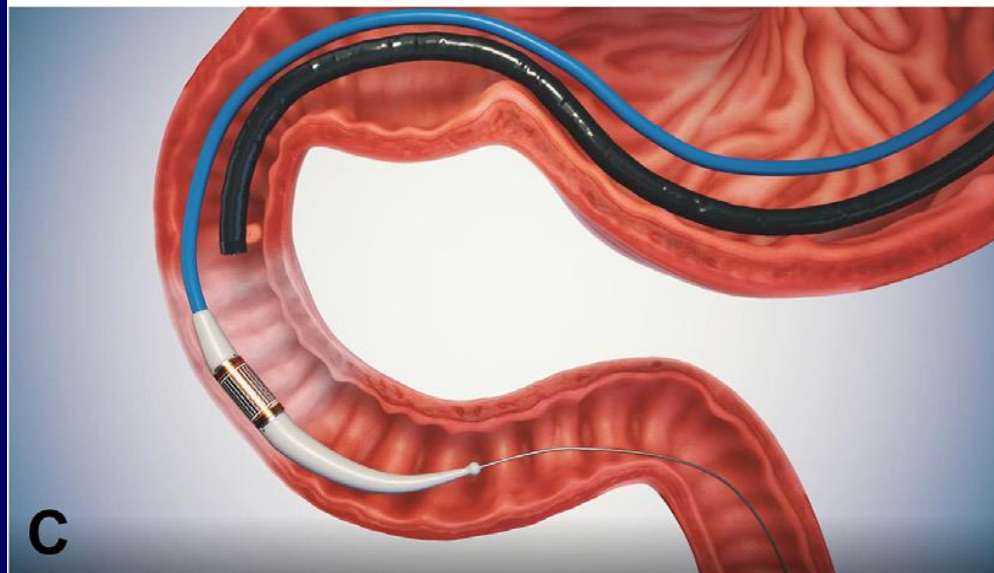
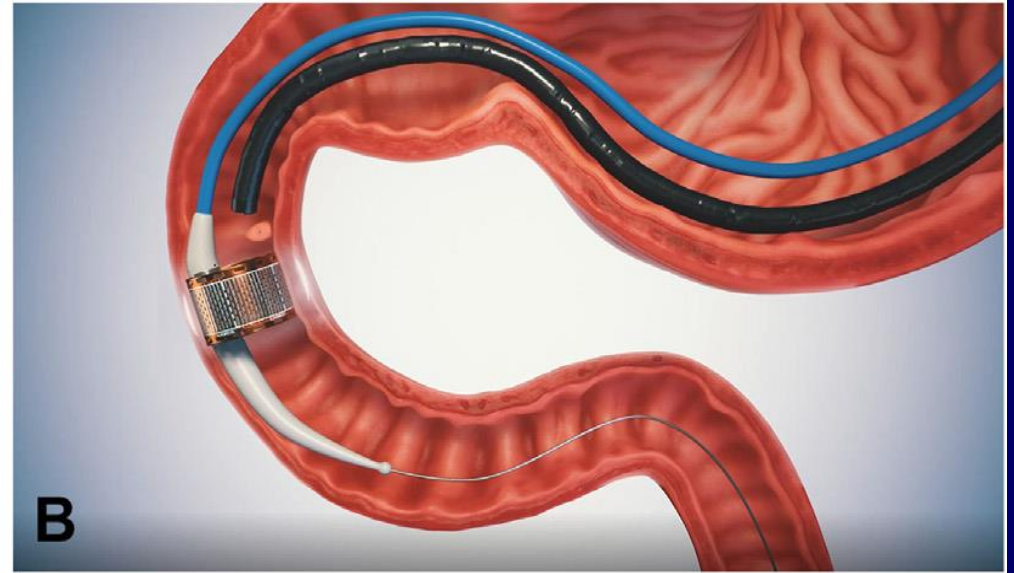
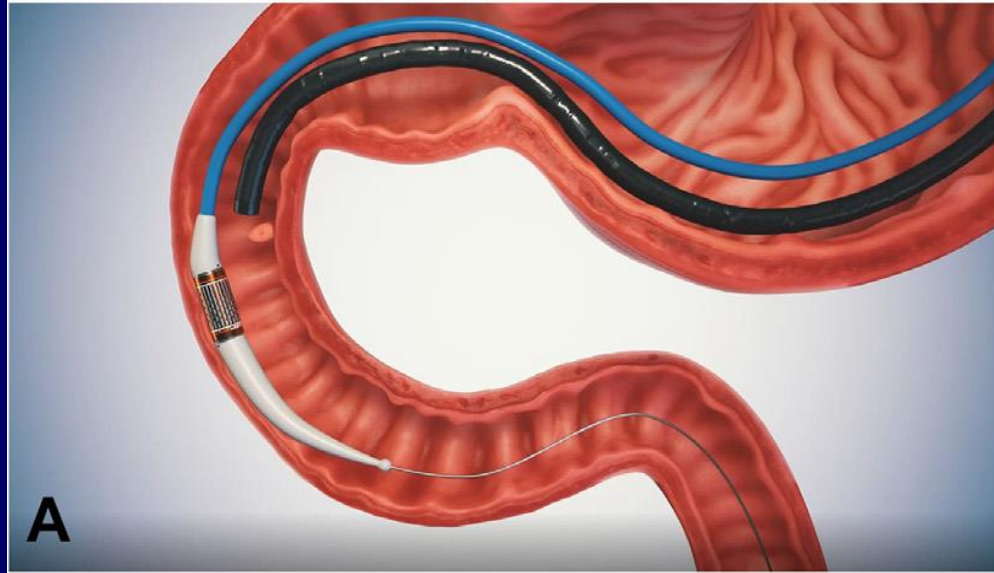
EndoGenex ReCET Therapy

ReCellularization via Electroporation Therapy (ReCET™)

- High voltage, ultra short pulsed electric field
- Increases cell permeability resulting in mucosal cellular apoptosis
- Preserves extracellular matrix and myocytes
- Rapid re-epithelialization due to preserved tissue architecture
- Non-thermal (< 4 °C average increase in probe temperature)
- Controlled depth of penetration

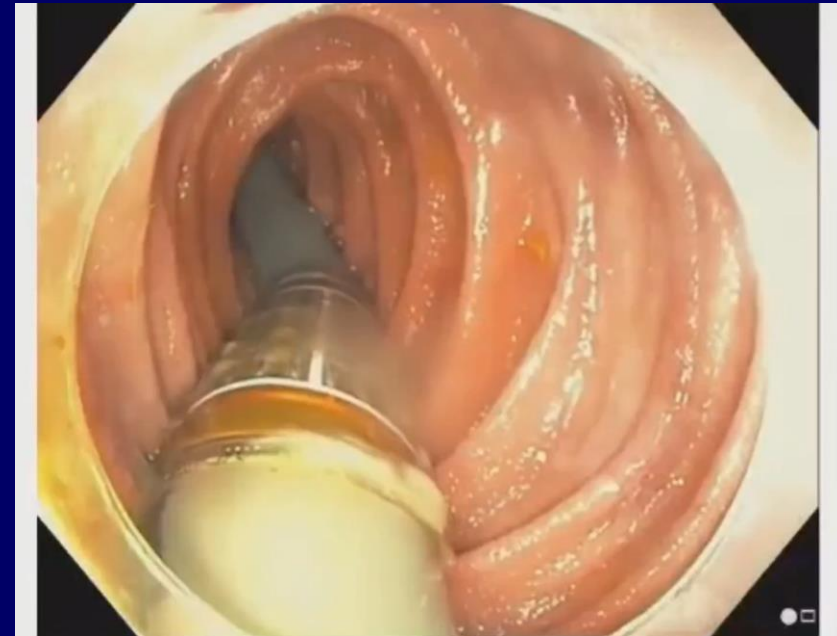


Endogenex ReCET Eletroporation Device



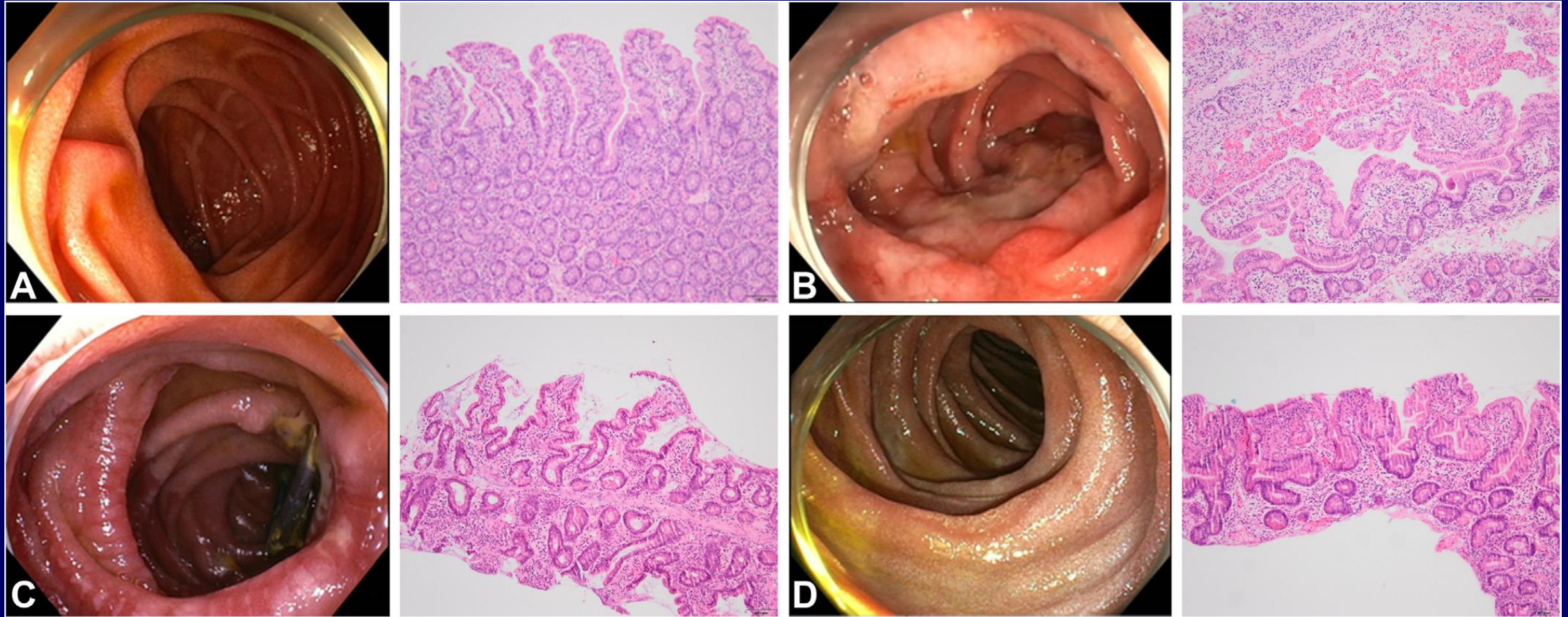
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- Increases cell permeability resulting in mucosal cellular apoptosis
- Preserves extracellular matrix and myocytes
- Rapid re-epithelialization due to preserved tissue architecture
- Non-thermal (< 4 °C average increase in probe temperature)
- Controlled depth of penetration
- Advanced over guidewire; direct endoscopic vision & fluoroscopic guidance
- Treatment delivered in 2 cm segments, repeated sequentially from D2
- Technical success in 100% of patients (≥ 6cm treated)
- Mean treatment length 11.1 ± 2.6cm (range 6 – 18 cm)



Dr Adrian Sartoretto DDW 2023

Effect of electroporation ablation on duodenal mucosa



A: Before Ablation B: Right after Ablation C: 4 Days after Ablation D: 1 month after Ablation

EndoGenex Regent 1 Trial Results

	Week 24			Week 48		
	Change from Baseline (95% Confidence Interval)			Change from Baseline (95% Confidence Interval)		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
ΔHbA1c (%)	0.09 (-0.65,0.84)	-0.81 (-1.42,-0.21)	-1.35 (-1.91,-0.79)	0.03 (-0.65,0.72)	-1.00 (-1.57,-0.43)	-1.70 (-2.22,-1.18)
ΔBody weight (%)	-1.78 (-4.5,0.94)	-4.93 (-7.12,-2.74)	-5.99 (-8.02,-3.98)	-1.23 (-4.17,1.70)	-1.79 (-4.20,1.19)	-6.16 (-8.37,-3.95)
ΔFasting glucose (mmol/L)	-0.21 (-1.58,1.17)	-2.60 (-3.72,-1.48)	-3.30 (-4.37,-3.30)	0.68 (-0.78,2.14)	-2.30 (-3.50,-1.10)	-3.66 (-4.79,-2.53)
ΔHOMA-IR	0.20 (-0.63,1.03)	-1.23 (-1.87,-0.59)	-0.97 (-1.59,-0.35)	1.42 (-0.02,2.86)	-0.90 (-2.04,0.24)	-1.17 (-2.31,-0.03)
TIR (%)	68.4 (56.2, 80.5)	76.3 (66.5, 86.2)	84.7 (75.6, 93.7)	68.2 (55.6, 80.8)	71.5 (61.0, 82.1)	86.1 (77.4, 96.2)
ΔTotal Cholesterol (mmol/L)	-0.64 (-1.30,0.03)	-0.13 (-0.68,0.42)	-0.41 (-0.91,0.10)	-0.55 (-1.12,-0.00)	-0.37 (-0.84,0.10)	-0.82 (-1.24,-0.40)
ΔLDL (mmol/L)	-0.60 (-1.23,0.03)	-0.09 (-0.41,0.60)	-0.28 (-0.74,0.18)	-0.244 (-0.75,0.26)	-0.11 (-0.53,0.31)	-0.56 (-0.93,-0.18)
ΔHDL (mmol/L)	0.03 (-0.06,0.12)	0.05 (-0.02,0.12)	0.03 (-0.35,0.91)	0.01 (-0.09,0.11)	0.54 (-0.03,0.14)	-0.02 (-0.09,0.06)
ΔTriglycerides (mmol/L)	-0.32 (-0.99,0.36)	-0.67 (-1.23,-0.11)	-0.42 (-0.92,0.09)	-0.50 (-1.14,0.14)	-0.75 (-1.29,-0.22)	-0.74 (-1.22,-0.26)

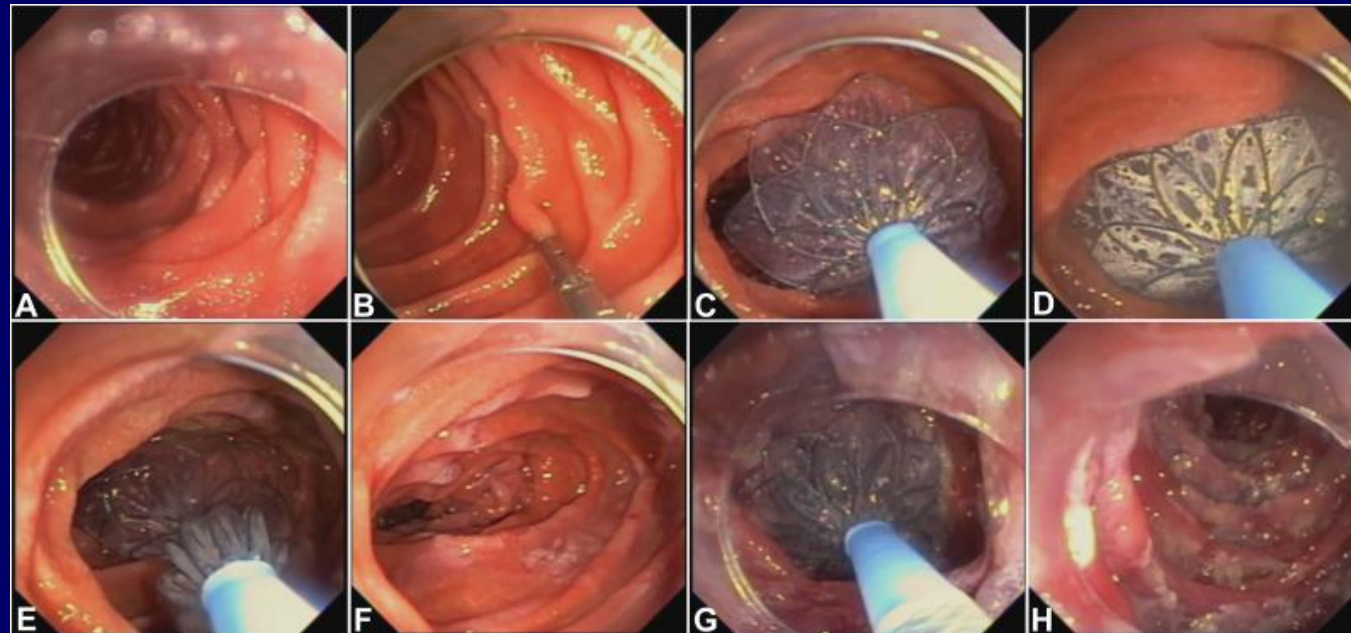
Group 1, Group 2 and Group 3 represent ascending doses of energy application

ReCET in combination with semaglutide therapy

	Baseline	6 months	P value	12 months*	P value
Number of patients	14	14	NA	13	NA
Secondary glyceimic endpoints					
HbA1c, mmol/mol	55 (53-57)	48 (40-52)	.004	47 (43-53)	.010
FPG, mmol/L	8.8 (7.6-10.6)	6.8 (6.1-8.7)	.004	6.6 (5.8-7.2)	.003
Fasting insulin, pmol/L	80 (55-105)	50 (30-58)	.013	43 (27-63)	.023
Fasting C-peptide, nmol/L	0.57 (0.36-0.69)	0.59 (0.47-0.87)	.530	0.59 (0.44-0.87)	.100
HOMA-IR	5.84 (3.92-7.50)	2.47 (1.50-3.25)	.013	1.78 (1.05-2.71)	.002
Time in range, %	72 (46-85)	92 (79-96)	.019	89 (76-97)	.011
Secondary metabolic endpoints					
Weight, kg	90.7 (82.3-104.2)	77.6 (75.4-93.4)	<.001	74.0 (67.2-98.6)	.002
BMI, kg/m ²	28.8 (25.1-31.2)	24.9 (23.0-27.0)	<.001	22.6 (22.1-27.1)	.002
Waist circumference, cm	107 (97-111)	95 (85-99)	.002	91 (79-101)	.002
Microalbuminuria, mg/L	17 (8-40)	10 (6-36)	.432	14 (7-28)	.814
Total cholesterol, mmol/L†	4.33 (3.88-5.07)	3.94 (3.41-5.34)	.177	4.01 (3.85-5.26)	.530
HDL, mmol/L†	1.26 (1.16-1.39)	1.22 (1.14-1.42)	.510	1.40 (1.16-1.60)	.050
LDL, mmol/L†	2.42 (2.09-3.01)	2.00 (1.58-3.39)	.124	2.11 (1.78-3.06)	.107
Triglycerides, mmol/L†	1.41 (0.97-1.71)	1.36 (0.82-2.22)	.593	0.93 (0.59-2.23)	.814
Liver fat fraction, %	9.2 (6.0-15.4)	6.3 (4.3-10.5)	.030	4.2 (3.0-10.0)	.016
Treatment satisfaction					
DTSQs	33 (26-37)	36 (35-37)	.054	36 (35-38)	.049
DTSQc	NA	12 (10-13)	NA	12 (9-13)	NA

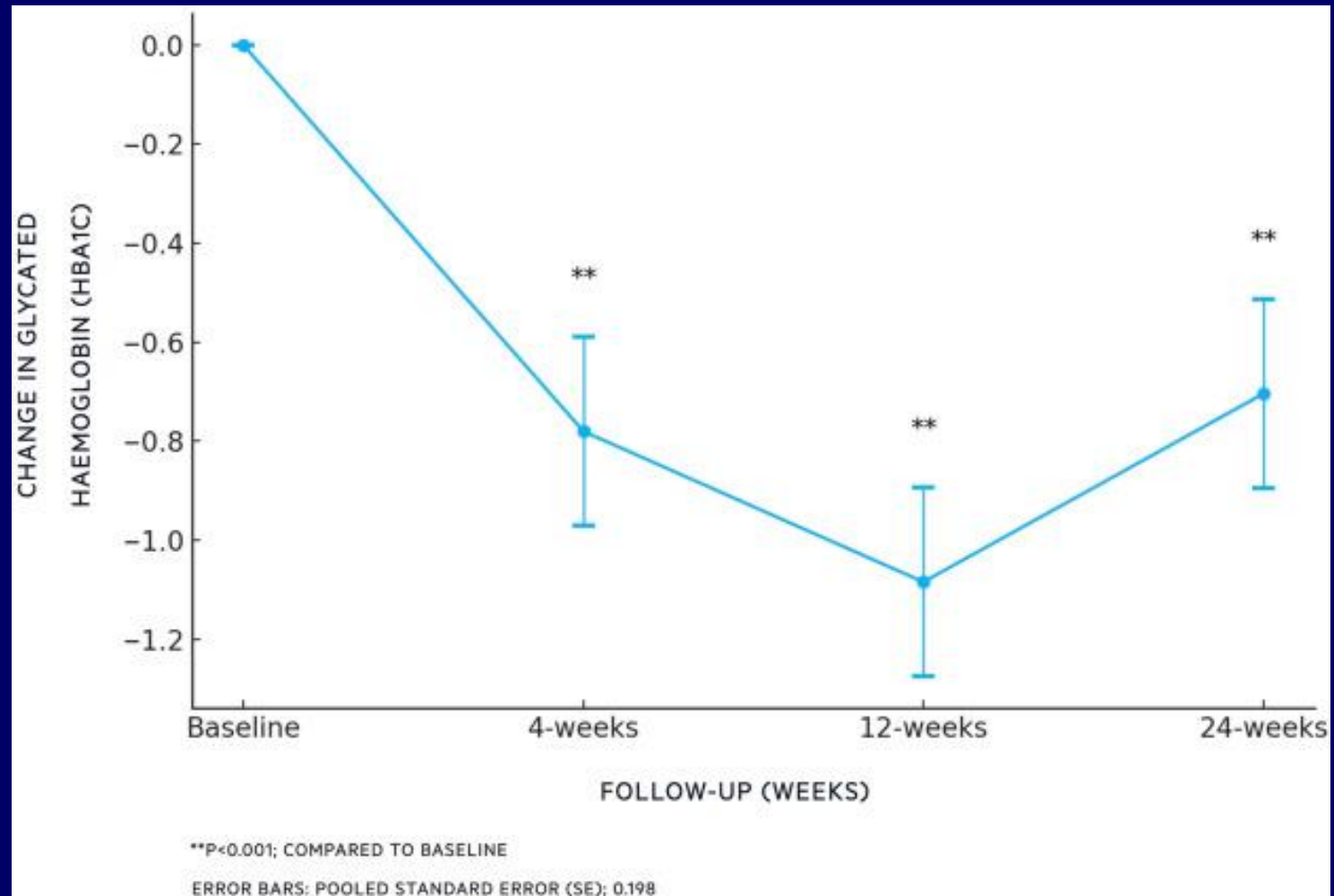
Aqua Medical Vapor Ablation

Condensing Vapor trapped between two silicon covered baskets as a heat source for ablating the duodenal mucosa



Vapor ablation effect on HbA1c

Results from FIM feasibility study



The dual efficacy effect of DJLB's maximizes metabolic outcomes

Glycemic Control

- Average 1.5% A1c drop
- 55% of patients reach therapeutic goal
- Better fasting and postprandial glucose control
- No increased risk for hypoglycemia

Weight Loss

- Average 13% weight loss
- Progressive and continuous

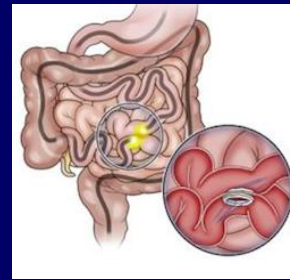
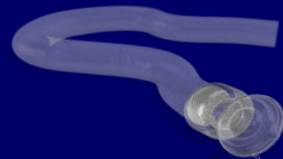
Cardio-metabolic Improvement

- CV risk factor reduction
- Significant reductions in blood pressure, total cholesterol, low density lipoproteins, and triglycerides

Combo Therapies



+



A landscape photograph showing numerous icebergs of various sizes and shapes floating in a dark, calm body of water. The icebergs have a distinct blue-green hue. In the background, dark, silhouetted mountains rise against a sky filled with heavy, grey clouds. The overall mood is somber and dramatic.

**Necessity... the mother of
invention.**

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Rakesh Kalapala

Associate Editor

Drrakesh.kalapala@aighospitals.com

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