Duodenal mucosal hydrothermal ablation: a new procedure designed for metabolic gain

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Disclosure

- Fractyl Laboratories employee and shareholder

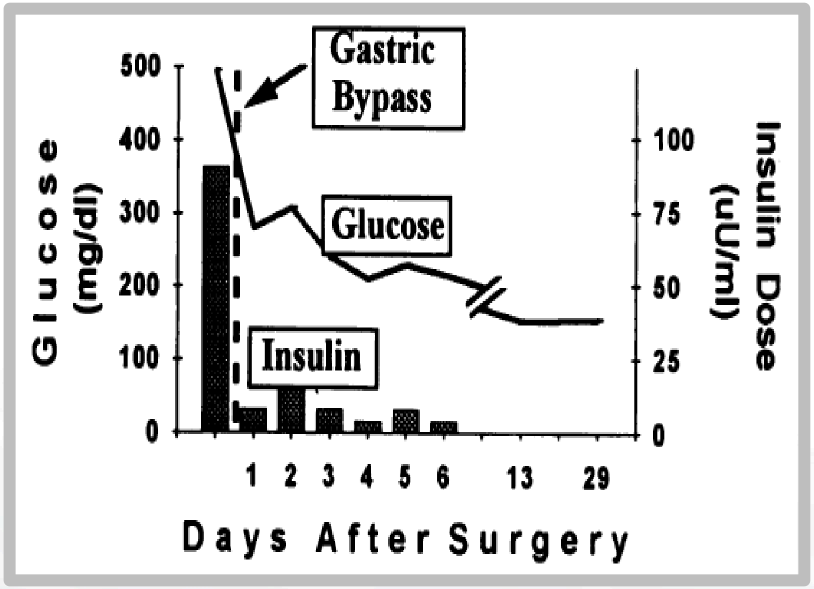
Global Pandemic of Metabolic Disease

- Insulin resistance is a key pathophysiological defect at the core of T2D, fatty liver disease and cardiovascular disease
- In 2040, 650M people around the globe will have T2D (1 in 10)[(1)]
- Currently, 40+ different pharmacological agents available for T2D in US yet 50% of diabetics remain poorly controlled through disease progression, pharmacological failure and/or treatment non-compliance[(2)]
- Fatty liver disease will soon be the main driver of end stage liver disease and need for organ transplant → with currently no available treatments for fatty liver disease
- Bariatric surgery has manifested a potent effect to improve dysmetabolic conditions and has uncovered a key metabolic role of the gastro-intestinal tract
- Yet bariatric surgery may not be a scalable solution to address population-level metabolic disease

[(1)] IDF 2015; [(2)] Lipska K et al D Care 2016; [(3)] Bazick et al D Care 2016; [(4)] Sanofi IR deck

Gastric Bypass Surgery Epiphany

Improved Glycemic Control Post RYGB



Clinical Benefits of RYGB

- Potent glycemic improvement in T2D[1]
- Anti-diabetic effect is in part weight independent[2]
- Glycemic effect tied to background β cell function[3]
- Disease prevention of both T2D & NAFLD[4]
- Histologic resolution of NASH
- Return of ovulation in PCOS
- Reduced CV disease
- Improved patient satisfaction[5]

Bariatric surgery offering a window into the metabolic role of the GI tract

Sources: [1] Mingrone et al. NEJM.366(17); [2] Pories et al. Ann Surg. 222(3): 339-50; 1995; [3] Nannipieri et al. JCEM. 96(9); [4] Carlsson et al. NEJM. 367(8); [5] Mingrone et al. Lancet 386 (9997), p964-973

Gastric Bypass Surgery Epiphany

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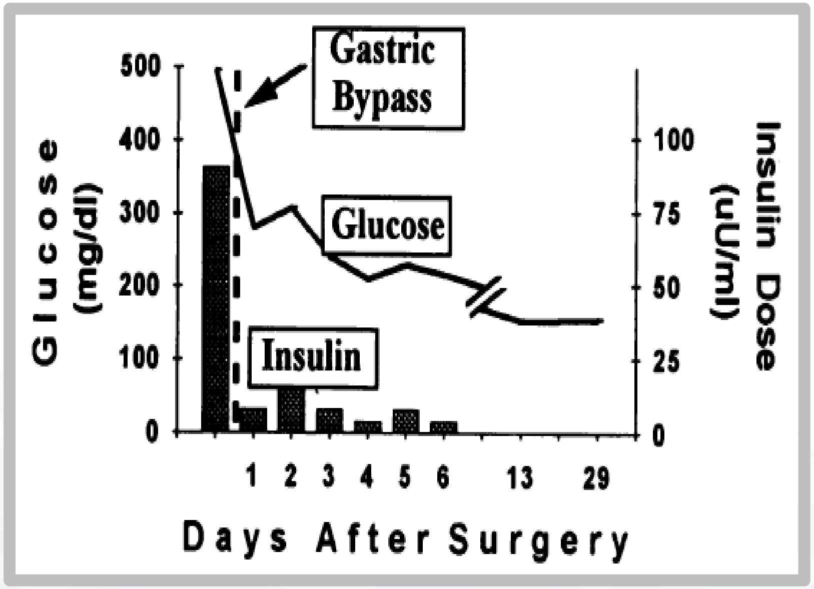

Mechanistic Explanation

- Early post-surgery hypocaloric effect
- Specific signaling from duodenum
- Hindgut incretin effect
- Bile acids
- Microbiome
- Shrinking Adipose-TG depot
- Malabsorptive contribution

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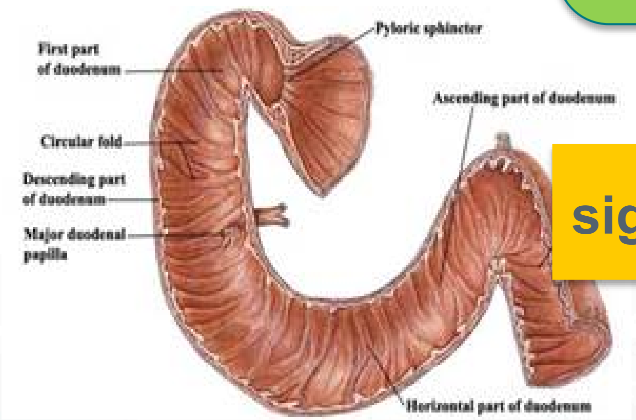
Metabolic Role of the Duodenum

Duodenum



signal

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

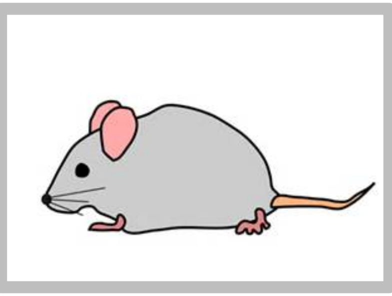
Evidence from intervention
- RYGB
- Roux re-exposure
- Endoluminal sleeve

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

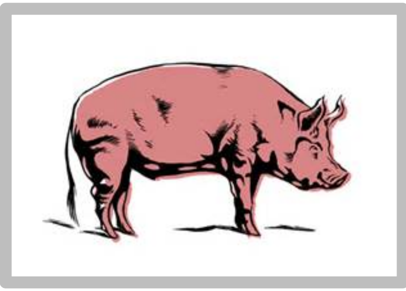
(1) Dirksen et al. Diabetes Care. 2010;33(2):375-377; (2) Cummings DE et al. IFSO 2016; (3) Adachi et al Endocr J. 2003;50(3):271-279; (4) Bailey et al. Acta Endocrinol (Copenh). 1986;112(2):224-229; (5) Gniuli et al. Diabetologia. 2010;53(10):2233-2240

Duodenal Ablation: Early Proof of Concept

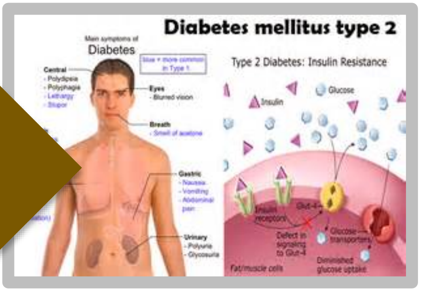
Rodent



Porcine

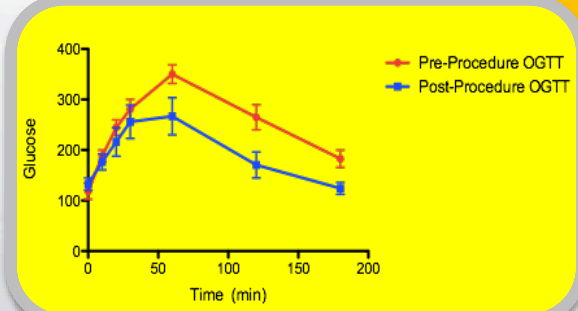


Human



GK rat POC

- Denuding duodenum caused lowering of hyperglycemia
- No effect seen in non-diabetic rodent



Ablation method

- Novel balloon catheter
- Hydrothermal heat exchange
- Superficial mucosa re-surfacing – no deep structure damage

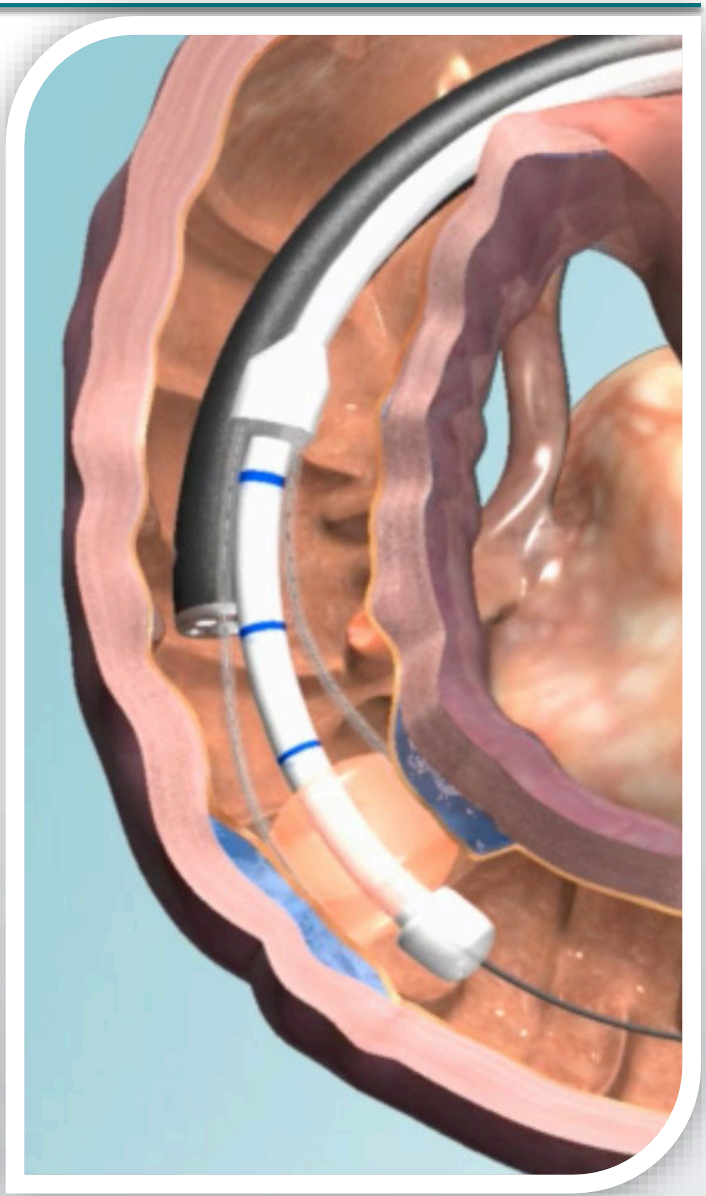
First-in-man

- Single site (Chile)
- T2D patients (n=48)
- OAD treated

Subsequent study in multiple centers (EU)

Duodenal Mucosal Resurfacing Procedure

- Duodenal Mucosal Resurfacing (DMR) is designed to rejuvenate the duodenal mucosal surface, replicating the duodenal exclusion of RYGB
- DMR conducted during upper GI endoscopy:
  - Utilizes techniques familiar to endoscopists
  - Single-use disposable catheter system
  - Same day, minimally invasive procedure conducted <1 hour
  - Software & integrated sensors designed to minimize operator and procedural error
- DMR hydrothermal ablation resurfaces a targeted post-papillary duodenum segment of ~10-12 cm



DMR: endoscopic view

Pre-Procedure Duodenum → Lifted Duodenal Mucosa → Ablated Duodenum → Three-month Follow-up

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

DMR Overall Safety and Tolerability

- Total ~100 cases in early FIH and ongoing multicenter study
  - Includes cases with new single catheter
- Post-procedure: patients adhere to 2 week eucaloric diet
  - liquid → puree → semi-solid
- Post-procedure: favorable tolerability profile with minimal GI symptoms
- Three duodenal stenoses in early FIH experience → each successfully treated with single non-emergent balloon dilation and no later sequelae
- No device/procedure related SAEs in last ~65 cases after implementation of improved mucosal lift procedure
- No apparent hypoglycemic risk
- No evidence of malabsorption
- No late adverse events observed (50+ patients >12 months)

Legend
FIH: first-in-human

First-in-Human Study: Patient Characteristics

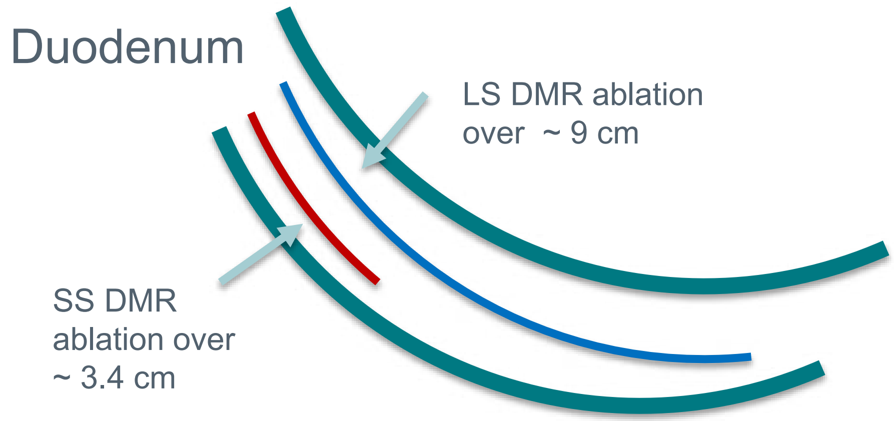
- Open label, single-arm, single center feasibility study in Santiago, Chile
- Patient entry: A1C 7.5-12%, BMI 24-40, age 28-75, 1-2 OAD (no insulin)
- 44 consecutive patients enrolled
  - 4 patients were not treated (1 duodenal anatomy, 2 failed screening endoscopy, 1 procedure duration)
  - 1 patient with anti-GAD Ab (exclusion criteria) treated and followed for safety alone

PATIENTS ENROLLED	(N=44)
Age, mean years +/- standard deviation ("SD")	53.3 +/- 7.5
Male	28 (63.6%)
BMI, mean kg/m2 +/- SD	30.9 +/- 3.5
Systolic BP, mmHg +/- SD	122.1 +/- 14.4
Duration T2D, mean years +/- SD	5.7 +/- 2.2
HbA1c, % +/- SD	9.5 +/- 1.3
FPG, mg/dL +/- SD	184 +/- 58
Hepatic Steatosis on baseline ultrasound	11 (25%)
Oral Anti-diabetic Rx	
Metformin, n	44 (100%)
Sulfonylurea, n	20 (44%)

Rajagopalan, H et al., Diabetes Care, Aug 2016

Escalating Ablation Length

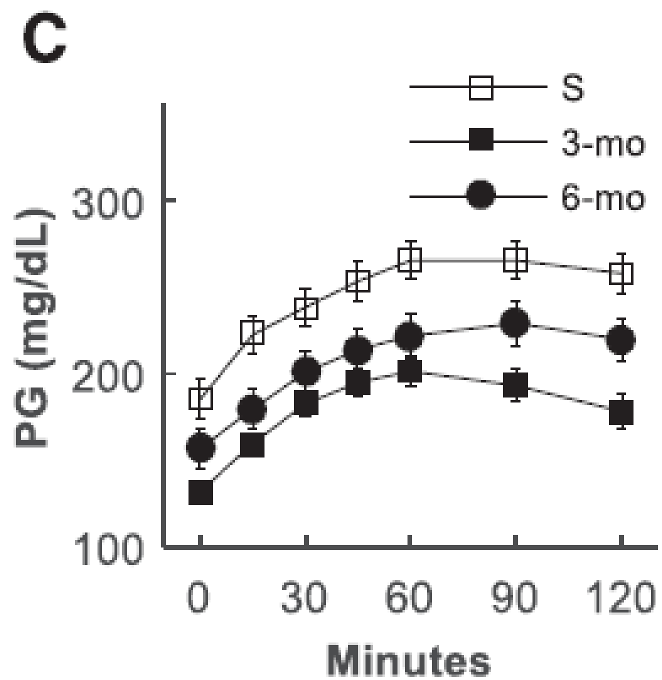
- Ablation length was increased from short segment DMR to long segment DMR as FIH trial progressed
- Patients blinded to ablation length and managed in identical fashion
- Fasting glucose improvements observed as early as 1 week post-procedure
- Statistically significant improvement in fasting glucose versus baseline of 64 mg/dl noted in LS DMR vs 26 mg/dl in SS DMR
- Net medication reductions in LS DMR cohort post-procedure



	Month 3	Month 6
Long segment (n=28)	-2.5 ± 0.2%	-1.4 ± 0.3%
Short segment (n=11)	-1.2 ± 0.5%	-0.7 ± 0.5%

DMR Effects on Meal Challenge Glycemia

Meal challenge plasma glucose (PG 0-120 min) in LS-DMR subjects (n = 28)



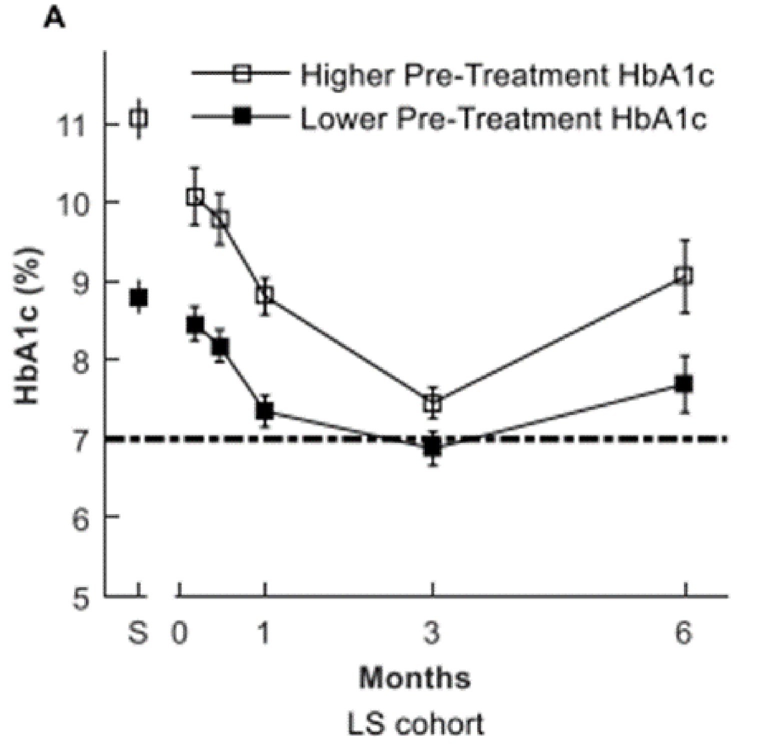
LS cohort, change from screening;
For PG(t=0): p<0.001 at 3-mo, p=0.07 at 6-mo
For PG AUC: p<0.001 at 3-mo, p<0.05 at 6-mo

Legend
LS-DMR: patients receiving long segment (~10cm) DMR ablation

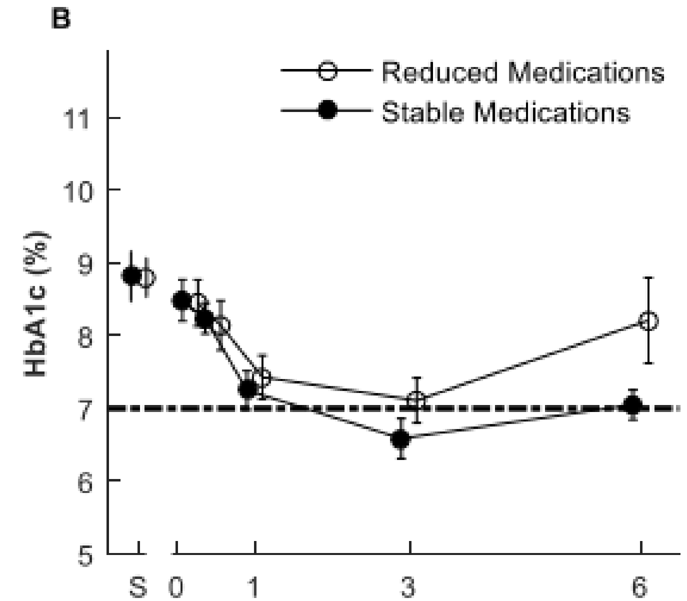
Rajagopalan, H et al., Diabetes Care, Aug 2016

DMR Lowered A1C (0-6 Month Data)

A1C change in LS-DMR subjects with higher (>10%) and lower (<10%) entry A1C



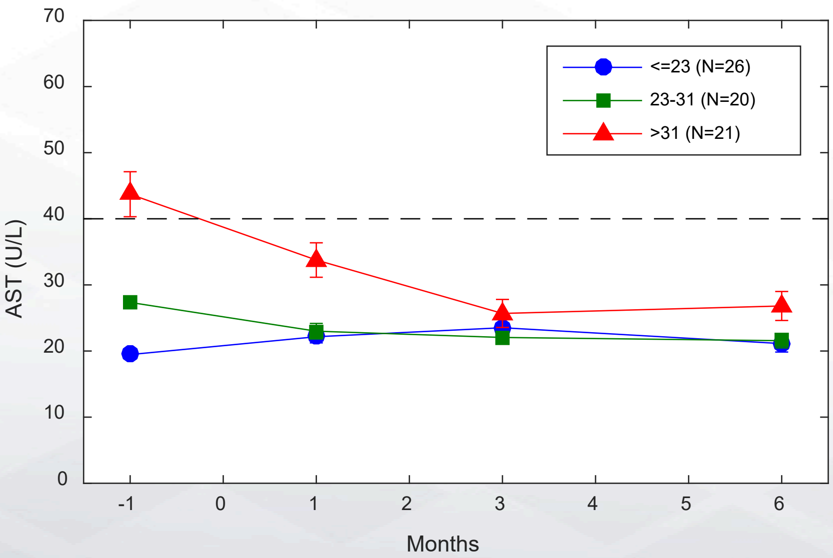
A1C change in LS-DMR subjects with lower entry A1C (<10%) where background OAD was either stable or reduced

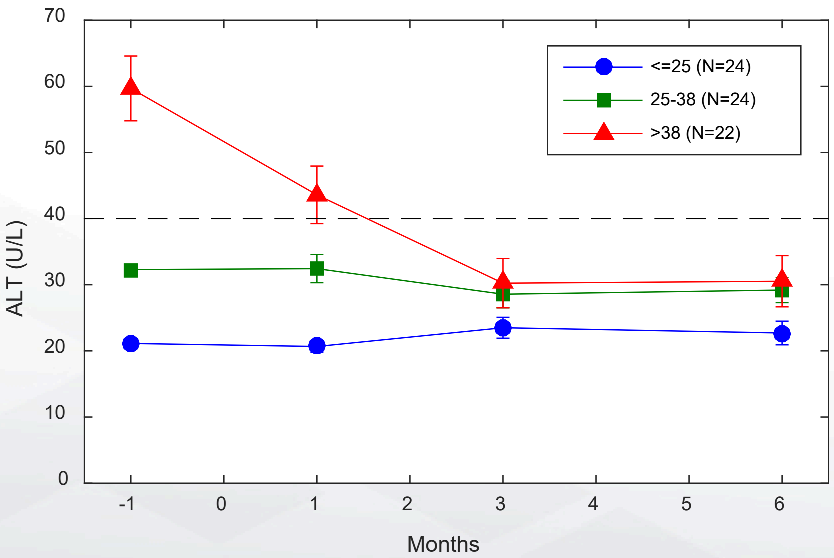


Rajagopalan, H, et al., Diabetes Care, 2016

DMR Lowered Hepatic Transaminases

- Consistent lowering of hepatic transaminases (ALT and AST) in combined FIH and multi-center cohorts
- DMR is associated with a modest weight effect (2-3kg) in short term that returns to baseline by 6 months
- Graphs demonstrate change in AST and ALT by tertile starting levels

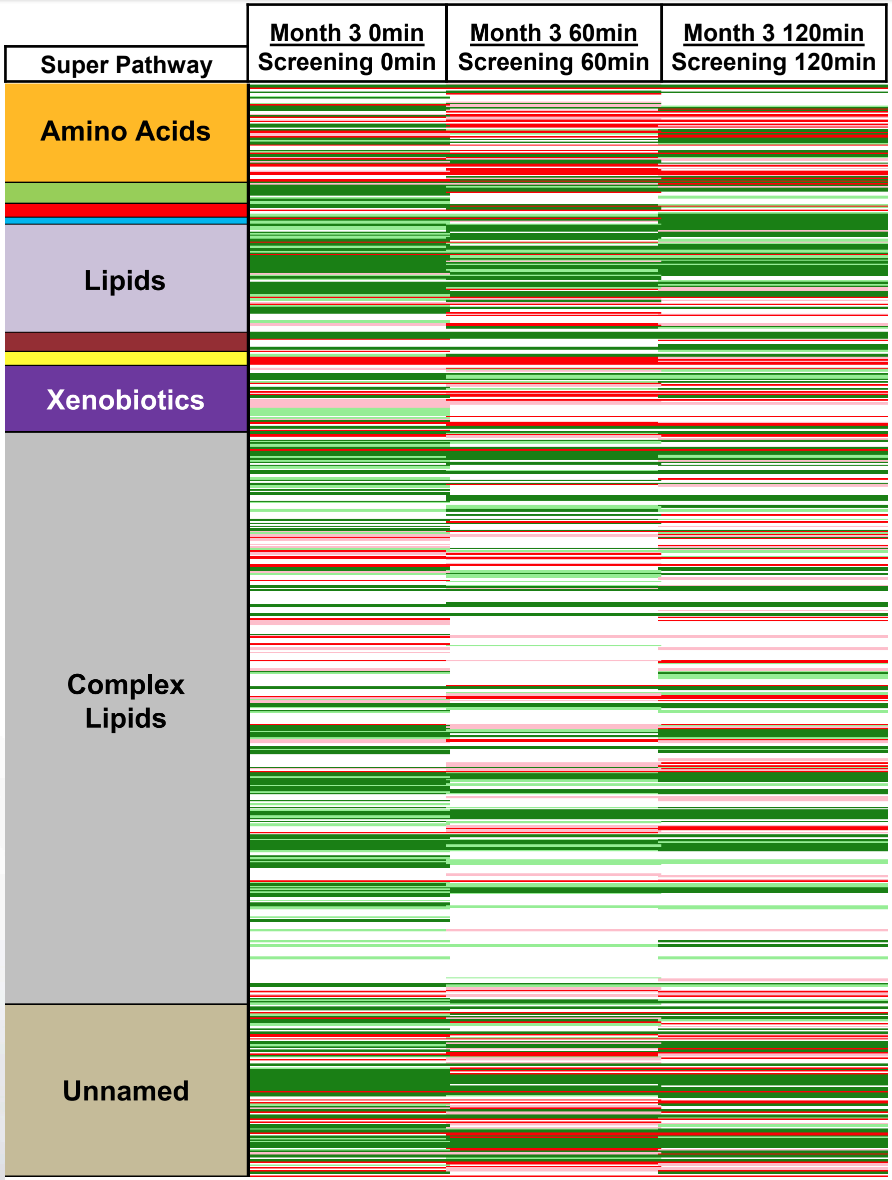




DMR Metabolomic Signature (0-3 Month Data)

- Meal challenge samples (0-3 months)
- Metabolomic analysis

- Improved glucose handling
- Improved insulin sensitivity (↓αHBA)
- ↓TAGs, DAGs
- ↓FA β-oxidation
- Improved mitochondrial function (↓ dicarboxylic acids)
- ↓inflammation (↓HETE) – marker of NAFLD→NASH
- ↓lipid peroxidation – seen with insulin sensitizing
- ↑anti-oxidant capacity (↓ glutathione catabolism)
- Altered 2° bile acids (microbiome-related?)



Conclusions

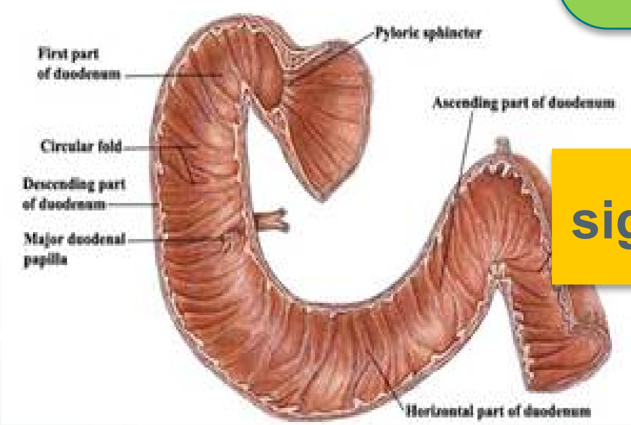
- **Increasing evidence that the duodenum plays an important metabolic role**
- **Duodenal mucosal resurfacing (DMR) appears to exert an insulin sensitizing effect that impacts cardiometabolic indices**
  - ❑ **implications for T2D, fatty liver disease and other insulin resistant conditions**
  - ❑ **raising the potential for a <u>compliance-independent</u> approach to disease management**
- **Future study is necessary to understand**
  - ❑ **safety in larger numbers of users and patients**
  - ❑ **mechanism**
  - ❑ **efficacy and durability**
  - ❑ **clinical utility in the treatment of insulin resistant conditions**

Metabolic Role of the Duodenum

Physiological role?

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

Duodenum



signal

Evidence from intervention

- RYGB
- Endoluminal sleeve
- DMR hydrothermal ablation

Evidence of pathophysiology

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

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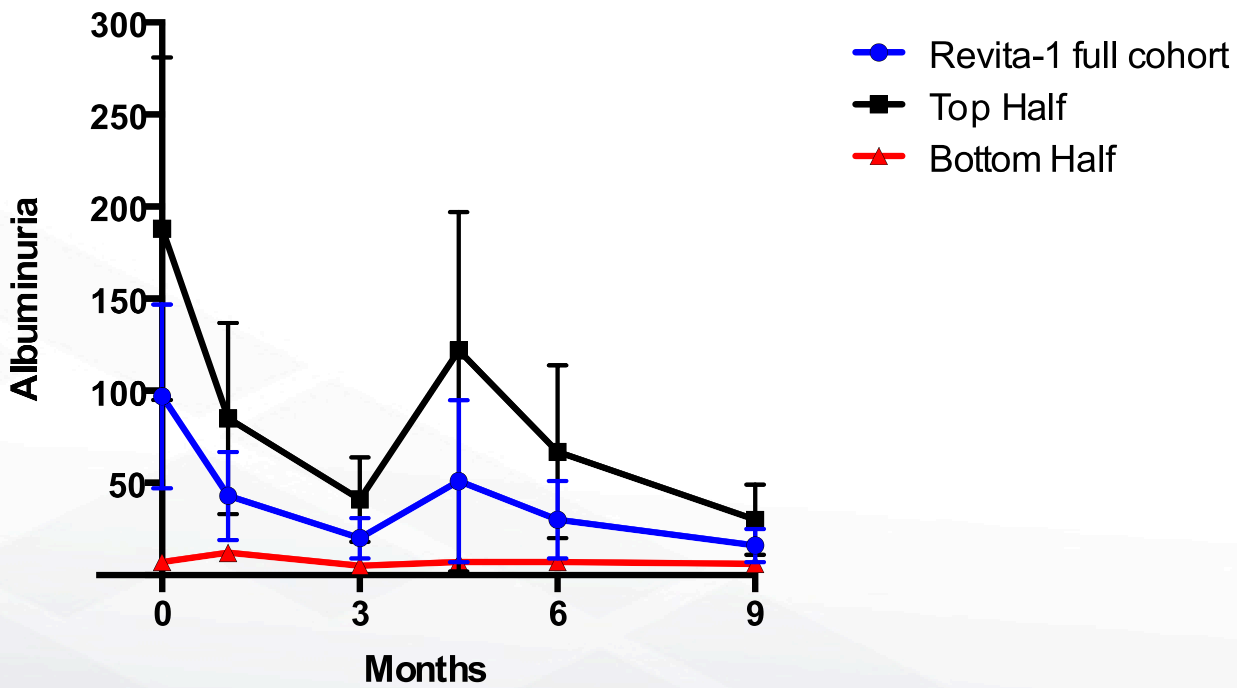
DMR Lowers Microalbuminuria

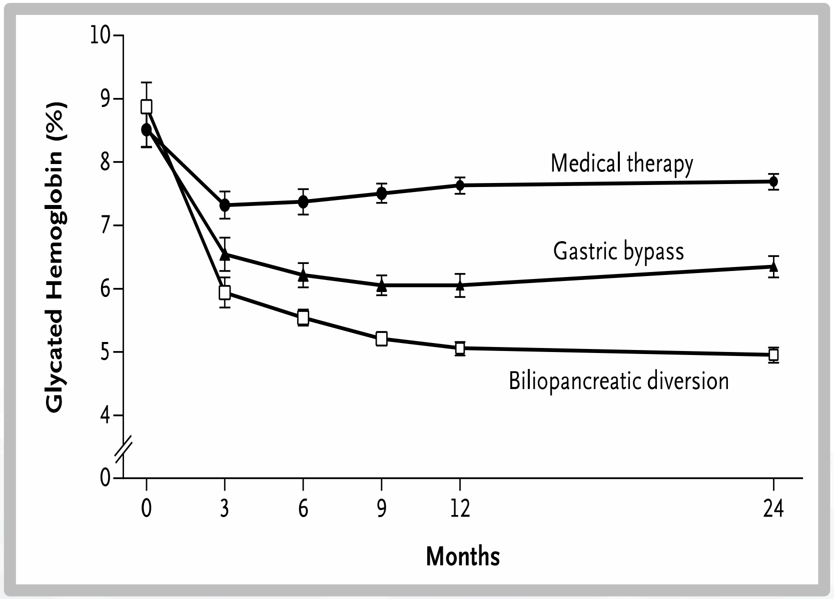
Microalbuminuria sampling from EU multi-center trial (Revita-1)



Number of patients	20	17	19	12

Gastric Bypass Surgery Epiphany

Improved Glycemic Control Post RYGB



Clinical Benefits of RYGB

- Superior glycemic effect (T2D)[1]
- Weight independent anti-diabetic effect[2]
- Glycemic effect tied to background β cell function[3]
- Histologic resolution of NASH
- Prevent disease onset T2D/NAFLD[4]
- Return of ovulation in PCOS
- Reduced risk of CV disease
- Improved patient satisfaction[5]

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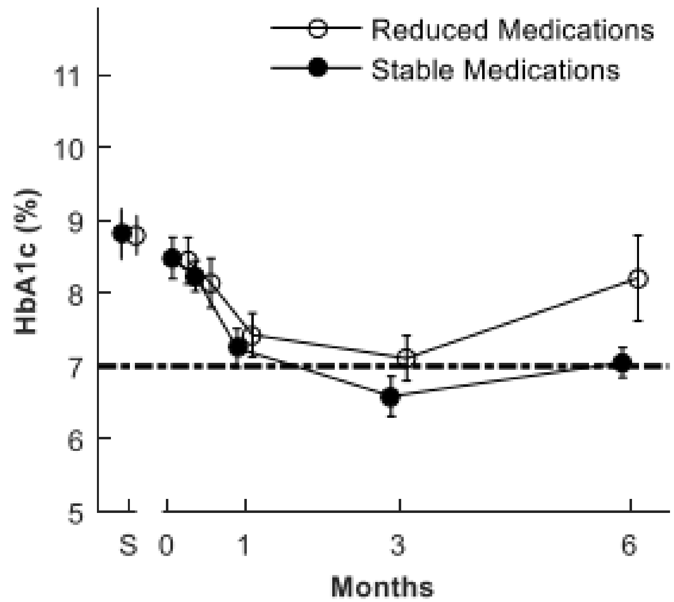
Procedure Animation

First-in-Human Trial

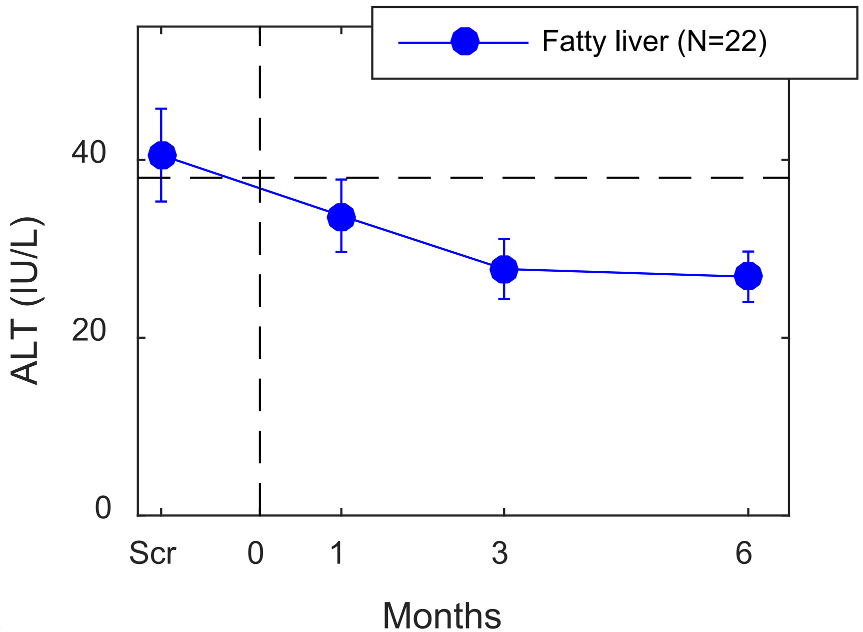
HbA1c Reductions



LS Lower Pre-Treatment HbA1c cohort
Stable vs. Reduced Medications

Patients whose medical regimen remained stable through the 6-month follow-up period demonstrated sustained & durable drops in HbA1c.

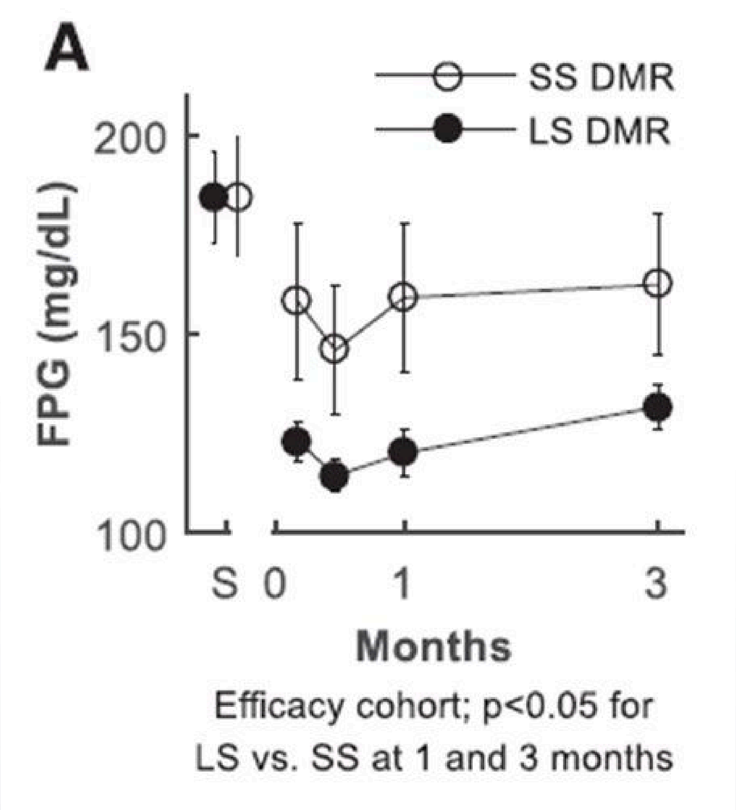
ALT in Subjects with Fatty Liver



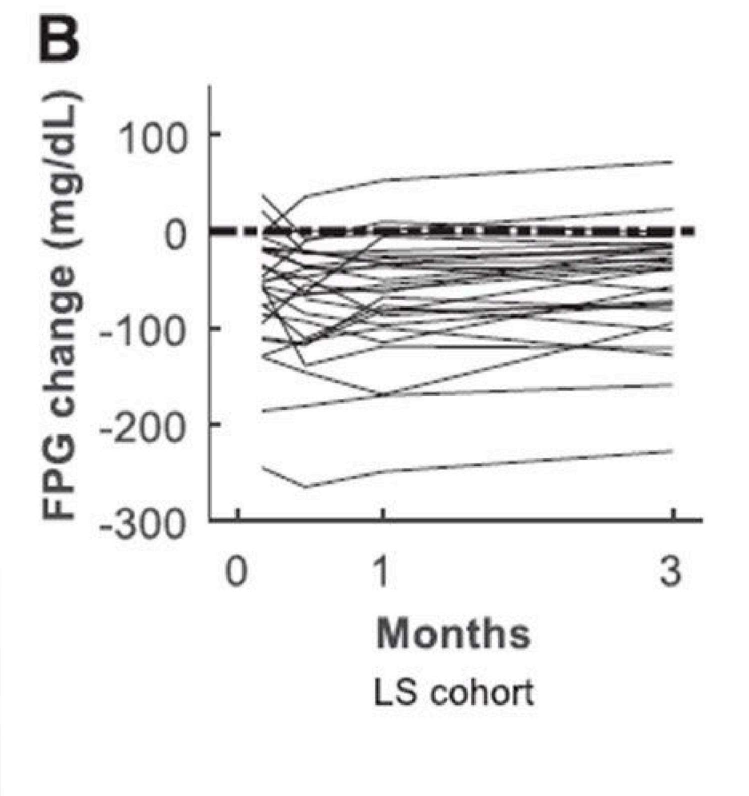
Patients with fatty liver show significant reductions in ALT, a common marker liver inflammation, suggesting impact on NAFLD/NASH.

Glycemic Efficacy Greater with Long-Segment DMR

Effect of short segment (SS, white circles) and long segment (LS, black circles) DMR treatment on FPG plotted to 3 months (n = 39)*

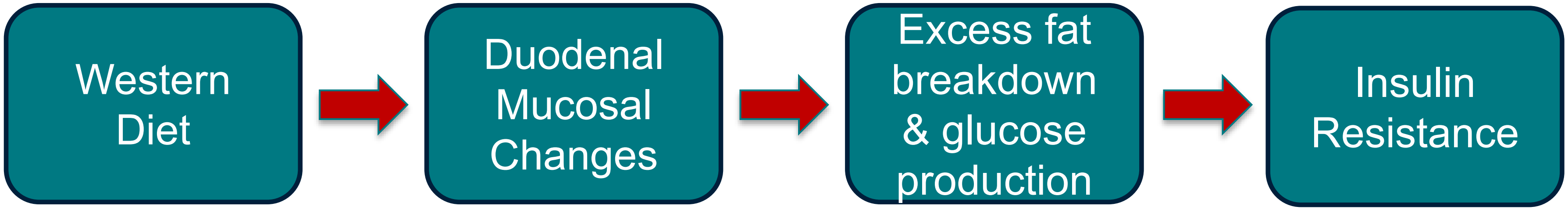


FPG change from screening plotted to 3 months in individual subjects who received LS-DMR (n = 28)*



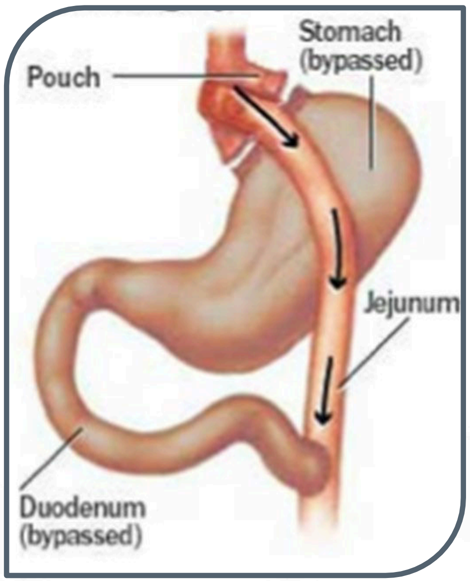
Rajagopalan, H et al., Diabetes Care, 2016; *Data are reported as mean ± SD, S = pre-procedure value.

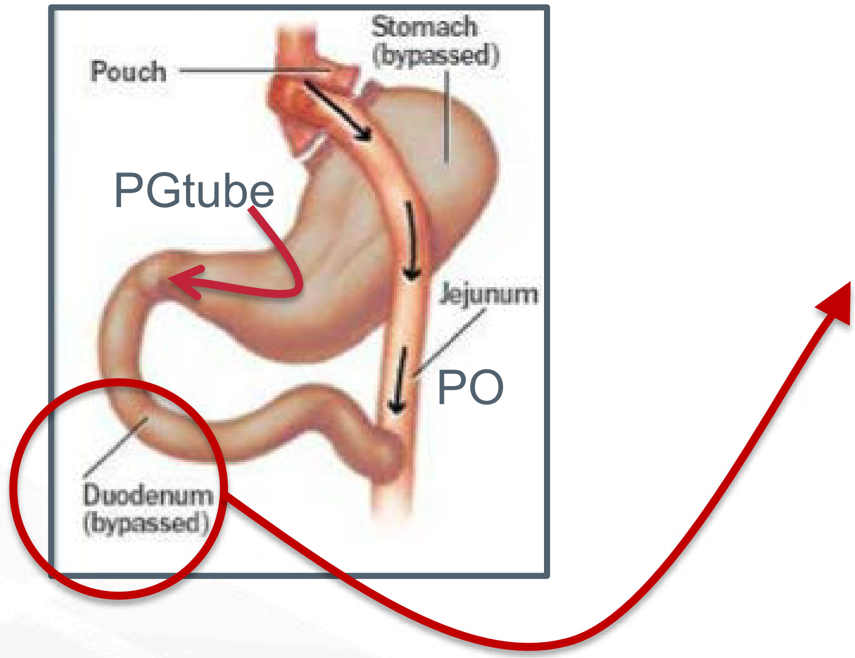
Grand Unifying Theory (G.U.T.)



- Sugar in the duodenum appears to cause hypertrophy of mucosa
- Changes lead to excess lipolysis in adipocytes and gluconeogenesis in the liver (amplified “fasting” signal)
- In the absence of glucose utilization, this leads to a buildup of hepatic fuel intermediates and mitochondrial dysfunction
- Hepatic and systemic insulin resistance ensues
- Potentially reversible with duodenal resurfacing (akin to laser skin resurfacing)

Bariatric Surgery Provides Key Insight to Solution





RYGB exerts broad metabolic benefits → Duodenal bypass alone reduces hepatic insulin resistance[1,2] → Duodenal mucosa maladapted by Western diet[3-5]

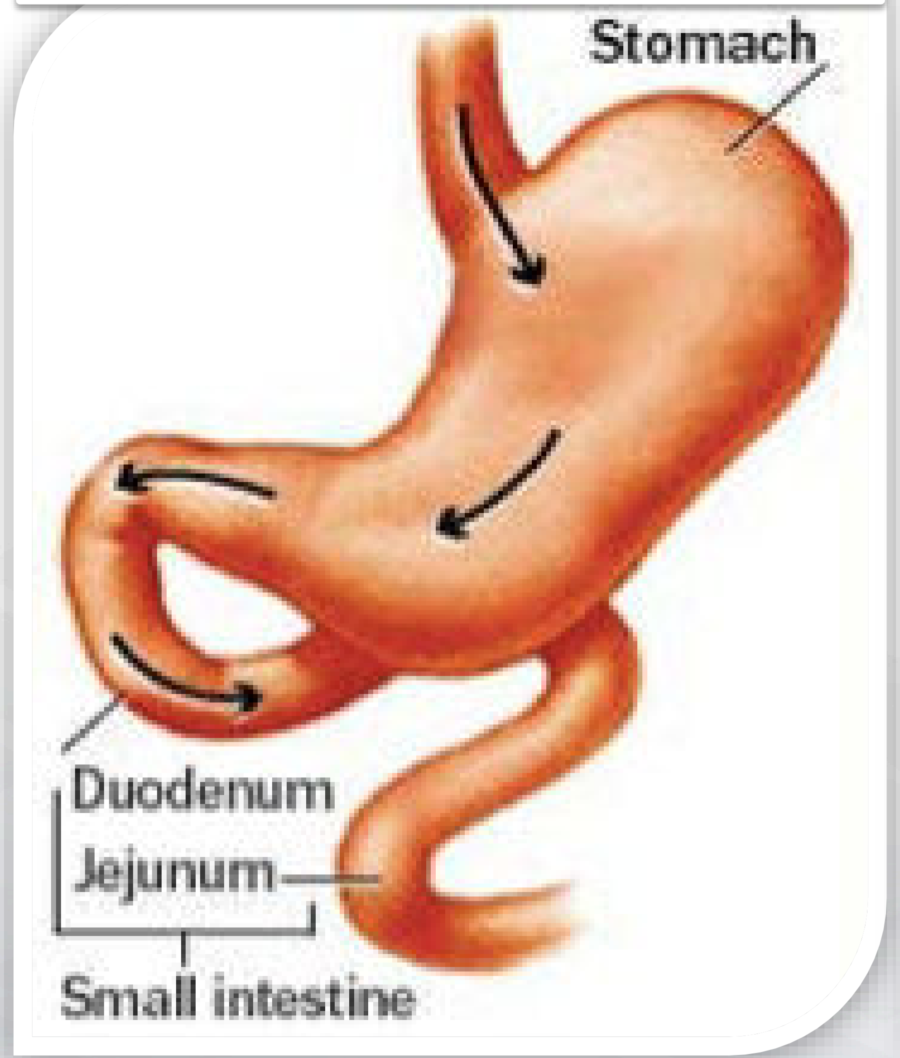
[1] Dirksen et al. Diabetes Care. 2010;33(2):375-377; [2] Cummings DE et al. IFSO 2016; [3] Adachi et al Endocr J. 2003;50(3):271-279; [4] Bailey et al. Acta Endocrinol (Copenh). 1986;112(2):224-229; [5] Gniuli et al. Diabetologia. 2010;53(10):2233-2240

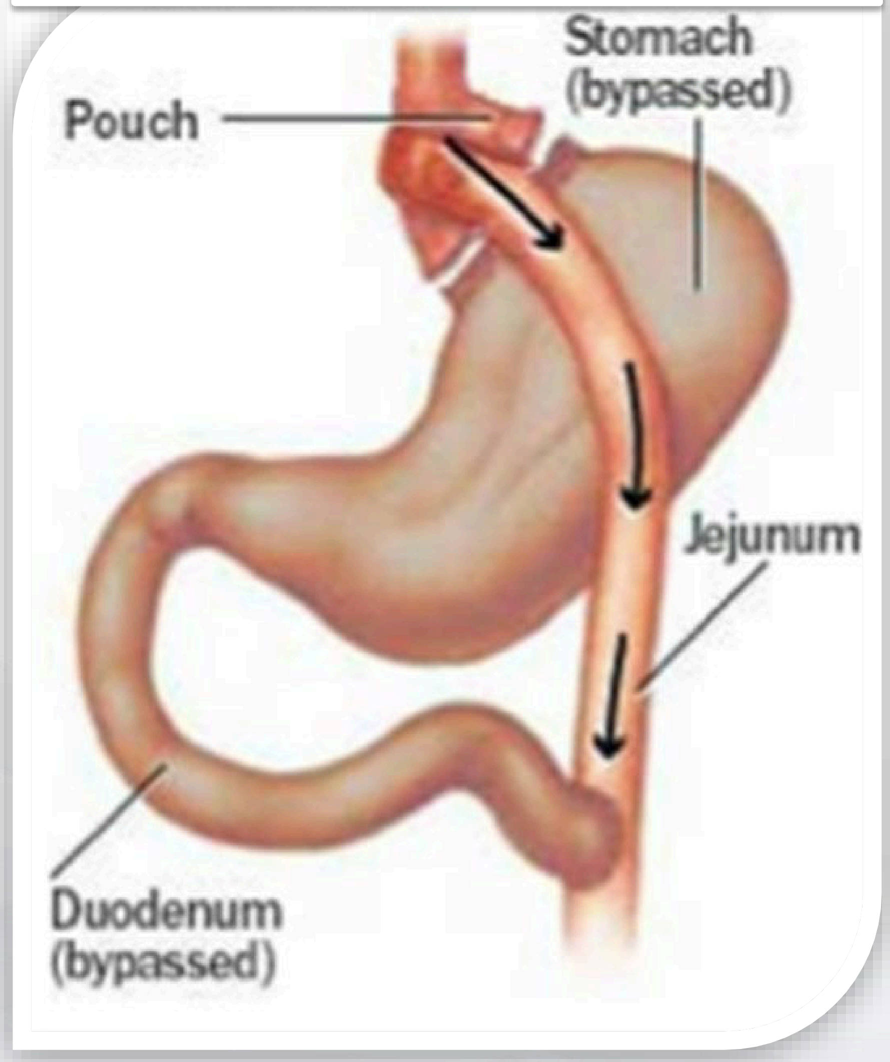
DMR State of Play

- DMR as a safe and scalable intervention
  - Well tolerated procedure with favorable safety/tolerability profile
- DMR as a compliance-independent approach to disease management
  - Can overcome real world limitations of complicated drug regimens, side effects, and compliance challenges
- DMR as an insulin sensitizing procedure
  - Disease modification addressing root cause of insulin resistance with broad metabolic improvements relevant to T2D, NAFLD/NASH, PCOS
- Future studies will be directed at demonstrating safety/efficacy, optimizing performance, and establishing clinical utility in broader populations

Duodenal Bypass a Key Component

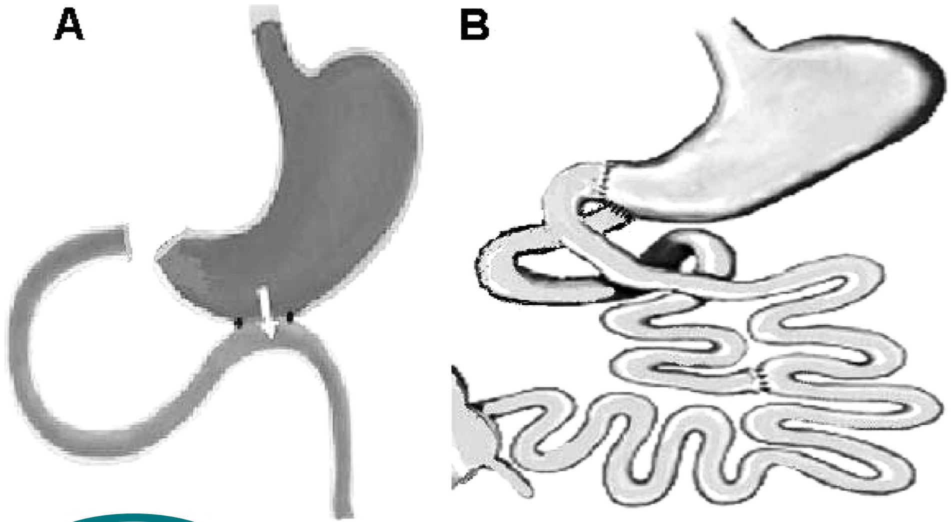
Before Surgery	After Surgery

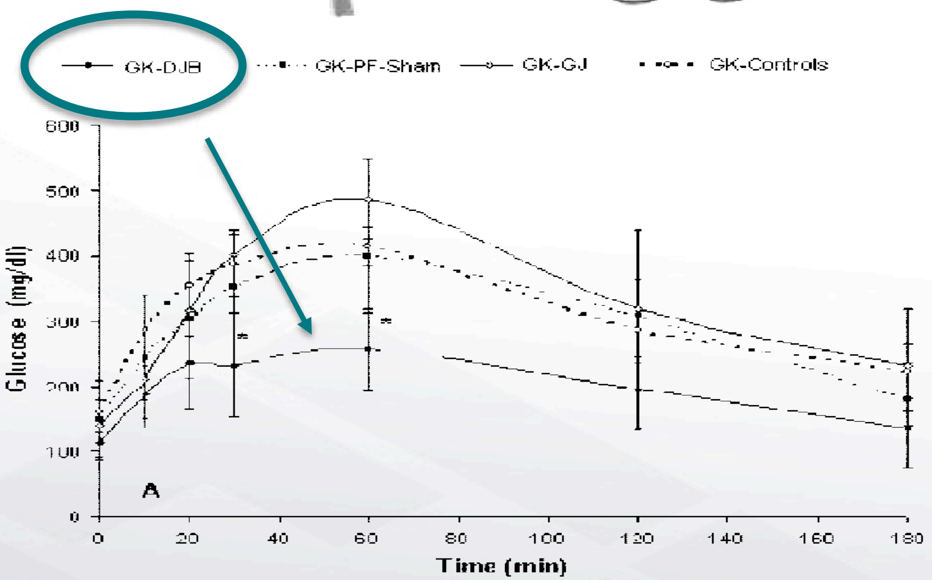




Duodenal-Jejunal Bypass vs. Gastrojejunostomy

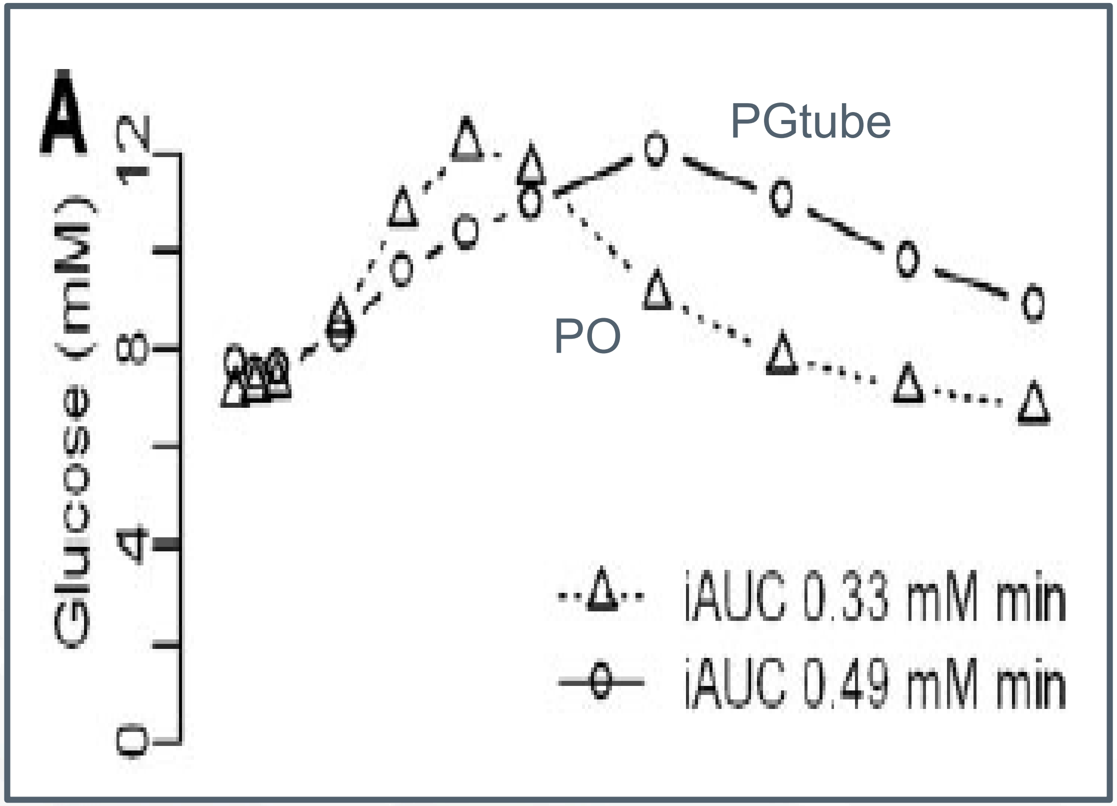
- Goto-Kakizaki rats each received one of several surgeries
- Glucose evaluated by glucose tolerance test
- Duodenal-jejunal bypass improves glucose control
- Numerous follow up studies elucidating insulin sensitization, improvement in liver fat, fibrosis post-DJB

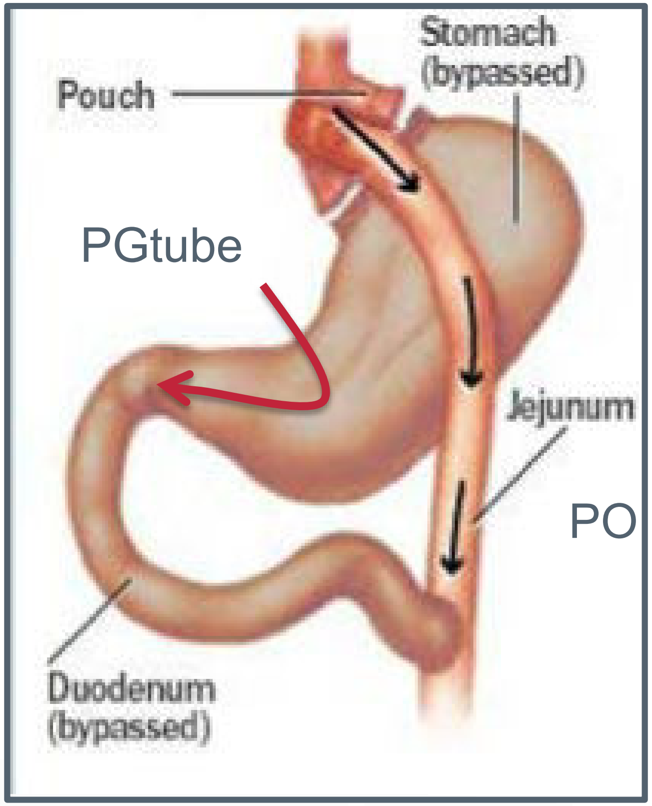




Rubino *et al* Annals Surg 2006

Post RYGB: Re-exposing the Duodenum to Nutrients





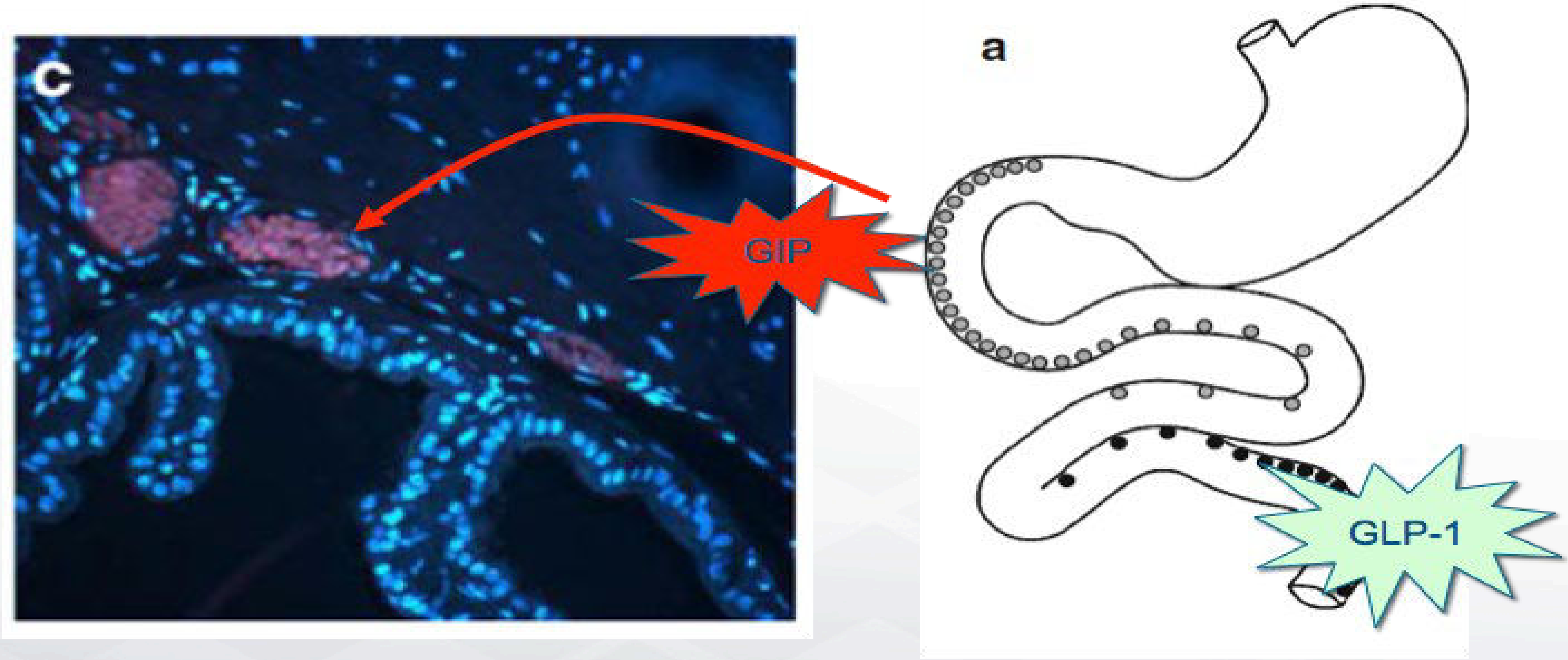
Acute re-introduction of nutrients into the bypassed duodenum (Roux limb) via PG tube caused an immediate worsening of glycemia

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

Evidence that Duodenal Mucosa is Maladapted

Small bowel abnormal in obese and diabetic genetic rodent models and fat/hexose challenged rodents

- Duodenal and proximal jejenal hypertrophy[1]
- Duodenal entero-endocrine (GIP secreting) cell hyperplasia[2][3]



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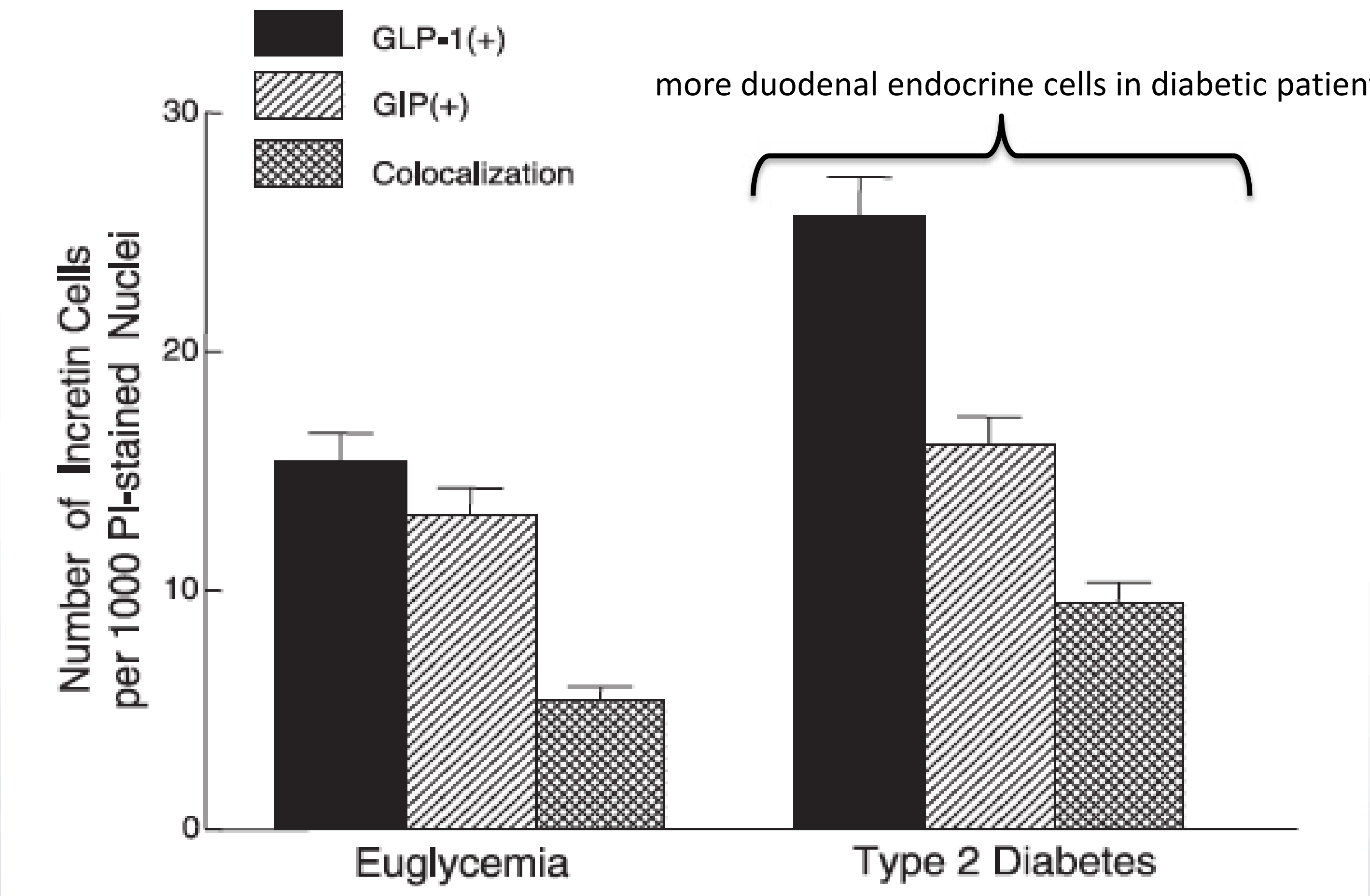
Abnormal enteroendocrine populations in T2D subjects

Non-diabetic (n=36) and T2D (n=17) subjects underwent duodenal biopsy and metabolic characterization

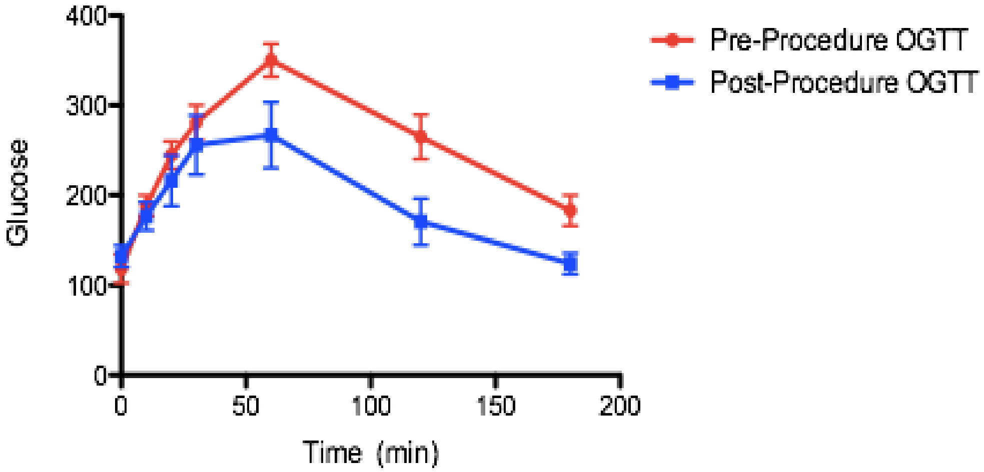


Theodorakis et al. AJP Endocrinol Metab. 2006;290(3):E550-E559.

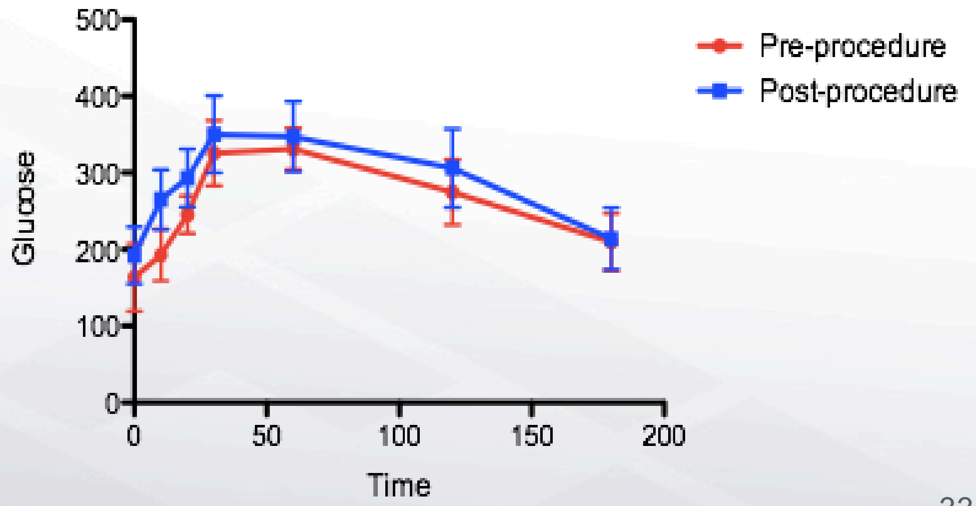
Rodent proof of concept

- Goko-Kakizaki diabetic rodents studied
- Denudation of duodenal mucosa conducted through mechanical abrasion
- 35%↓ of hyperglycemia post oral glucose gavage
- Glucose lowering not observed in sham study or in non-diabetic Wistar rodents

OGTT before and after abrasion



OGTT before and after sham



Manuscript in preparation

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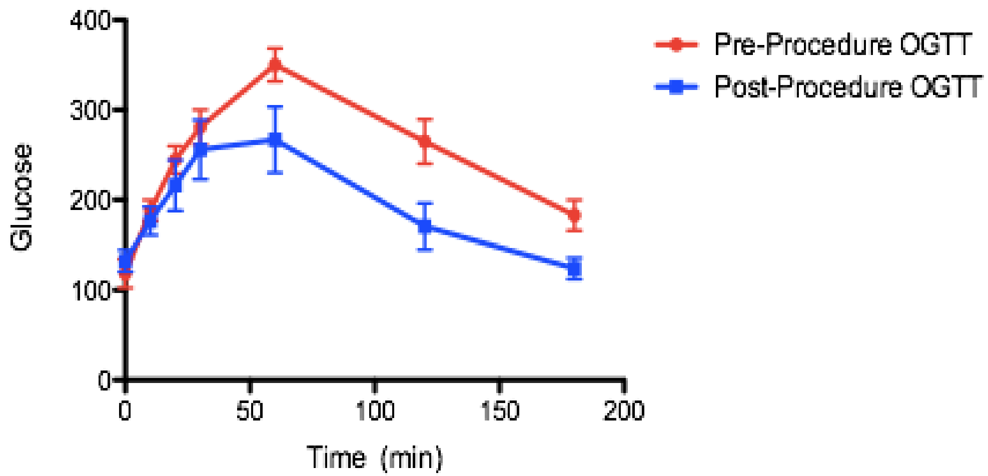
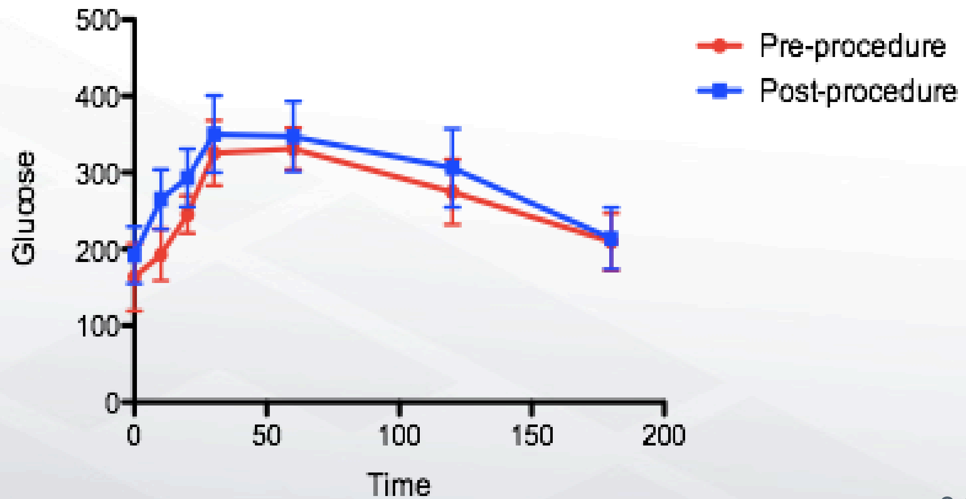


OGTT before and after sham



Manuscript in preparation

Clinical Roadmap to Date

First in Human
Single center
Open label
"Procedure Definition"

- Initial safety and feasibility for T2D
- Long segment DMR more effective (dose effect)
- Mechanistic basis of DMR as insulin sensitizing
- Diabetes Care Aug 2016, Video GIE ~ Sept 2016

Revita-1
Multicenter
Open label
"Patient Selection"

- Reproducibility of outcomes across EU centers
- Medication management more controlled
- Used to refine patient entry criteria for RCTs
- Introduced next generation catheter

Revita-2
Multicenter Ph2b equiv.
Sham RCT
"Efficacy Demonstration"

- Beginning Q4 2016 in ~ 12 EU centers
- Aim: Test efficacy in sham-controlled conditions
- Aim: Elaborate on metabolic mechanisms
- Aim: NAFLD/NASH clinical endpoints (e.g. MRFF)