

DUODENAL MUCOSA: A TARGET FOR TREATING METABOLIC DISEASE

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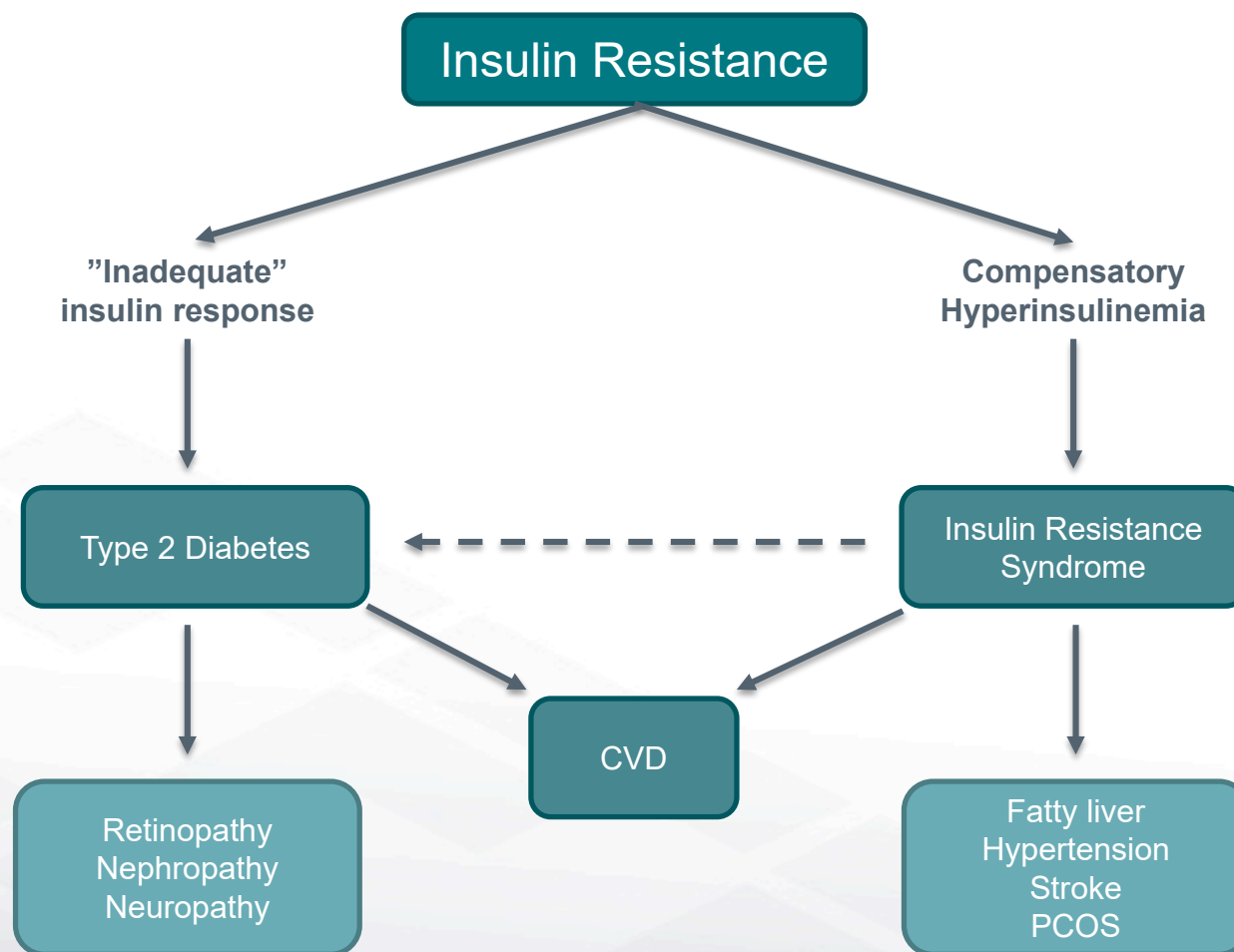
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Targeting the Duodenal Mucosa

- Bariatric surgery epiphany
- Relevance of duodenal exclusion
- Duodenal pathophysiology
- Duodenal Mucosal Resurfacing for metabolic gain

The central role of insulin resistance in metabolic diseases



RYGB is the most effective treatment for T2D...but why?

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes

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Bariatric Surgery versus Intensive Medical Therapy in Obese Patients with Diabetes

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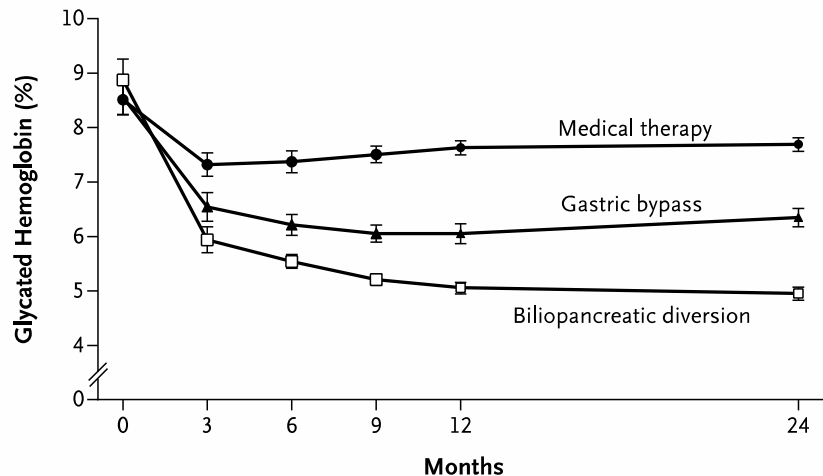
Bariatric Surgery and Prevention of Type 2 Diabetes in Swedish Obese Subjects

“Some doctors say gastric bypass surgery appears especially beneficial...reducing the stomach to the size of a small pouch and bypassing a portion of the intestine, which potentially **changes certain gastrointestinal hormones** or other factors.”

- WSJ 7/1/15

Gastric Bypass Surgery experience provides key insight to a solution

Improved Glucose Control Post Gastric Bypass Surgery

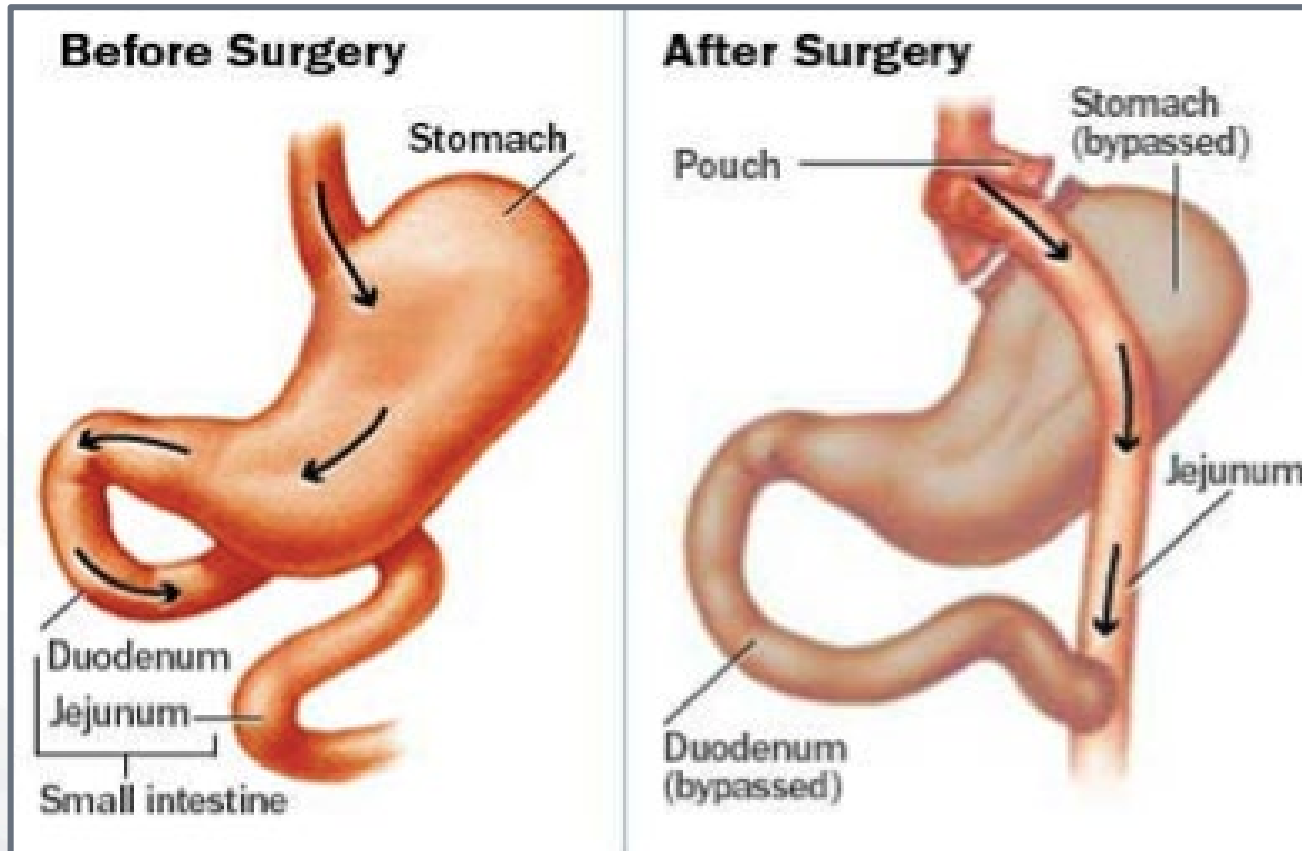


Clinical Benefit of Gastric Bypass Surgery

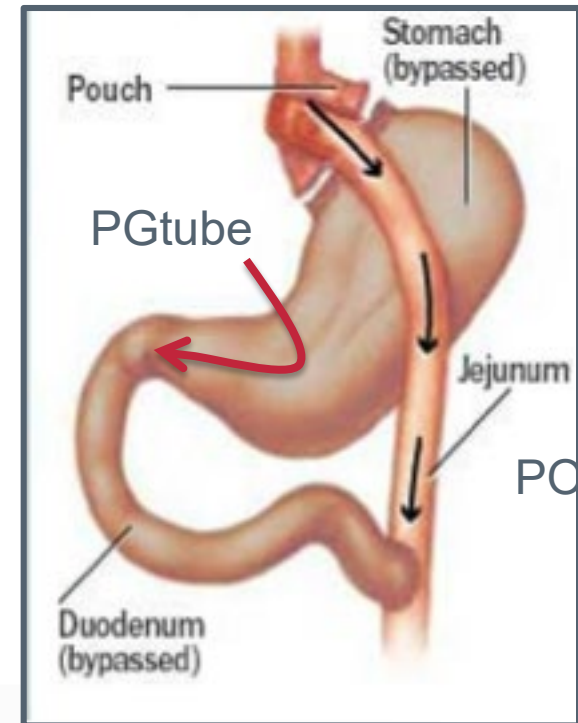
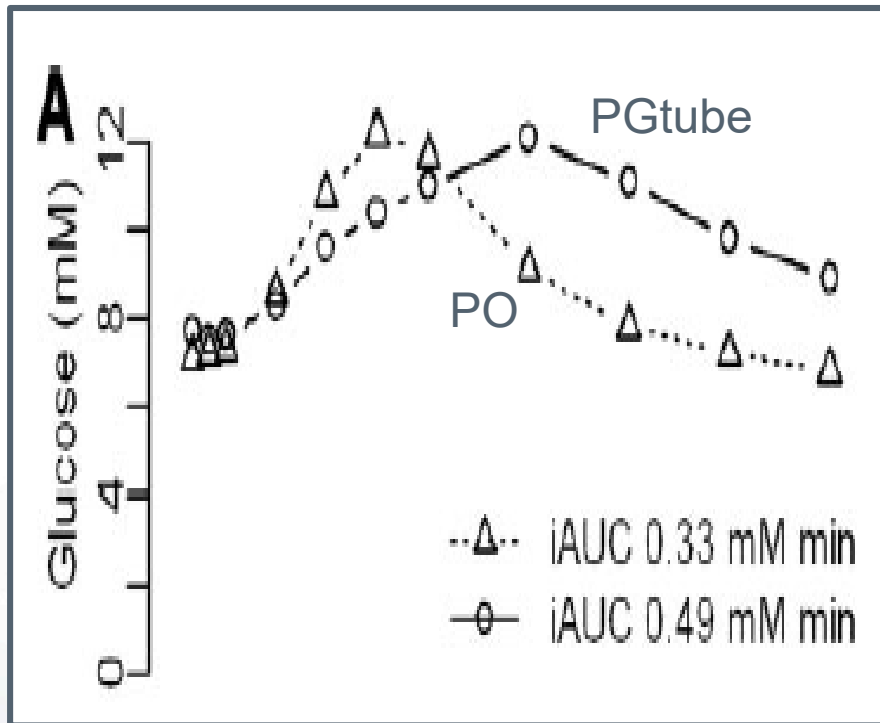
- Superior glycemic effect (T2D)¹
- Weight independent anti-diabetic effect³
- Can prevent disease onset (T2D/NAFLD)²
- Glycemic effect tied to background beta-cell function⁴
- Greater patient satisfaction⁵

Mechanistic evidence suggests that the early metabolic improvement is 'insulin sensitizing'

Bypass of the duodenum a key component of bariatric surgery

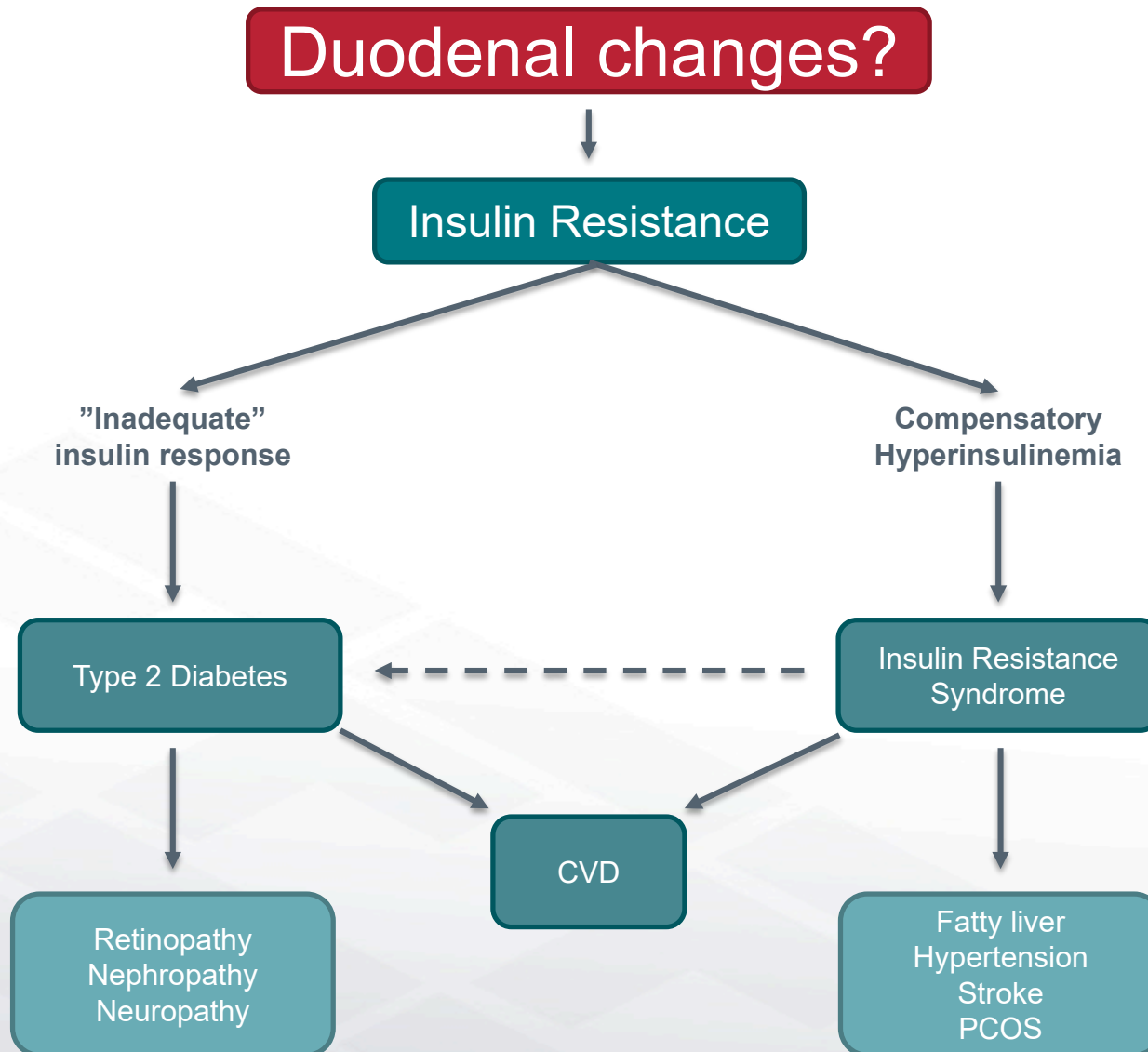


Post RYGB: re-exposing the duodenum to nutrients immediately reproduces dysglycemia



Acute re-introduction of nutrients into the bypassed duodenum (Roux limb) via PG tube caused an immediate worsening of post-prandial glucose excursion (~50%↑)

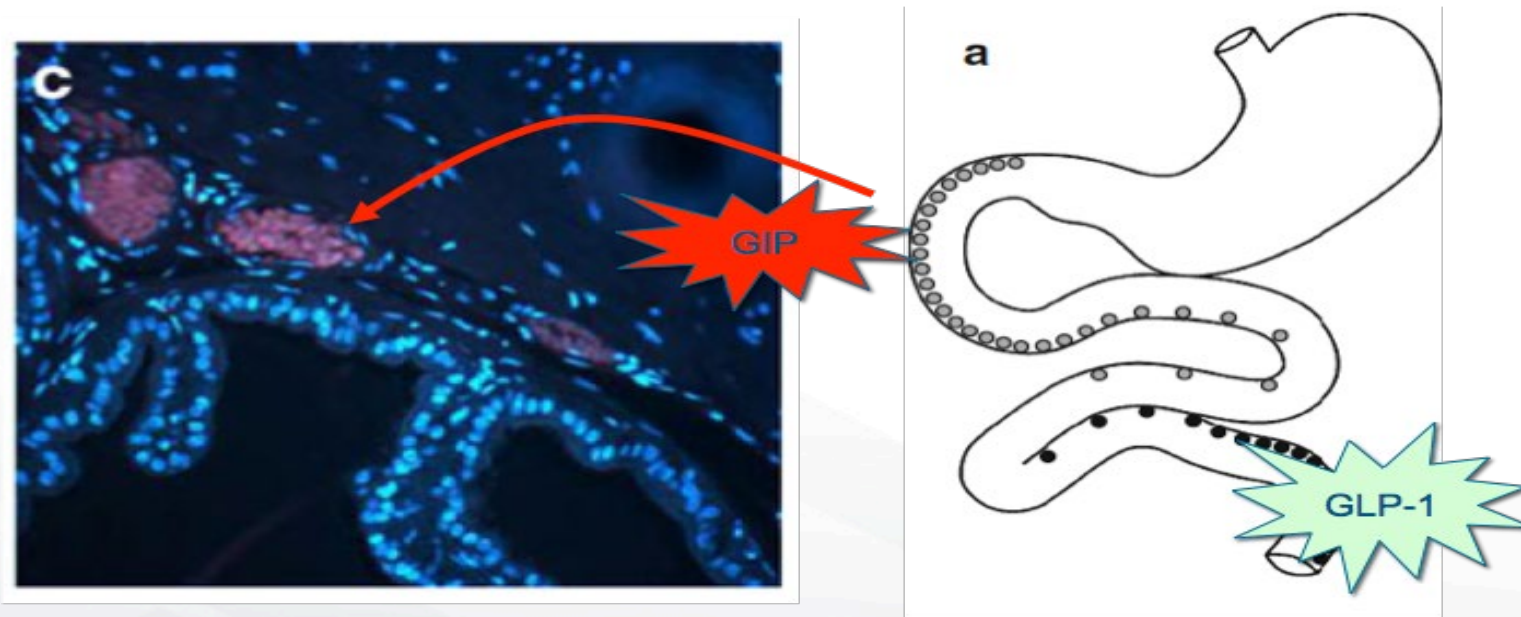
Could the duodenum be a key driver of insulin resistance?



Evidence that duodenal mucosa is maladapted in obesity and diabetes

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

- duodenal and jejunal hypertrophy¹
- duodenal entero-endocrine (GIP secreting) cell hyperplasia²³



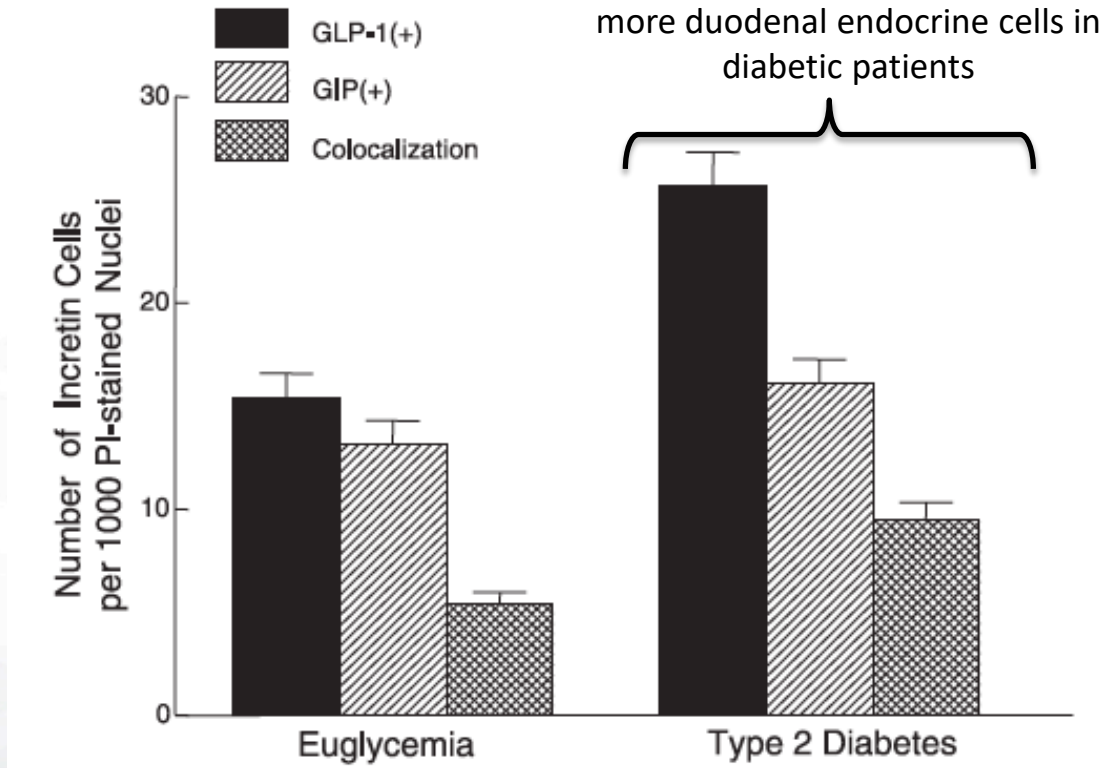
¹Adachi et al *Endocr J.* 2003;50(3):271-279

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

³Gniuli et al. *Diabetologia.* 2010;53(10):2233-2240

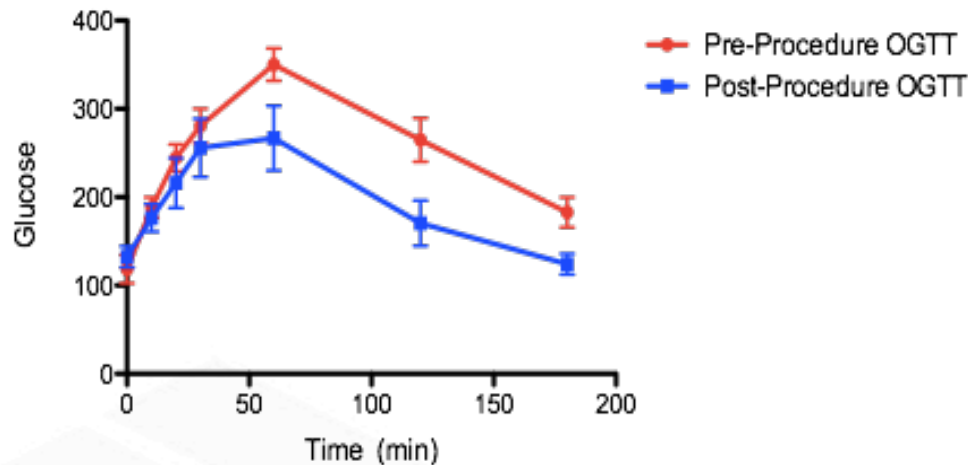
Duodenal mucosa has abnormal enteroendocrine populations in T2D subjects

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



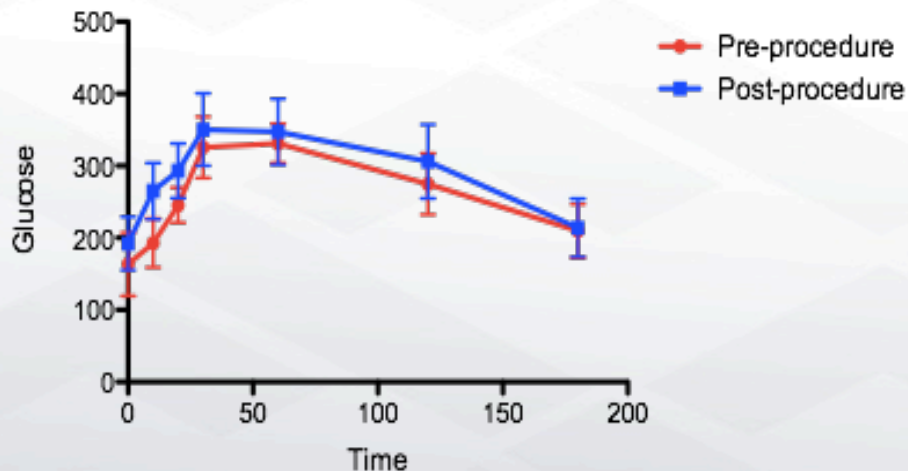
Denuding the duodenal surface lowers hyperglycemia: rodent proof of concept

OGTT results in GK rats before and after duodenal abrasion



- 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 rodents

OGTT results in GK rats before and after sham procedure

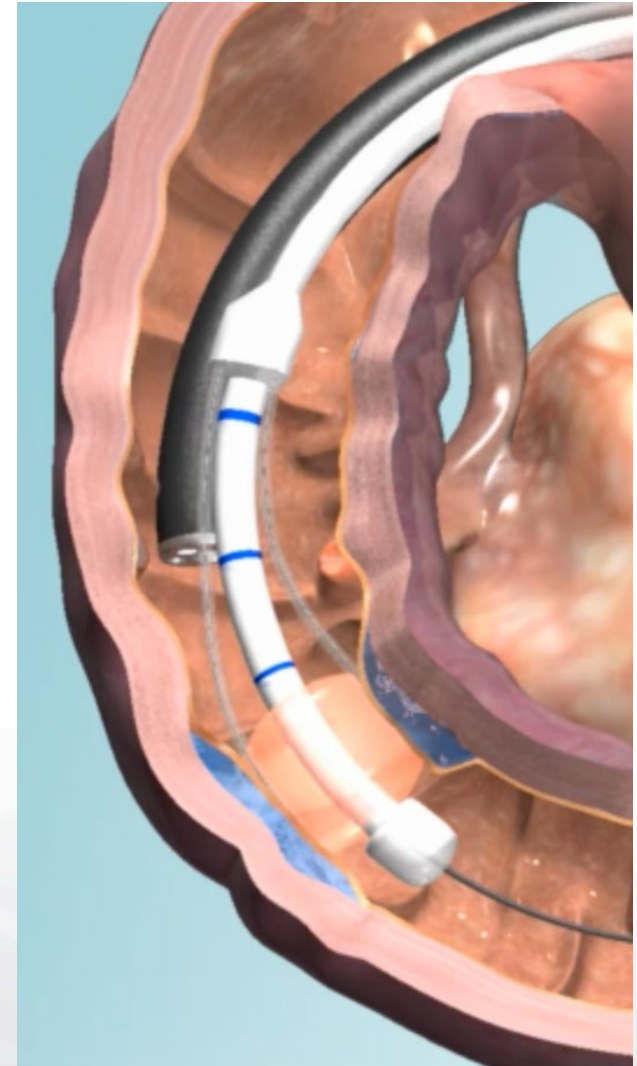


Mucosal resurfacing is a compelling way to target the apparent duodenal pathological defect

Approach	Considerations
Pharmacological	<ul style="list-style-type: none">• No targets yet identified• Glucose lowering versus disease modifying• Drugs may not solve population level chronic disease problem
Duodenal resurfacing	<ul style="list-style-type: none">• Ablation is an established tool in other tissues• Could address root cause epithelial changes in a precise manner• Can potentially become a patient-friendly intervention (e.g. offering a metabolic reset and circumventing burdens of compliance)

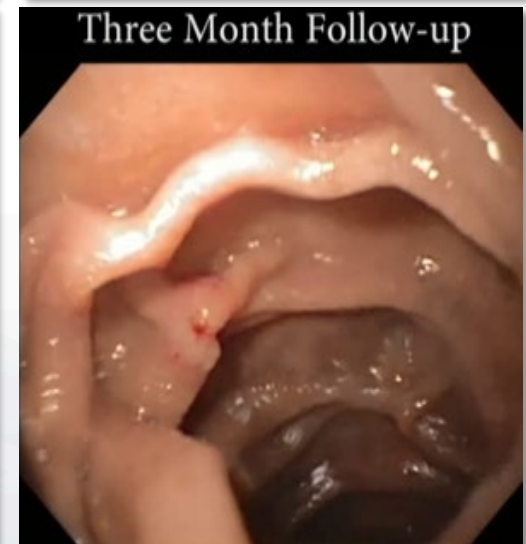
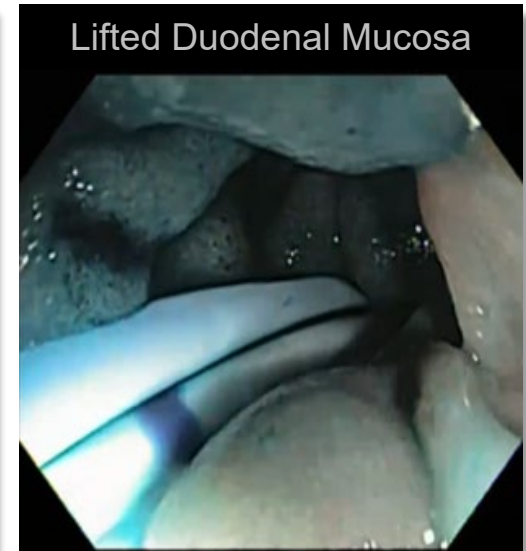
Duodenal Mucosal Resurfacing (Revita System)

- Duodenal Mucosal Resurfacing (DMR) procedure resurfaces the duodenal mucosa post-thermal ablation
- Designed to provide a metabolic reset to approximate the duodenal exclusion in the from bypass surgery
- Procedure conducted during upper GI endoscopy:
 - Control console and single-use disposable catheter
 - Same day minimally invasive procedural therapy conducted <1 hour
 - Techniques familiar to GI endoscopists
 - No implant, surgery, or suturing
 - Saline expansion of submucosa
 - Hydrothermal mucosal ablation



DMR early clinical experience: endoscopy view

- To date, 80 T2D patients have undergone DMR (S America, EU)
- Procedure implemented well by endoscopists and well tolerated by patients
- 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 full mucosal healing
- Three stenosis observed in early use but none since procedure modification
- No other major complications



Patient Case Study

43 year old male
 Diabetes duration 5 years
 BMI 31.3 kg/m²
 Treatment Metformin, SU
Intervention: endoscopic DMR
 Mild GI symptoms post-DMR for 1 day

	Pre-DMR	3 mo	6 mo
HbA1c (%)	9.5	7.2	7.2
FPG (mg/dl)	162	129	132
Body weight (kg)	91.6	87.7	89.3
ALT (IU/L)	35	25	27

Mixed meal tolerance test conducted pre-DMR and 6 months post-DMR

	minutes	0	15	30	45	60	90	120
Pre-DMR	glucose (mg/dl)	162	168	193	225	259	247	247
6 months	glucose (mg/dl)	132	141	172	185	198	215	211

Conclusions

- Duodenum appears to play an important gluco-regulatory role
 - Illuminated by bariatric surgical science
 - Apparent changes to duodenal mucosa may drive insulin resistance
- Duodenal mucosal resurfacing as an insulin sensitizing intervention
 - Potentially broad metabolic improvements in T2D and NAFLD/NASH
 - Compliance-independent approach to population-level disease control
 - Reduced reliance on polypharmacy is inherently attractive
- Early clinical work with favorable clinical signals
 - Future studies will be directed at demonstrating safety/efficacy, optimizing performance, and establishing clinical utility in broader populations