

3rd
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Symposium

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Duodenal Mucosa: A Target for Treating Metabolic Liver Disease in NASH and T2D

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DISCLOSURES

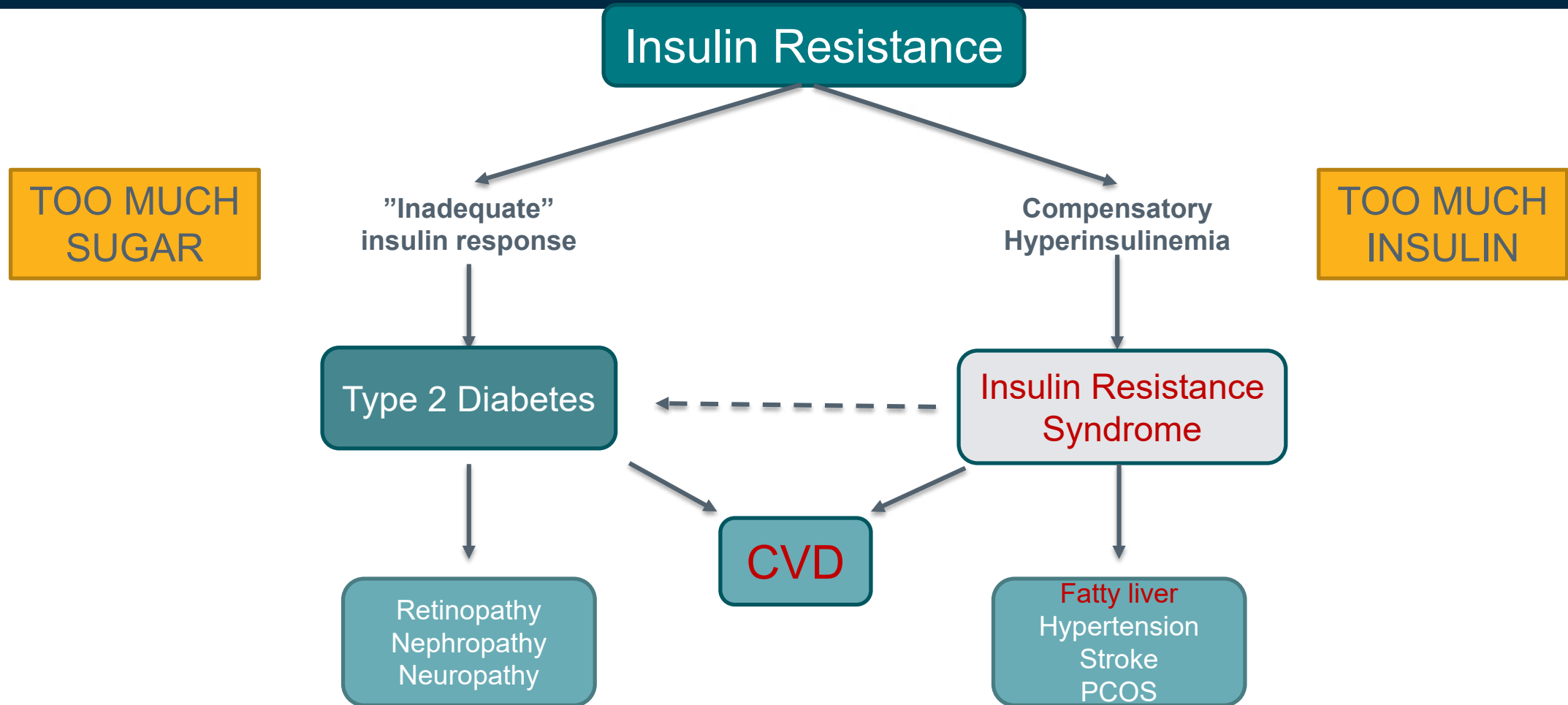
- ***Entrepreneur.*** Co-Founder and CEO of Fractyl Laboratories
- ***Cardiologist.*** Frustrated by the real world, population-level, inability to solve the known risk factors leading to cardiovascular disease and by use of insulin as a treatment for T2D
- ***Scientist.*** Enamored by what bariatric surgery can teach us about the role of the GI tract in human metabolism

Duodenal Intervention for NASH and T2D



- Insulin resistance syndrome is an important metabolic driver of NAFLD/NASH
 - Insulin sensitization can reverse fatty liver and NASH
- Duodenal bypass surgery best viewed as a metabolic intervention
 - Duodenal bypass has insulin sensitizing effect
- Emerging evidence highlights key role of duodenal mucosa
 - Adaptive changes to mucosa as a potential driver of metabolic disarray
- Role for endoscopic interventions as treatments for GI root cause
 - Insulin sensitizing, compliance-independent, patient friendly

The Central Role of Insulin Resistance in Metabolic Diseases

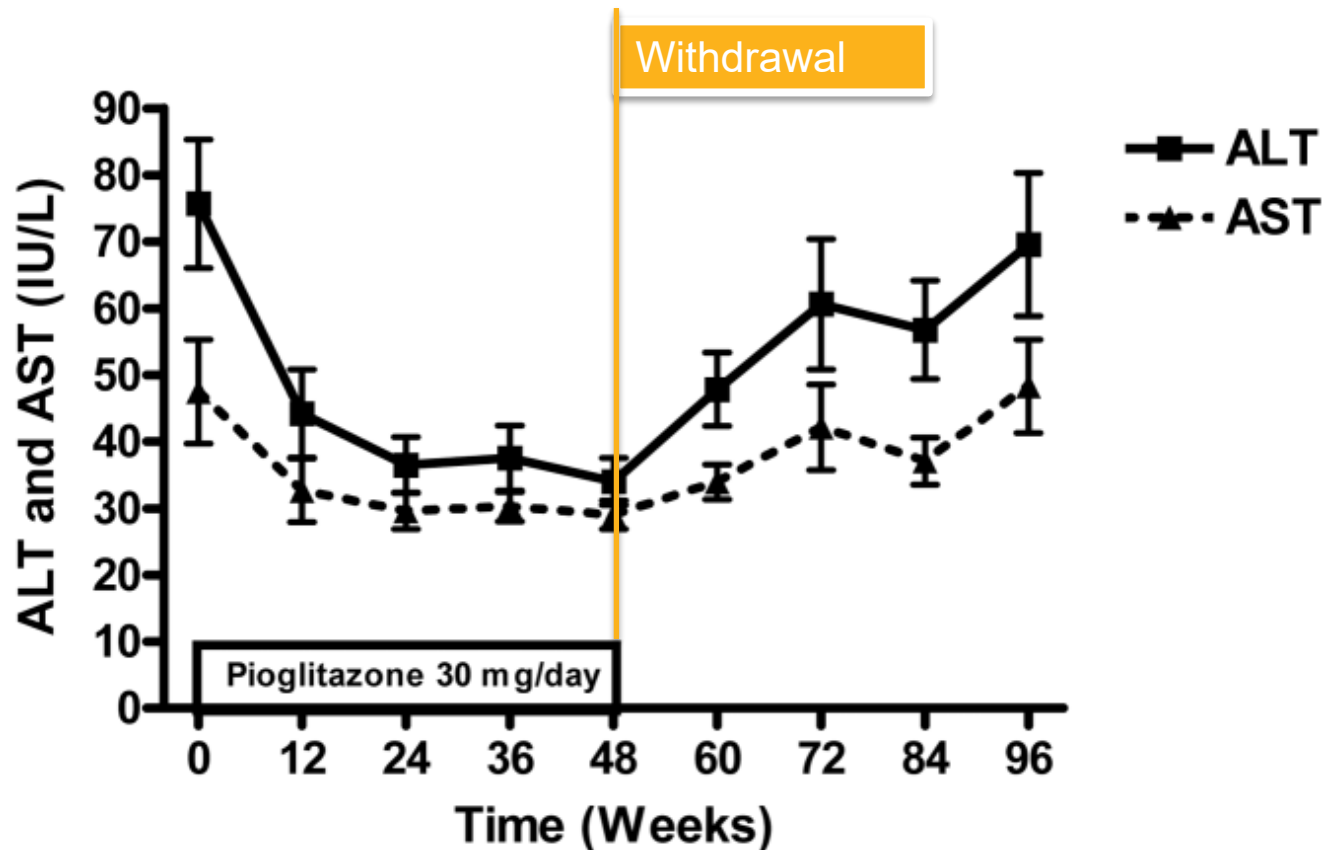


Adapted from AACE position statement

Insulin Sensitizing Drugs Can Resolve NASH in T2D Patients

Insulin Sensitizing Drugs (TZDs)
then withdrawal after 1 year

Clinical benefit of TZDs are now
well established



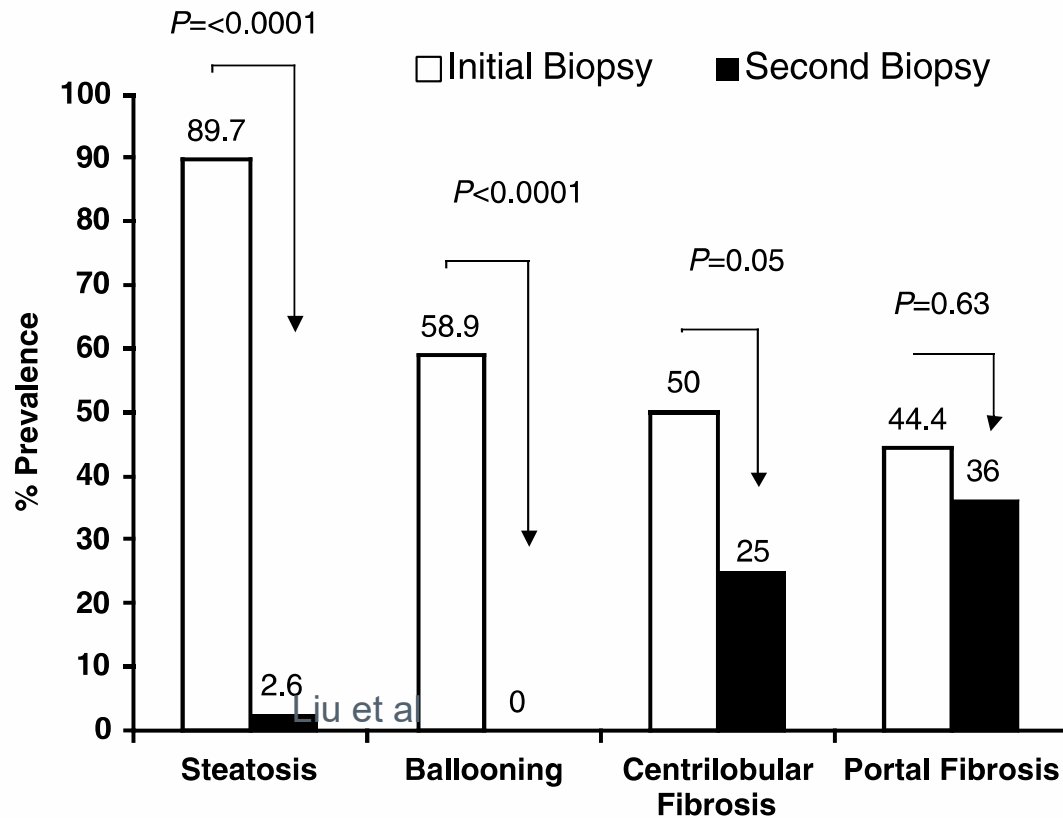
- Histologic resolution of NASH^(1,2)
- T2D
- CV disease
- Stroke
- Disease prevention (T2D)
- PCOS

(1) Cusi et al Annals Int Med 2016;
(2) Lutchman et al Hepatology 2007

Gastric Bypass Surgery Can Reverse and/or Prevent Insulin Resistant Metabolic Diseases

Improved NASH after Gastric Bypass Surgery

Clinical Benefit of Gastric Bypass Surgery



- NASH⁽⁴⁾
- T2D⁽¹⁾
- CV disease
- Disease prevention (T2D)⁽⁵⁾
- PCOS
- Greater patient satisfaction⁽⁶⁾

Insulin Resistance

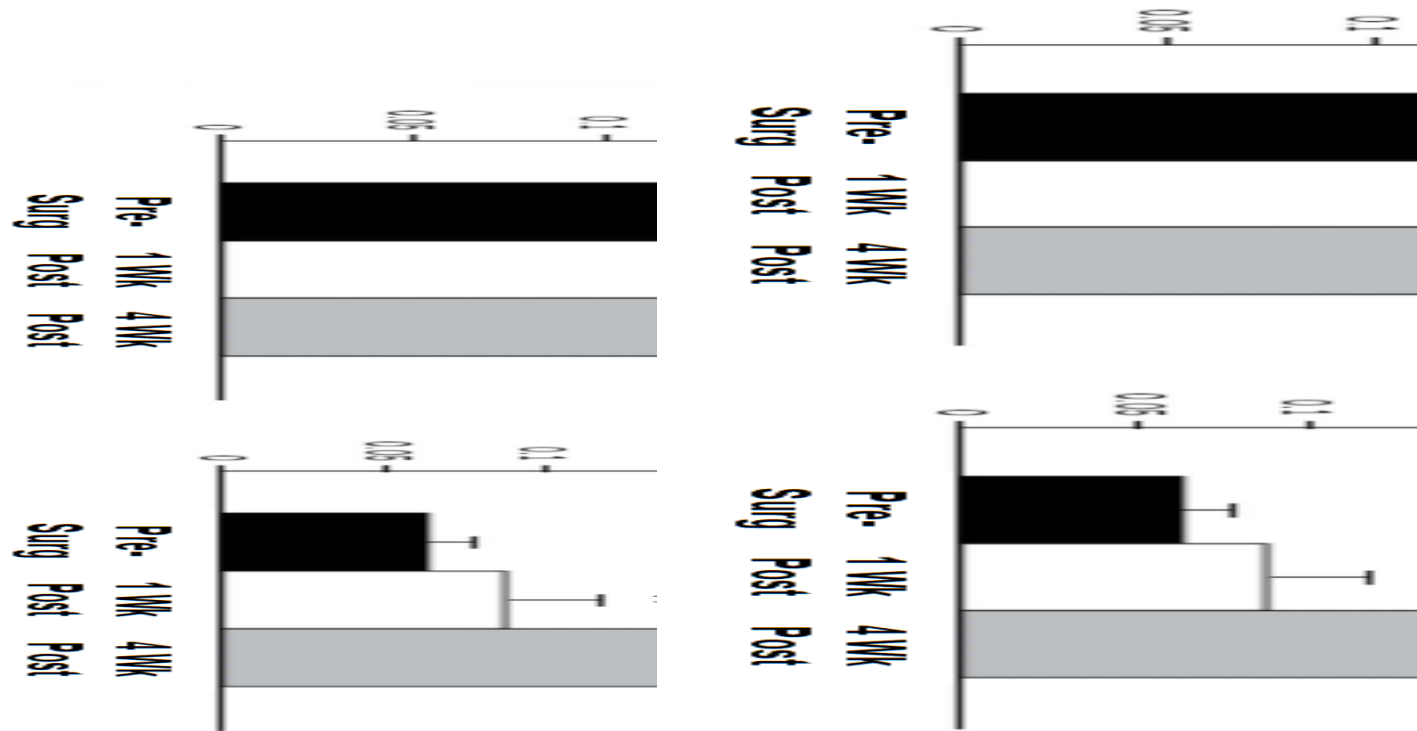
Bariatric epiphany

Duodenal mucosa

Metabolic endoscopy

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⁾ Liu et al. Obes Surg 17(4); ⁽⁵⁾ Carlsson et al. NEJM. 367(8); ⁽⁶⁾ Mingrone et al. Lancet 386 (9997), p964-973

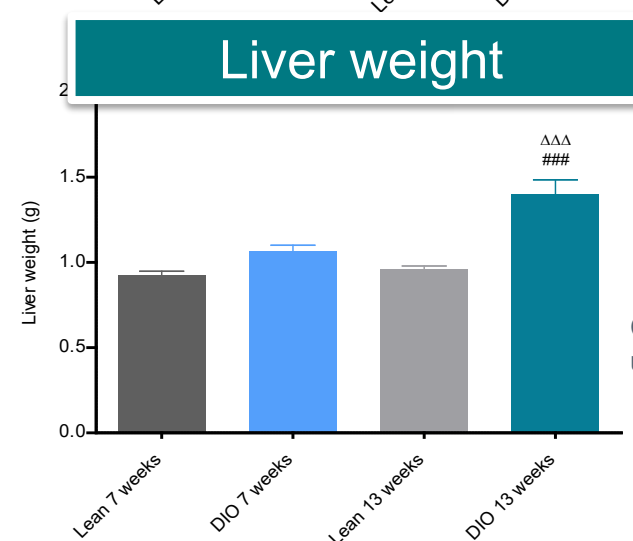
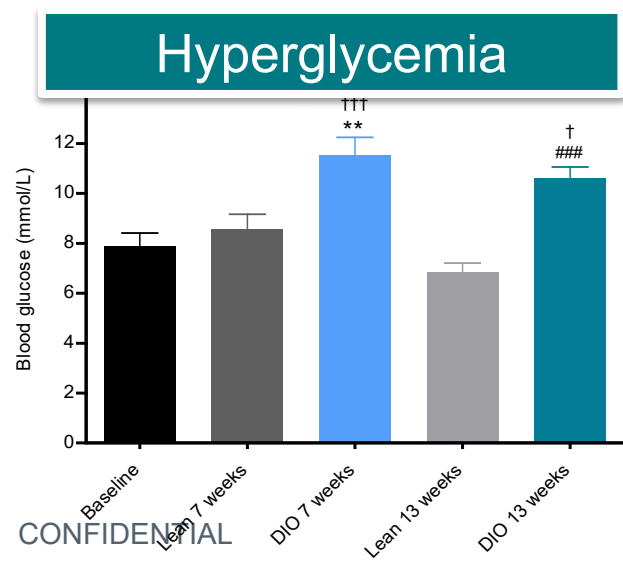
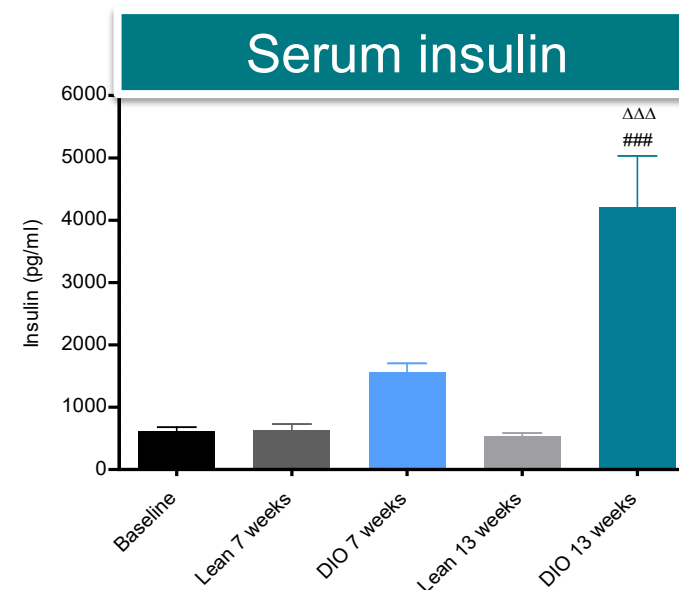
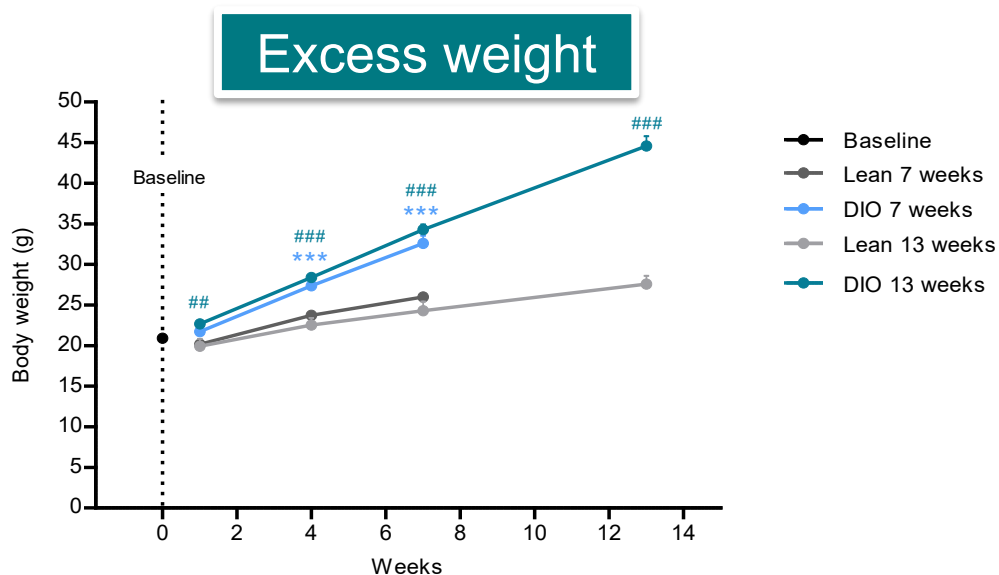
Duodenal Bypass Elicits Immediate Weight-Independent Insulin Sensitizing Effects



Kashyap SR...Schauer PR IJO 2010

- Insulin sensitivity measured by hyperinsulinemic clamp in patients with T2D
- Similar weight loss between gastric restriction and RYGB groups
- Much greater insulin sensitization in RYGB cohort

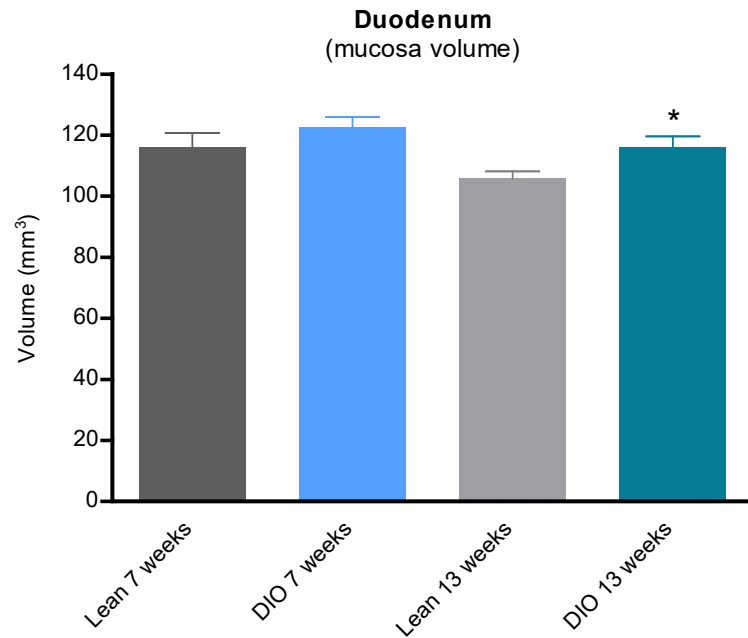
Exploring the Potential Role of the Duodenum: Metabolic Changes in DIO Mouse Model



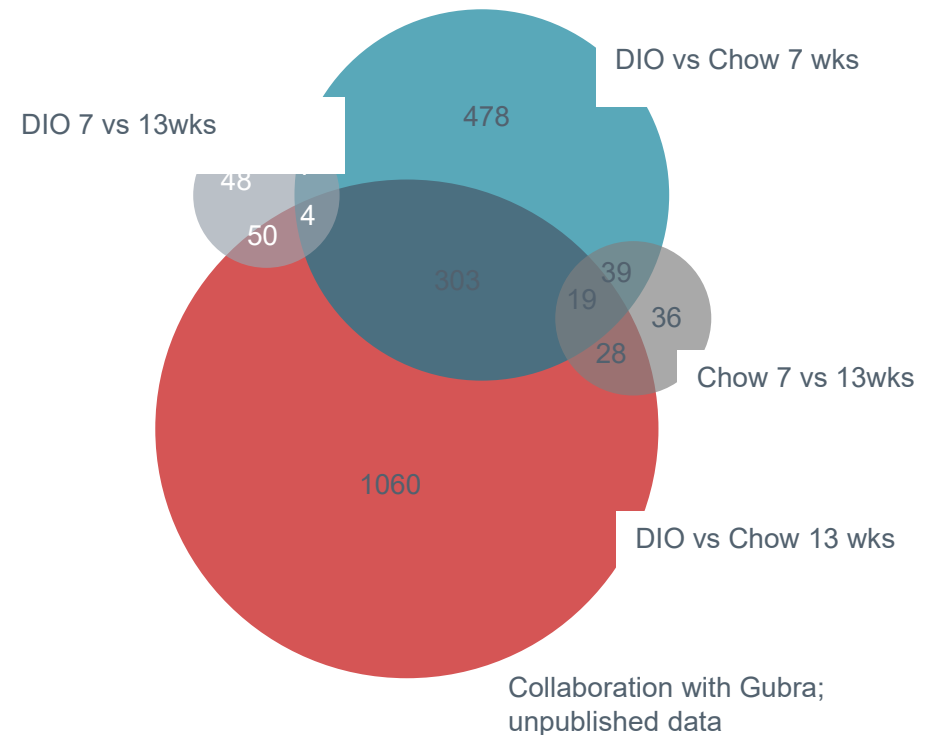
Collaboration with Gubra; unpublished data

Changes in Duodenal Mucosa Volume and Gene Expression in DIO Mouse Model

Duodenal mucosal volume expansion

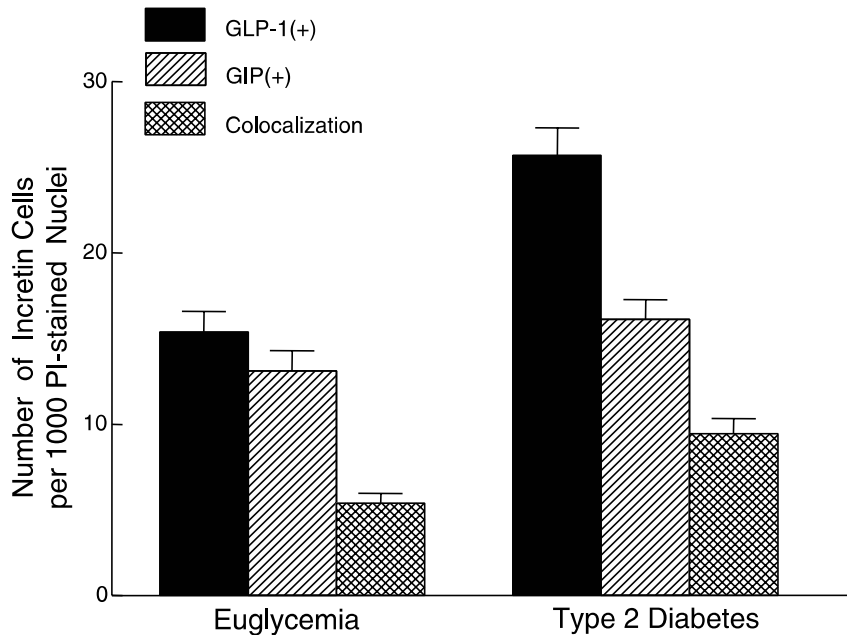


Massive gene expression changes in duodenal mucosa (RNA seq)



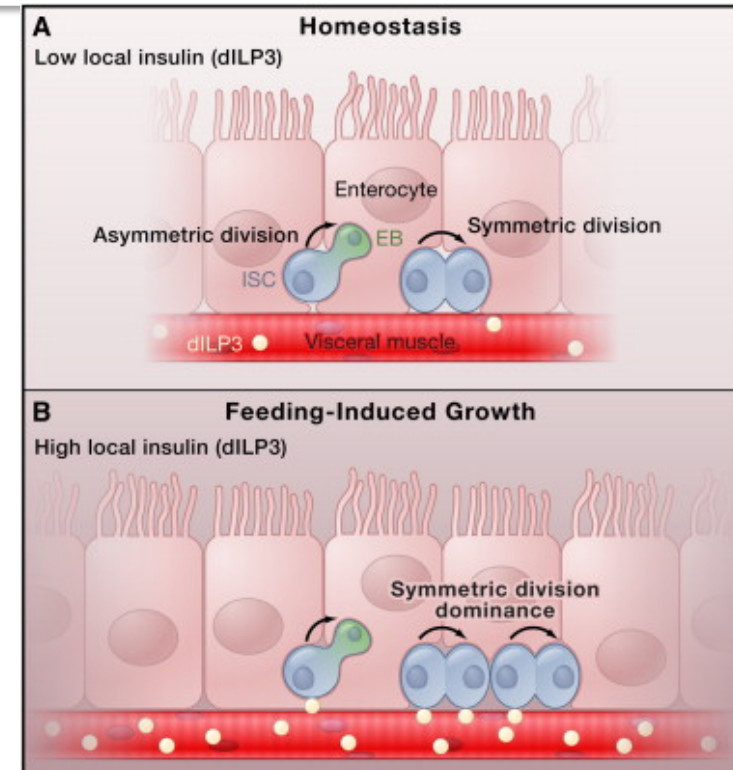
Changes in Duodenal Mucosa Volume and Gene Expression in DIO Mouse Model

...consistent with known increases in enteroendocrine cell numbers in human duodenal biopsies in T2D patients



Theodorakis et al

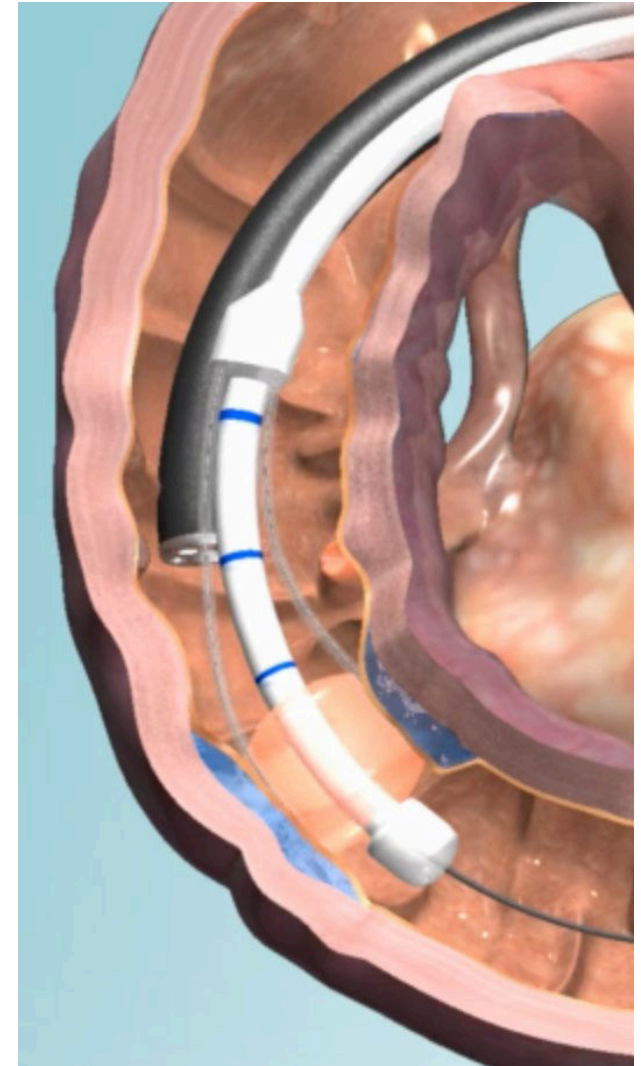
...potentially due to physiologic organ adaptation to dietary fat and sugar



O'Brien et al

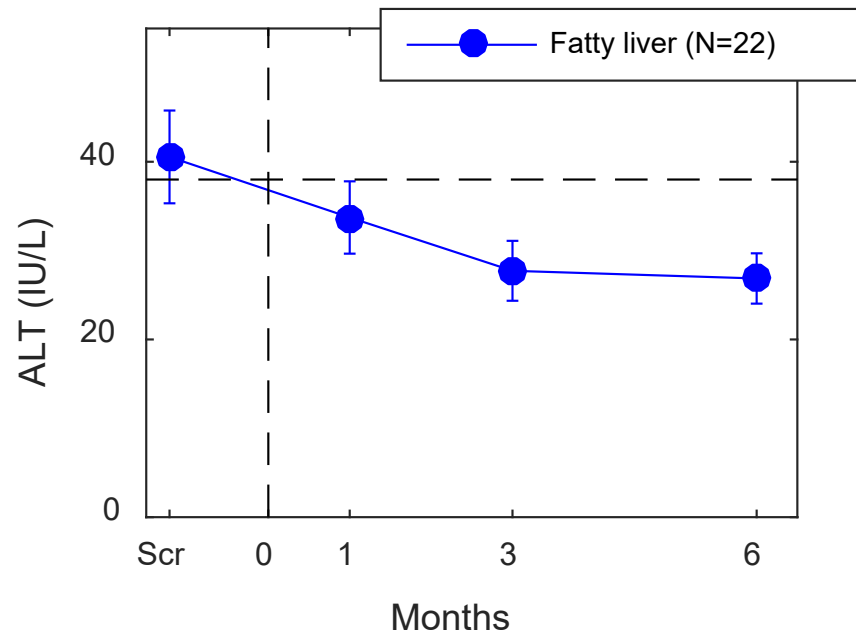
Duodenal Mucosal Rejuvenation (Revita™ DMR System)

- Duodenal Mucosal Rejuvenation (DMR) procedure resurfaces the duodenal mucosa post-thermal ablation
- Designed to 're-set' local abnormal signals emanating from the duodenal surface
- This approximates the duodenal exclusion in bypass surgery (as angioplasty is to CABG)
- Procedure conducted during upper GI endoscopy:
 - Minimally invasive upper endoscopic procedure conducted <1 hour
 - Techniques familiar to GI endoscopists
 - Saline expansion of submucosa
 - Hydrothermal mucosal ablation
 - Graduated diet post-procedure

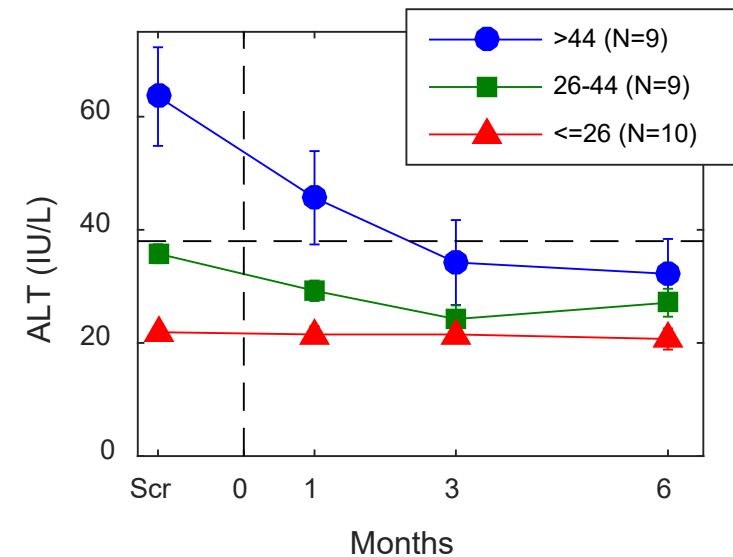


FIH Feasibility Study in T2D Patients with Radiological Evidence of NAFLD

ALT in Subjects with Fatty Liver



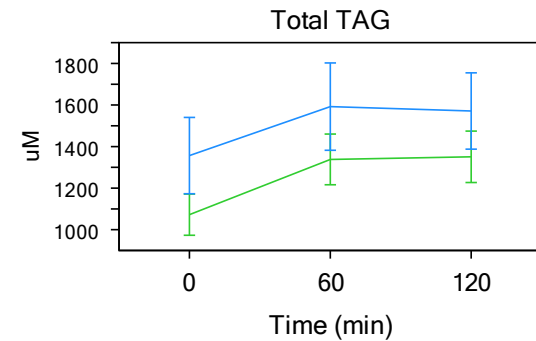
ALT in Subjects by Starting Tertile



Patients with T2D had pronounced and sustained improvements in liver transaminases in a weight-independent manner

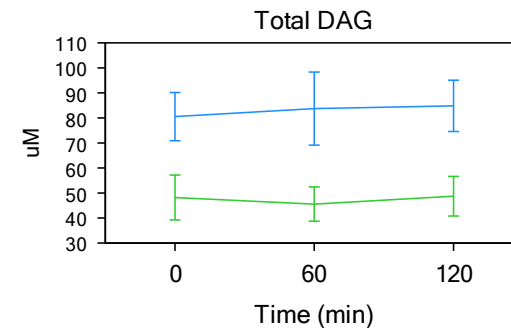
DMR Metabolic signature (substudy n=14)

- Meal challenge samples (fasting and post-prandial) at 0 and 3 months from FIH study analyzed by Metabolon, North Carolina
- Summary of findings
 - Improved insulin sensitivity ($\downarrow\alpha\text{HBA}$)
 - \downarrow FA β -oxidation
 - Improved mitochondrial function
 - \downarrow inflammation ($\downarrow\text{HETE}$) – marker of NAFLD \rightarrow NASH

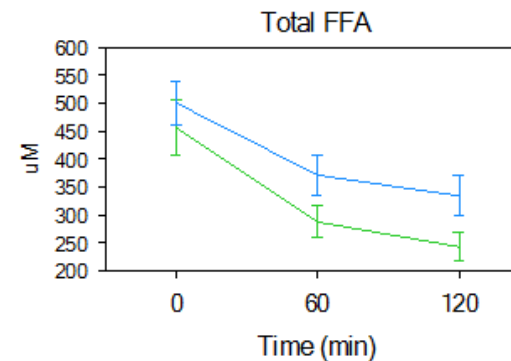


— Day 0
— Day 90

Reductions in triglycerides



Reductions in lipid intermediates



Reductions in post-prandial FFAs

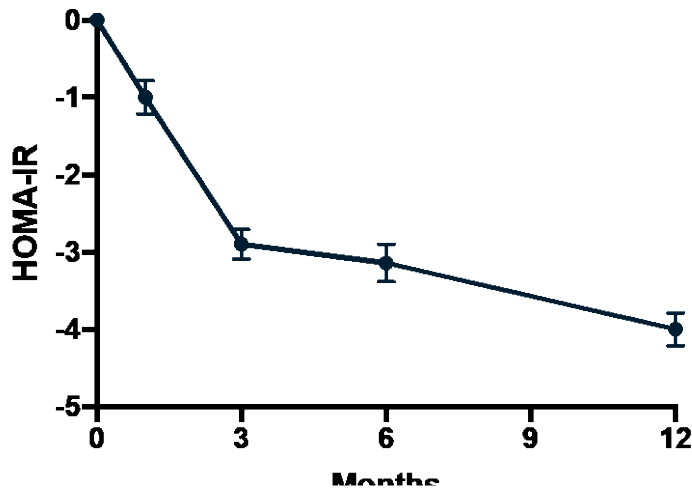
Collaboration with Sanyal and Metabolon; unpublished data

Revita-1 Markers of Insulin Sensitization

- Multicenter, open label, safety study in T2D patients
- ~ 50 patients; ~ 25 now at 1 year follow up
- **Minimal dietary counseling**
- Completed enrollment H2 2016
- Well tolerated procedure with no device or procedure related SAEs

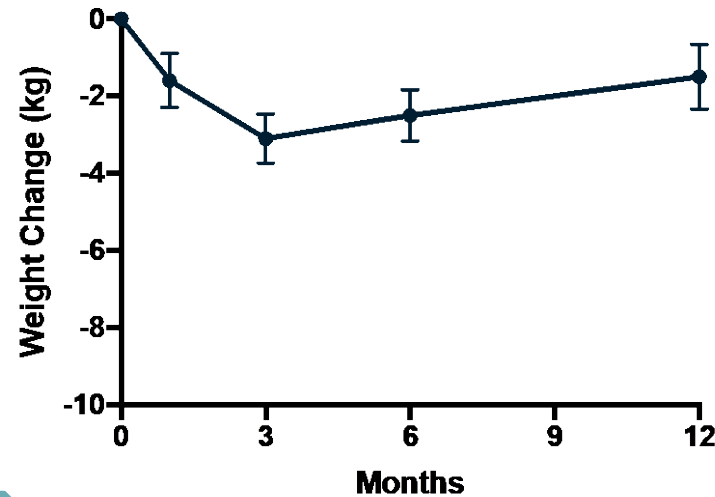
HOMA-IR

Revita-1 Study HOMA-IR



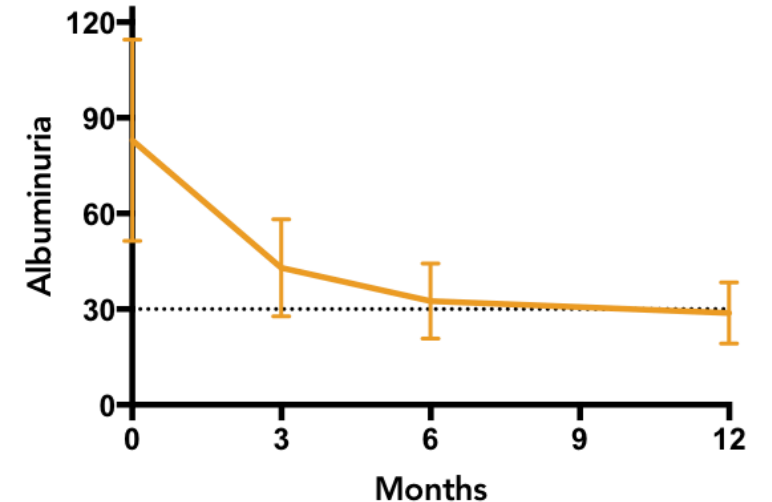
Weight Change

Revita-1 Study Weight



Albuminuria

Urinary Microalbumin (Kidney Function)
Revita-1



Insulin
Resistance

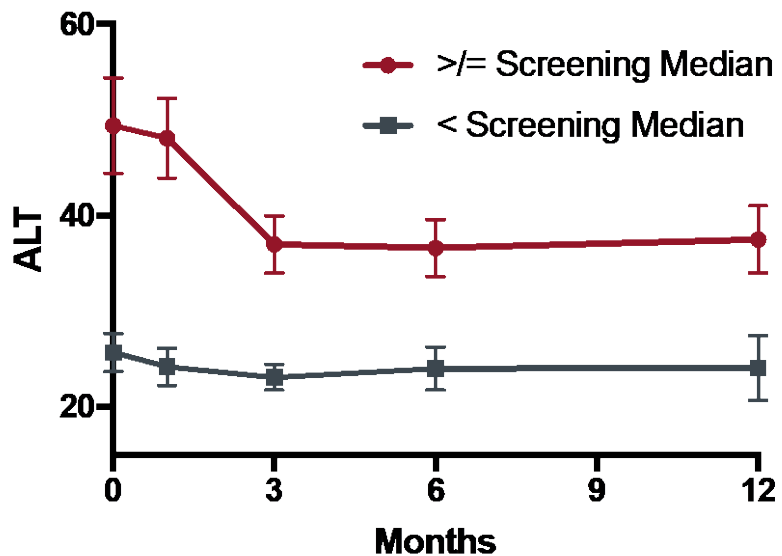
Bariatric
epiphany

Duodenal
mucosa

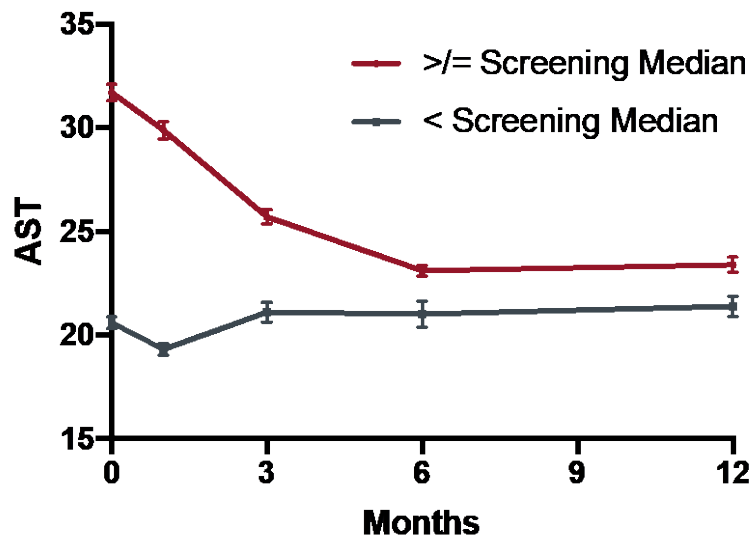
Metabolic
endoscopy

Revita-1 Experience Suggests Sustained Improvements in Hepatic Insulin Sensitivity

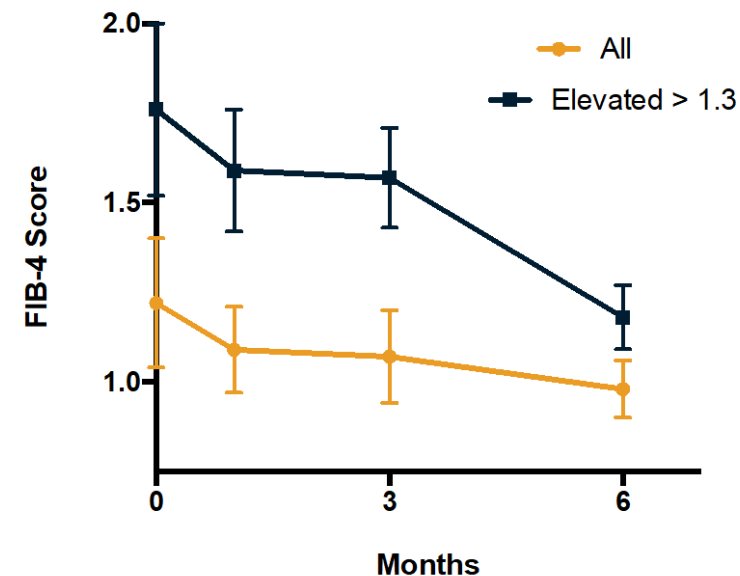
Revita-1 Study ALT



Revita-1 Study AST



FIB-4 in Revita-1b



- Study not actively enriched for fatty liver patients
- Future work will characterize liver in greater detail
- Expect to see synergistic benefit with focused lifestyle intervention

Insulin Resistance

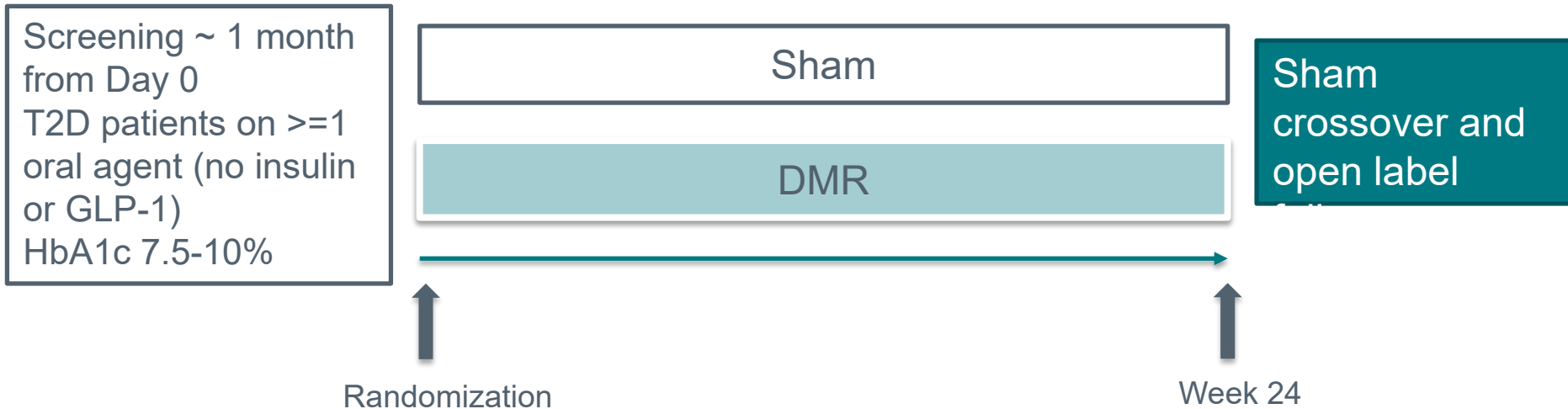
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Sham-Controlled T2D Study Now Underway with Secondary Liver Endpoints

Updated Revita-2 RCT



- ~ 75 patients at up to 15 centers
- Primary endpoints: HbA1c; safety
- Secondary endpoints: Liver MRFF

NASH Pilot Study Initiating 2017 H2

NASH Pilot Study

Biopsy-proven
NASH
Documented
insulin resistance

DMR + Lifestyle

Follow up
to 12
months

Week 24

- ~ 10-15 patients
- Primary endpoints: 6 mo MRFF
- Secondary endpoints: 12 mo biopsy

Insulin
Resistance

Bariatric
epiphany

Duodenal
mucosa

Metabolic
endoscopy

A Compelling New Approach for NASH and T2D



- Many fascinating mechanistic questions to be explored
- Apparently safe and scalable outpatient intervention performed by endoscopists/hepatologists
- Early suggestion of durable disease modifying impact without enforced lifestyle intervention
- Overcomes compliance challenges in real world setting
- Can effectively complement & enhance effectiveness of drugs that target later stage disease
- Can offer broad metabolic benefit for patients with T2D and NAFLD/NASH