Endoscopic Duodenal Mucosal Resurfacing (DMR) Improves Glycemic and Hepatic Parameters in Patients with Type 2 Diabetes: Data from a First-in-Human Study

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Disclosures

- Harith Rajagopalan, MD, PhD
  - Employee and shareholder: Fractyl Laboratories, Inc.
  - Fractyl Laboratories provided funding for this study

Background

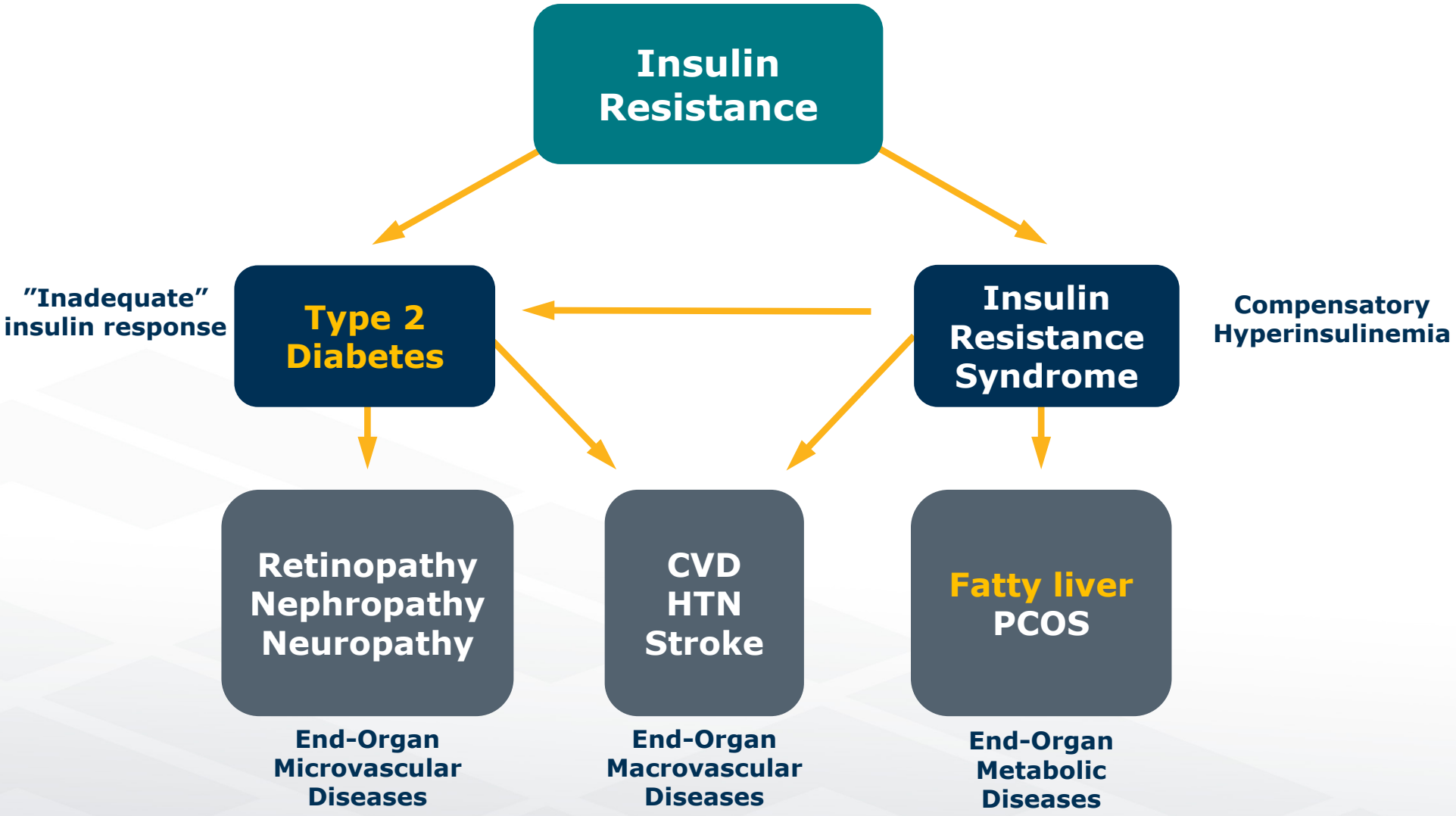
- Bariatric surgeries that prevent nutrient contact with the duodenum improve measures of metabolism in type 2 diabetes (T2D), including indicators of fatty liver disease

- Revita™ duodenal mucosal resurfacing (DMR) may offer similar metabolic benefit

Aim

- To assess procedural safety in patients with suboptimally controlled T2D
  - HbA1c > 7.5% on ≥ 1 anti-diabetic agent
- To evaluate the effect of Revita DMR on metabolic parameters

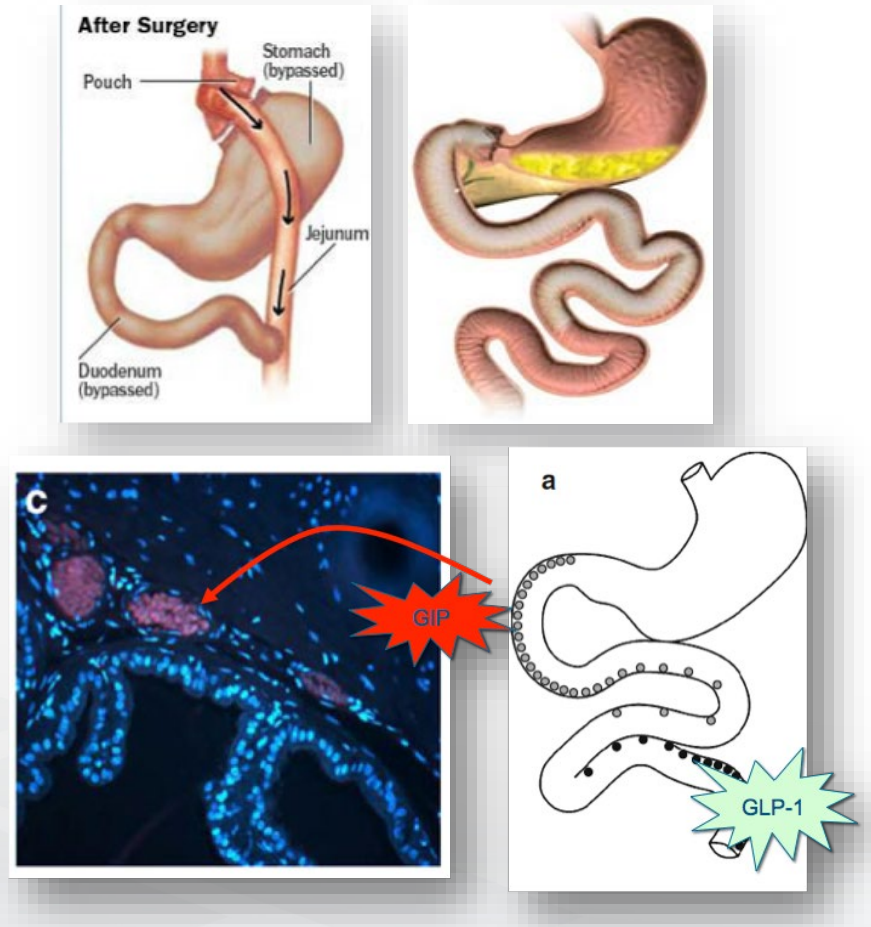
The Central Role of Insulin Resistance



Adapted from AACE position statement

Revita DMR: Pathophysiologic Principle

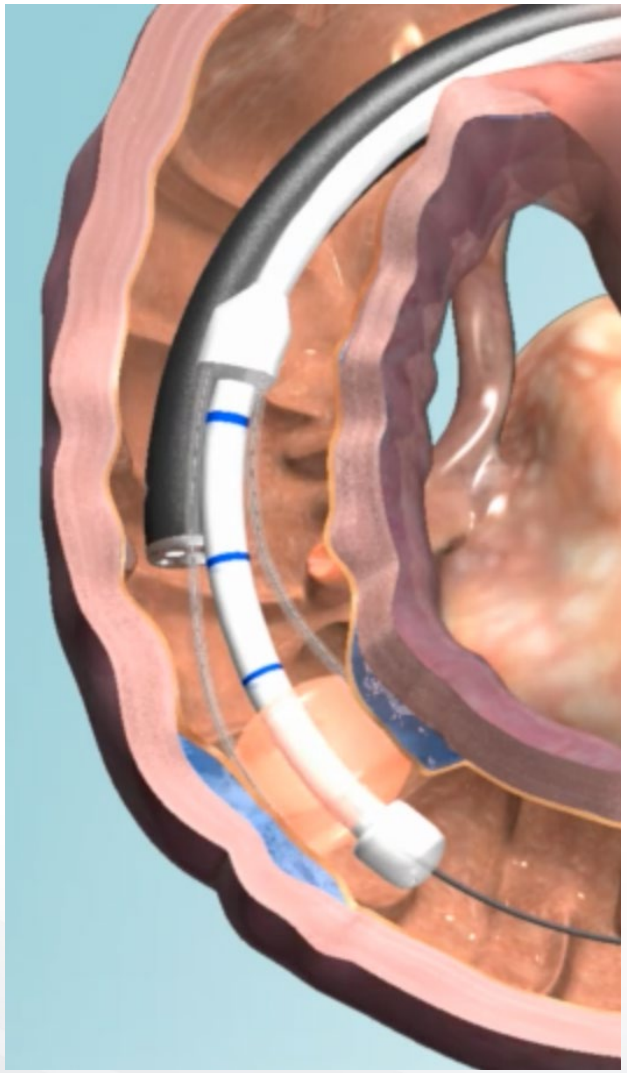
- Bypass of upper GI tract (surgery, sleeve) exerts potent effects on metabolism through insulin sensitizing pathways
- Nutrient re-exposure to the 'Roux' elicits return to hyperglycemia
- Abnormal hypertrophy of mucosa noted in diabetics' upper GI tract
- Abnormal entero-endocrine cell sub-population in upper GI mucosa of diabetic patients



Pories et al. Ann Surg. 222 (3): 339–50, 1995; Rohde et al. BMJ. 3(9), 2013; Dirksen et al. Diabetes Care. 33(2):0–2, 2010; Verdam et al. JCEM. 96(2):E379–83, 2011; Theodorakis et al. AJP. 290(3):E550–9, 2006; Gniuli et al. Diabetologia. 53(10):2233–40, 2010

Revita DMR Procedure

- Minimally invasive upper endoscopic therapy using an innovative balloon catheter
- Targets duodenal mucosa between Ampulla of Vater and Ligament of Treitz
- Procedural Steps
  - Size duodenum and lift sub-mucosal space with saline injection to create protective barrier
  - Circumferentially ablate superficial mucosa using a hydrothermal approach to stimulate regeneration
  - Procedure duration ~60 minutes
- No implant, sutures or surgery



First-in-Human Study: Methods

- Single center, single arm study performed in Santiago, Chile, in patients with suboptimally controlled T2D
- Thermal ablation performed on either a **short** (n=11; mean 3.4 cm) or **long** (n=28; mean: 9.3 cm) segment of duodenum
- Procedures performed by trained endoscopists with patients under anesthesia
- 2-week, low calorie, graduated diet for all patients post-procedure (liquids→soft→puree)
- No specific recommendation on post-procedure management of anti-diabetic medication
- Post-procedure endoscopies performed at 1 and 3 months

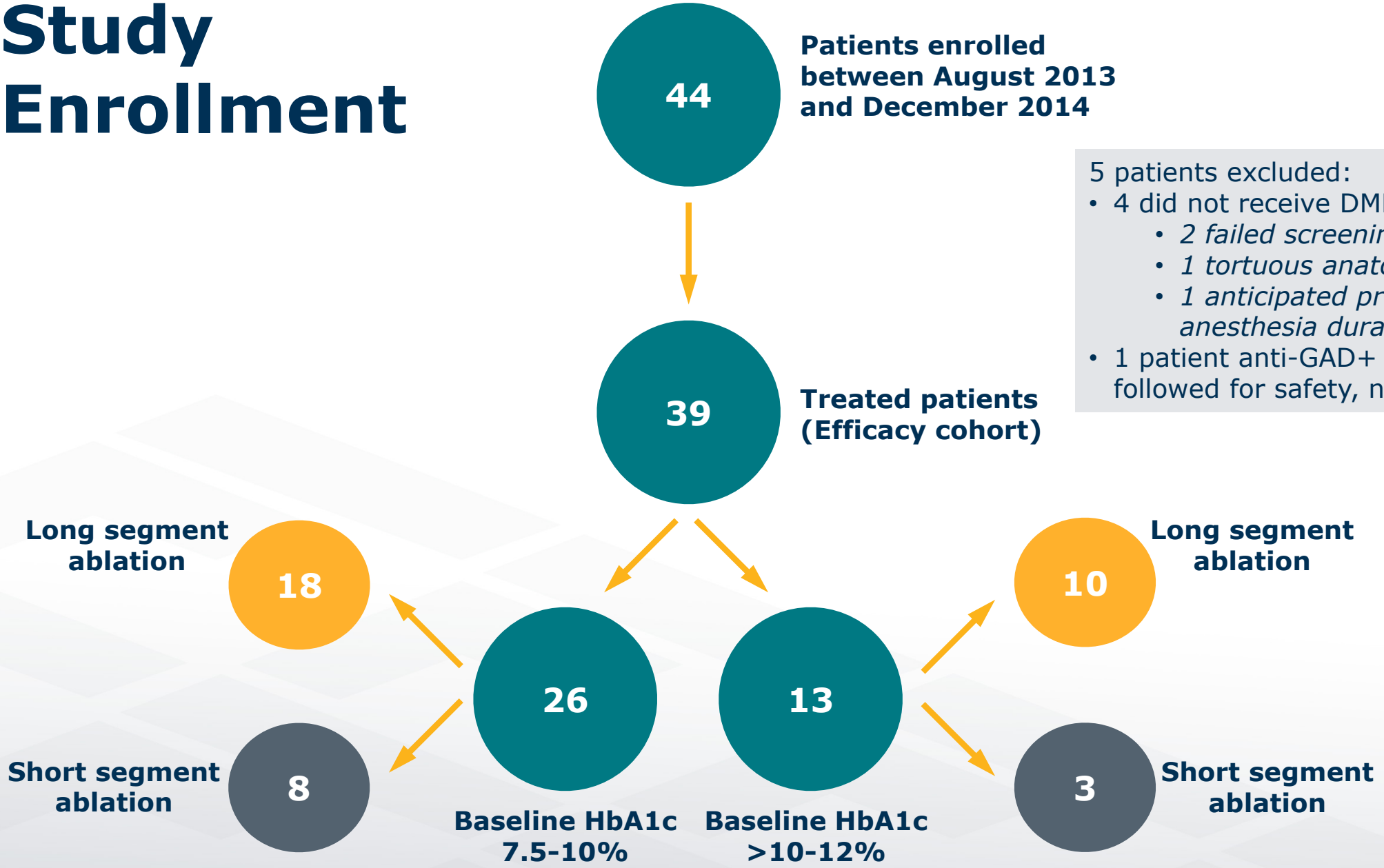
Study Details

- **Inclusion criteria**
  - Age 28-75
  - BMI 24-40
  - HbA1c 7.5-12%
  - Disease diagnosed <10 years
  - Fasting c-peptide >1 ng/ml
  - ≥ 1 oral anti-diabetes medicine (Rx)
- **Exclusion criteria**
  - Prior GI surgery that would preclude procedure
  - Anatomical abnormalities
  - Anti-GAD Ab+
  - Injectable anti-diabetes Rx

Patient characteristics	Value (N=44)
Age, yrs (range)	53.4 +/- 7.5 (38-65)
Sex, n (%)	
Female	16 (36)
Male	28 (64)
Weight, kg	84.4 +/- 11.9
Height, cm	165.3 +/- 8.4
BMI, kg/m^2	30.8 +/- 3.5
Systolic BP, mmHg	122.0 +/- 14.2
Diastolic BP, mmHg	77.0 +/- 8.1
Duration T2D, yrs (range)	5.7 +/- 2.2 (0.2-9.7)
HbA1c, %	9.6 +/-1.4
FPG, mg/dL %	187 +/-58
Oral anti-diabetic Rx	
Metformin, n (%)	42 (98)
Sulfonylurea, n(%)	16 (37)

Data are mean ± SD or n (%), unless otherwise indicated.

Study Enrollment



5 patients excluded:

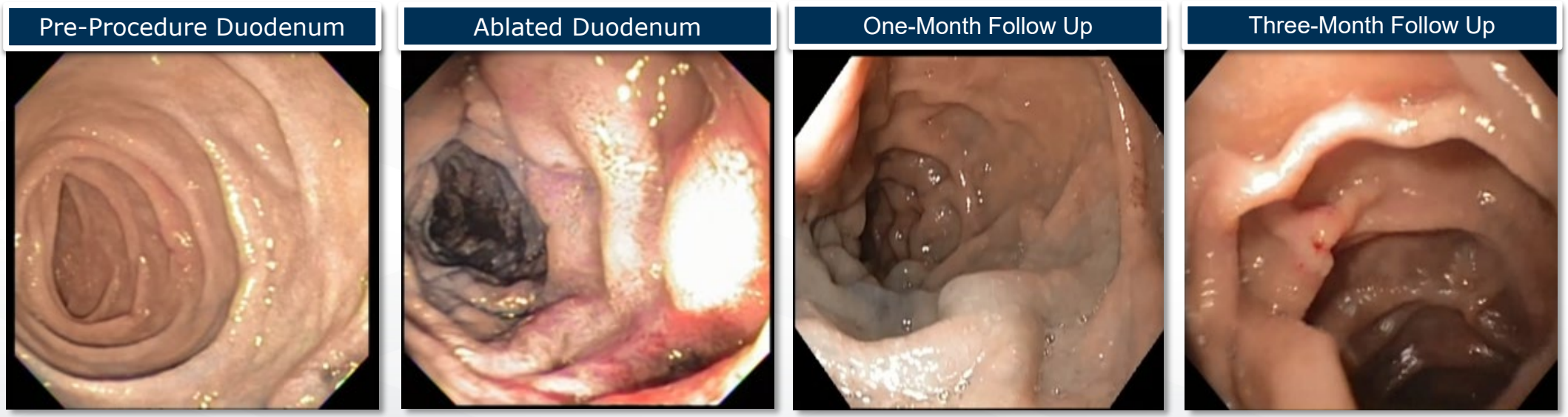
- 4 did not receive DMR
  - *2 failed screening endoscopy*
  - *1 tortuous anatomy*
  - *1 anticipated prolonged anesthesia duration*
- 1 patient anti-GAD+ (treated & followed for safety, not efficacy)

Safety & Tolerability

- Procedure well tolerated with minimal GI symptoms
- No difficulty tolerating oral diet in the days after the procedure
- AEs generally mild in severity & tended to occur in immediate post-procedure period
- Most common AE was transient abdominal pain due to air insufflation/endotracheal intubation (8/40 patients)
- Most significant AE was duodenal stenosis (3/40 patients)
  - All cases occurred within the first 6 weeks post-procedure
  - Non-emergent and resolved with endoscopic balloon dilation
  - No new cases after procedure and device improvements
- No GI bleeds, perforation, pancreatitis, malabsorption
- No severe hypoglycemia

Safety & Tolerability: Endoscopy Findings

- Follow up endoscopies at 1 & 3 months showed intact mucosa with unremarkable mucosal plicae, indicating full mucosal healing



Efficacy

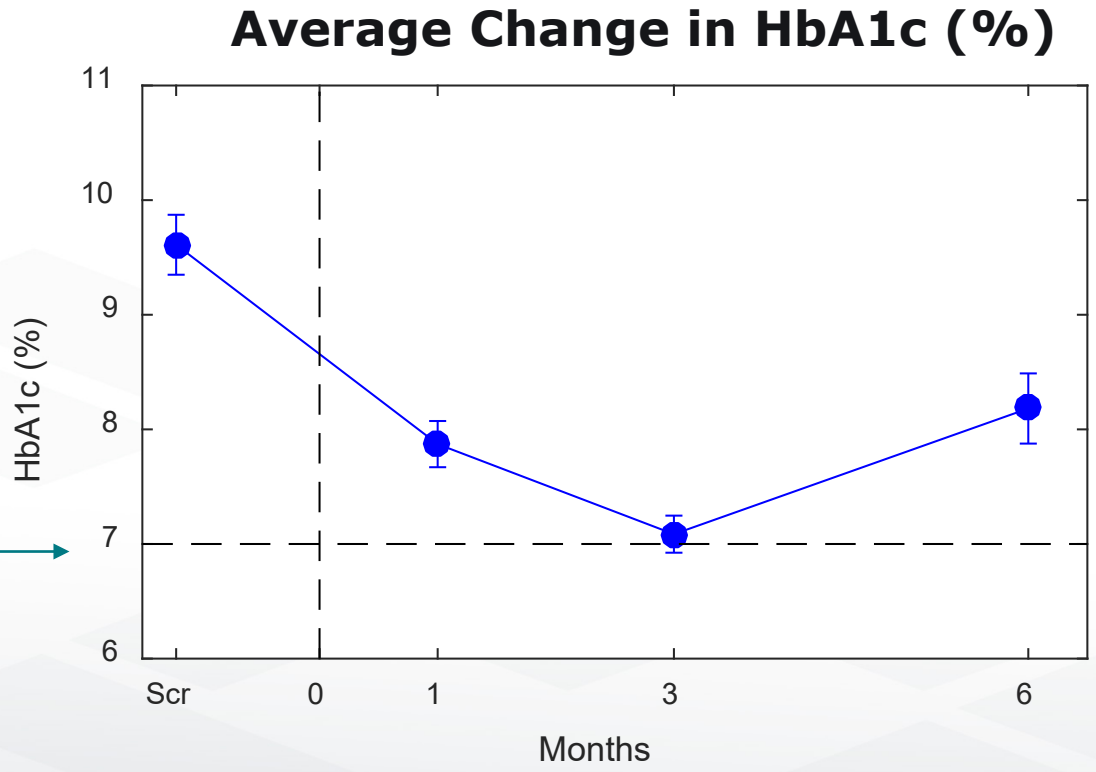
- DMR procedure elicited improvements in glycemia (meal challenge plasma glucose, HbA1c)
  - HbA1c reduction of 1.2% at 6 months in efficacy cohort (n=39)
- More robust glycemic effect observed among long segment cohort (n=28)
  - 2.5% reduction in baseline mean HbA1c at 3 months post-procedure vs 1.2% with short segment DMR ($p<0.05$)
- Modest weight reduction, but no correlation between weight loss and glycemic improvement
- Robust reduction in hepatic transaminase levels (AST, ALT)

Overview: Changes in Metabolic Parameters in LS Cohort

	Screening	1 Month	3 Month	6 Month	Normal*
HbA1c - %	9.6±1.4	7.9±1.1	7.1±0.9	8.2±1.6	4.0-6.0
Weight - kg	86±11	82±11	83±12	85±11	--
ALT - IU/L	40±23	32±17	27±14	27±12	≤ 38
AST - IU/L	32±17	27±11	23±8	22±6	≤ 40

**Normal range based on ranges reported by lab that processed the samples.*
All numbers reported as mean ± SD.

DMR Improves Glycemic Measures: Long Segment Cohort (n=28)



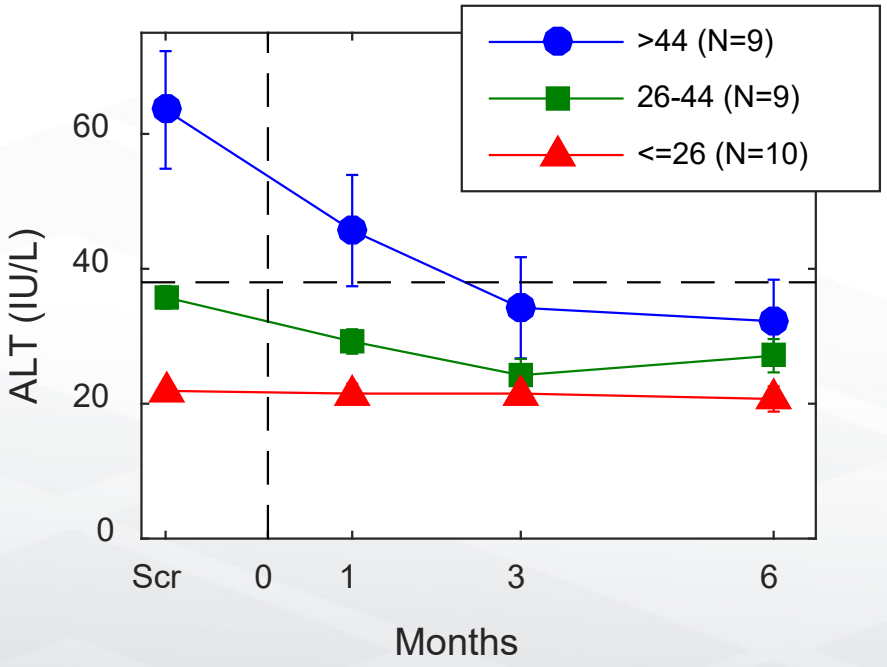
ADA/ EASD target

- HbA1c reduction of 1.4% at 6 months ($p<0.001$ for change from screening)
- 14/28 patients had reduction in concomitant anti-diabetic medications post-procedure

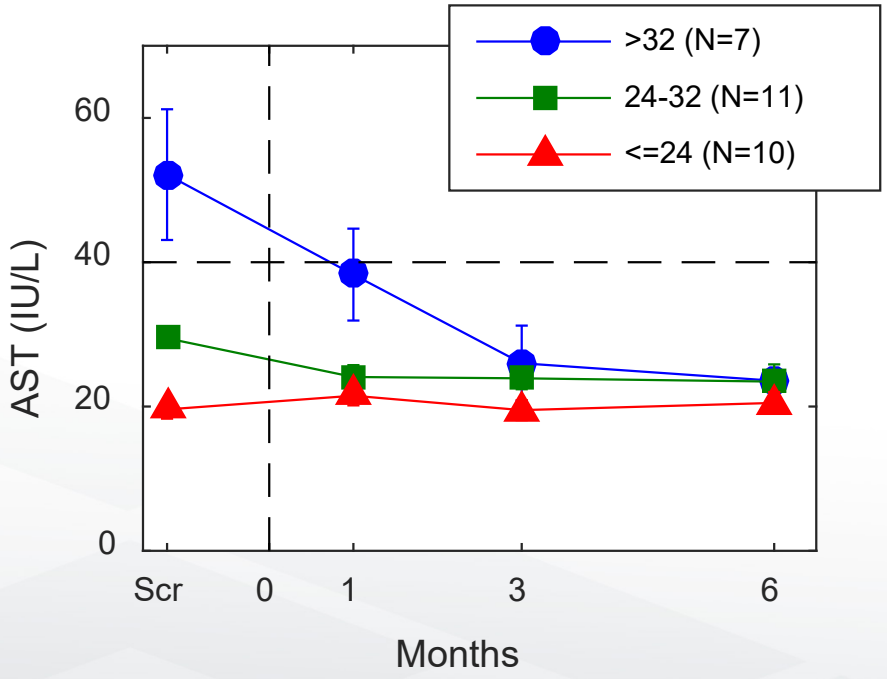
Hepatic Transaminase Changes by Tertile

- Lowering of ALT and AST more pronounced in subjects with elevated pre-treatment levels

ALT Tertiles
LS Cohort (n=28)



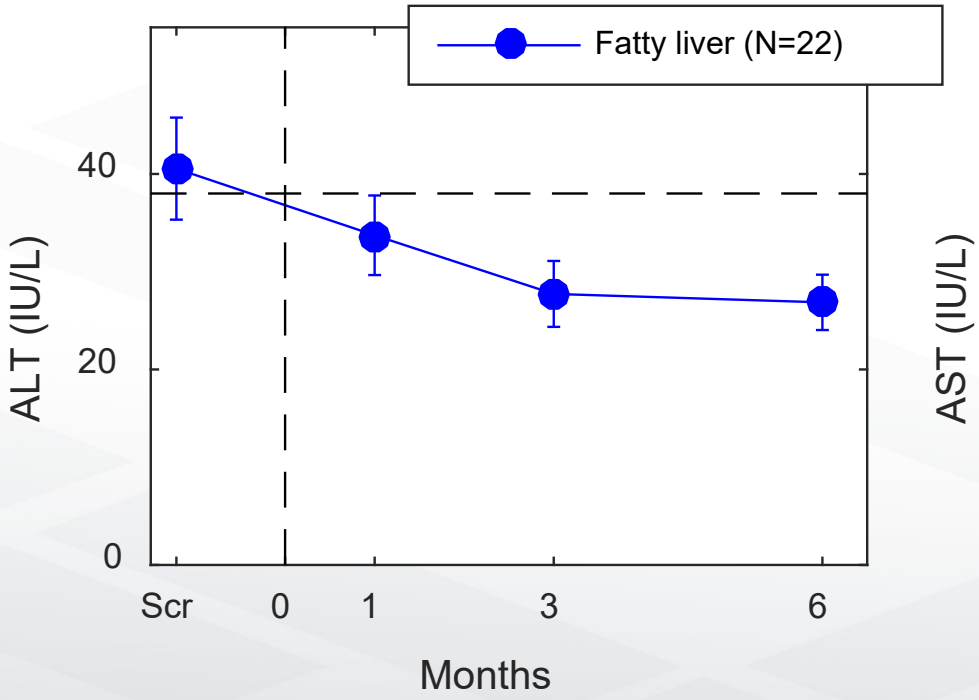
AST Tertiles
LS Cohort (n=28)



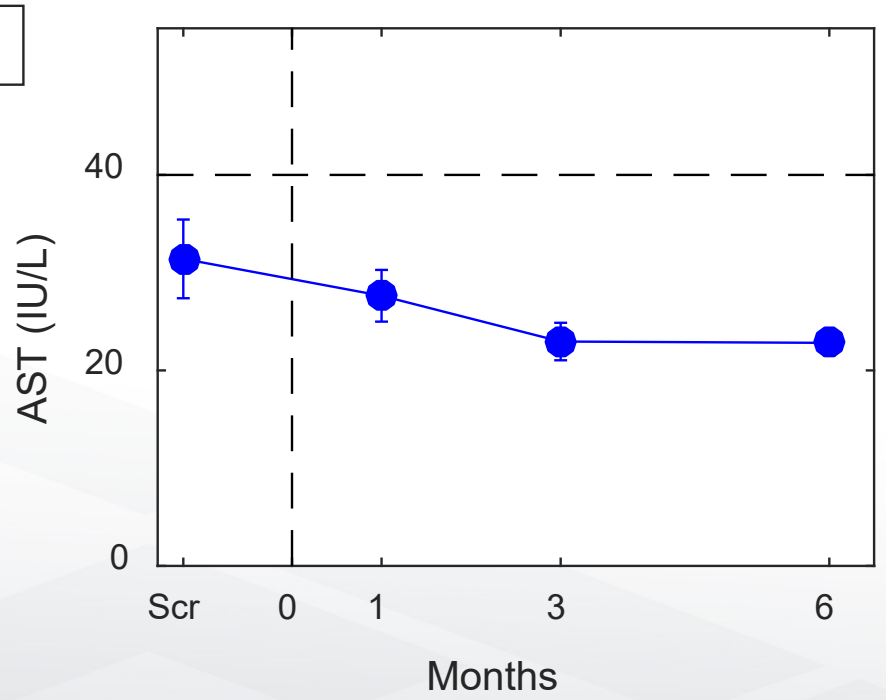
DMR Reduced ALT and AST in Patients with Radiological Evidence of NAFLD

- Metabolic benefits seen in 22 patients with incidental finding of fatty liver on ultrasound

ALT in LS Subjects with Fatty Liver



AST in LS Subjects with Fatty Liver



Conclusions

- DMR improves metabolic control in T2D patients, including a robust and sustained lowering of hepatic transaminase levels
- DMR offers the potential for a single-point intervention that improves both glycemia and fatty liver
- Further study in patients with fatty liver disease is warranted