KING'S HEALTH PARTNERS
DIABETES, ENDOCRINOLOGY, OBESITY

Pioneering better health for all

Endoscopic Duodenal Mucosal Resurfacing

IN PARTNERSHIP WITH

American Diabetes Association.

APRIL 8-10, 2019, NEW YORK CITY

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KING'S College LONDON

NHS Guy's and St Thomas' NHS Foundation Trust

NHS King's College Hospital NHS Foundation Trust

NHS South London and Maudsley NHS Foundation Trust

Conflict of Interest Disclosure

Dr. David Hopkins, FRCP

Employment: King's College Hospital NHS FT/ King's Health Partners

Paid Consultancy and speaking engagements:

- Advisory board work for Sanofi, Novo Nordisk, Roche
- Speaking engagements for Sanofi, Novo Nordisk, Eli Lilly AstraZeneca, Fractyl, Sunovion

Research Support to King's Health Partners: Novo Nordisk, Fractyl

Unpaid – charitable sector work:

Chair of Council of Healthcare Professionals, Diabetes UK

Agenda

- Duodenal mucosal hyperplasia
- Duodenal Mucosal Resurfacing
- Clinical Effectiveness
- Safety and Tolerability
- Future Directions

Background

There is a broad and increasing evidence base that the duodenum has a key role in glucose homeostasis:

- Evidence from bariatric surgical procedures – with profound improvements in insulin sensitivity and incretin secretion occurring early after surgery
- Evidence from animal studies showing improved glycaemia after duodenal exclusion
- Evidence from morphological studies demonstrating duodenal mucosal hyperplasia and changes in incretin secreting neuroendocrine cell populations in both animal models and in human studies of newly diagnosed diabetes.
- Evidence of changes in incretin secretion associated with morphological changes following high fat feeding in rodents

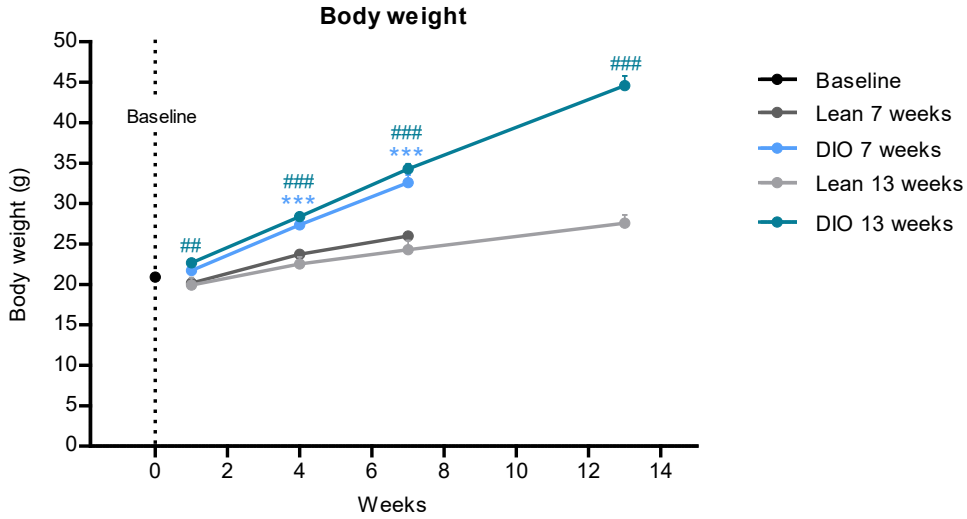
Mingrone et al NEJM 2012 Theodoorakis Am J Phys, Gniuli , Diabetologia, 2010

Animal models – diet induced obesity (DIO)

Mice fed a chow (lean) or high fat 'DIO' (diet induced obesity) , 60% fat, 20% sugar) diet

Sacrificed at 7 weeks or 13 weeks

Endpoints: Serology, metabolic profile, stereology, RNAseq, liver steatosis assessment



Group mean body weight (g) +SEM during the study period. ***P<0.001 vs. Lean 7 weeks. ##P<0.01, ###P<0.001 vs. Lean 13 weeks. Two-way RM ANOVA, Bonferroni post hoc test.

Ghosh, et al.. Poster, ADA Orlando, Florida, USA, June 2018.

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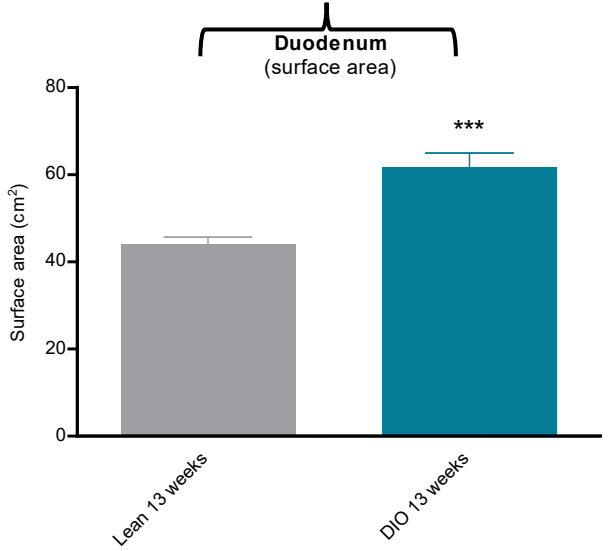
Increased duodenal mucosal volume and liver weight in DIO mice

50% increase in duodenal surface area in DIO mice compared to lean[4]

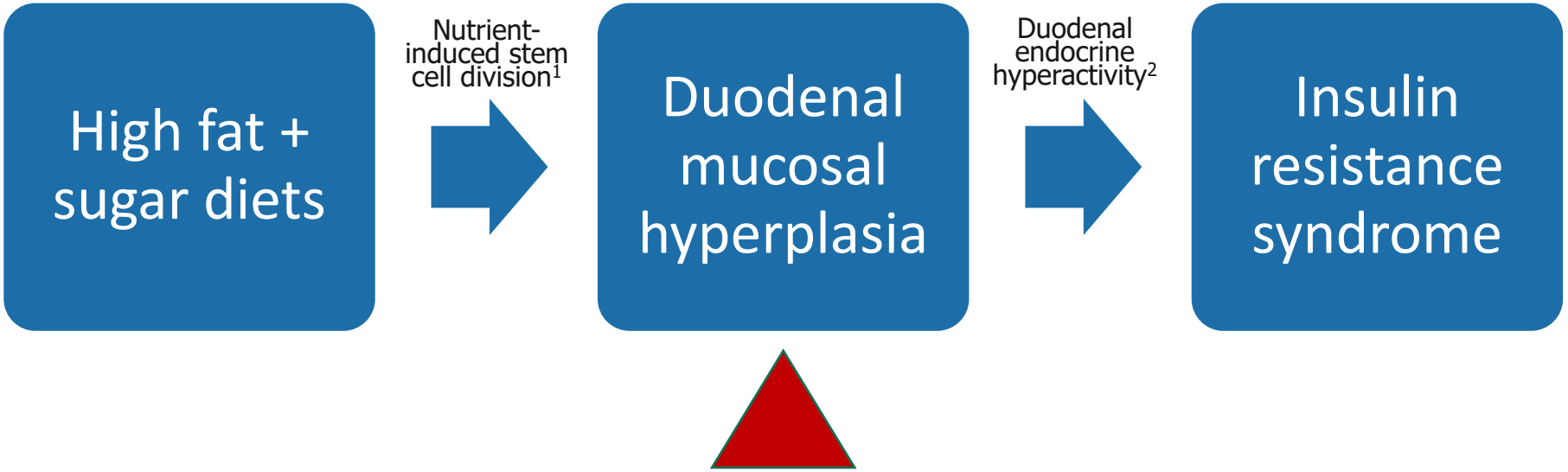


Mean total duodenal surface area +SEM estimated by stereology in mice following consumption of regular chow (lean) or high fat diet (DIO) for 7 or 13 weeks. *P<0.05 vs. Lean 13 weeks, unpaired t-test.

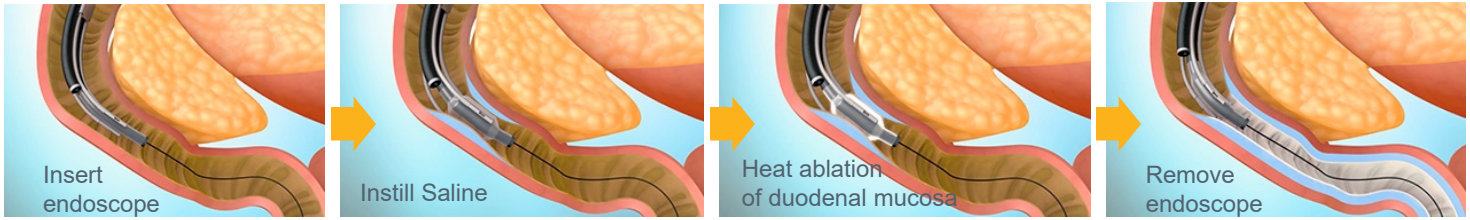
Measure, mean (SEM)	Lean- 13 wk	DIO - 13 wk	P- value
Liver weight**, g	0.96 (0.02)	1.4 (0.1)	<0.001
Duodenal weight**, mg	152 (3.4)	172 (5.9)	<0.001
Duodenal mucosal volume‡, mm^3	120 (2.4)	130 (3.7)	<0.05
Duodenal surface area‡, cm^2	44.0 (1.6)	61.6 (3.4)	<0.001

Mean Total Whole Intestine Volume +SEM estimated by stereology in mice fed a Lean vs DIO after 13 weeks **p<0.01 vs. Lean 13 weeks, unpaired t-test

Putative role of duodenal mucosal hyperplasia in metabolic disease



Revita™ DMR Procedure



- Minimally invasive, outpatient endoscopic procedure using a balloon catheter
- Procedural Steps
  - Targets duodenal mucosa between Ampulla of Vater and Ligament of Treitz
  - **Submucosal lift:** expand sub-mucosal space with saline injection to **create a protective thermal barrier**
  - **Hydrothermal ablation** of hyperplastic duodenal mucosa
  - Leads to healthy epithelial regrowth within 4-6 weeks
  - Median procedure duration 45 minutes
- Patients discharged as a day case and transition from liquid to solid diet post procedure over several days

Rajagopalan, H. et al. Diabetes Care 2016; 39:1-8
Cherrington, A. et al. Gastrointest Endoscopy Clin N Am. 2017;27:299–311
Galvao, N. et al. Video GIE 2016;1(1):10 – 11,

First-in-Human Study

- Single center,single arm study in 44 T2 diabetes patients
- DMR procedure:
  - Ablation of short segment (SS; mean 3.4 cm) or long segment (LS; mean 9.3 cm) of duodenal mucosa
- 2 week graduated diet all patients immediately post-procedure
  - (liquids → soft → puree)
- No specific protocol for management of anti-diabetic medications

Patient characteristics	N=44
Age, yrs (range)	53.3 +/- 7.5 (38-65)
Gender, n (%)	
Female	16 (36.4)
Male	28 (63.6)
Weight, kg	84.5 +/- 11.9
Height, cm	165.2 +/- 8.5
BMI, kg/m^2	30.9 +/- 3.5
Systolic BP, mmHg	122.1 +/- 14.4
Diastolic BP, mmHg	76.9 +/- 8.2
Duration T2D, yrs (range)	5.7 +/- 2.2 (1-9)
HbA1c, %	9.5 +/-1.3
FPG, mg/dL %	184 +/-58
Oral Anti-diabetic Rx	
Metformin, n (%)	44 (100)
Sulfonylurea, n(%)	20 (44)

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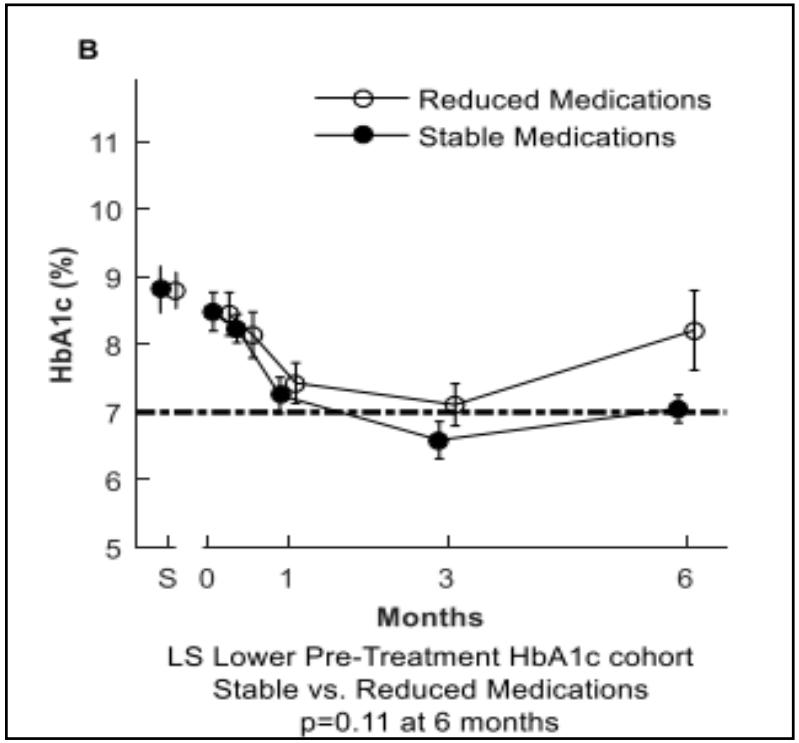
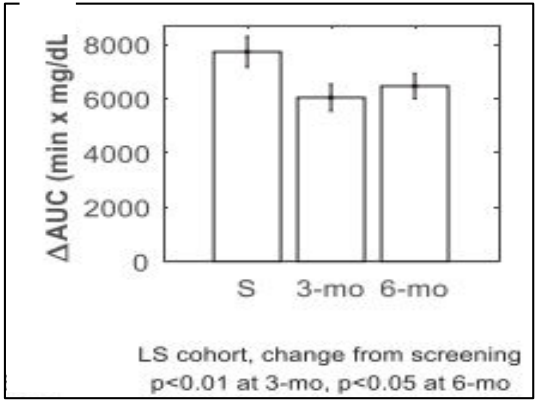
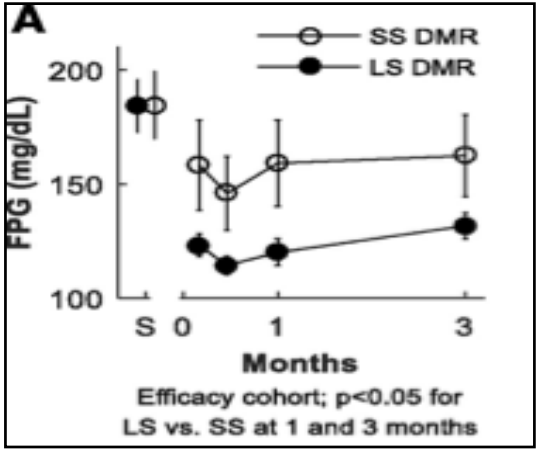
First-in-Human Study: Glucose control





Reductions in post-prandial glucose excursion sustained at 3 and 6 months post-DMR procedure

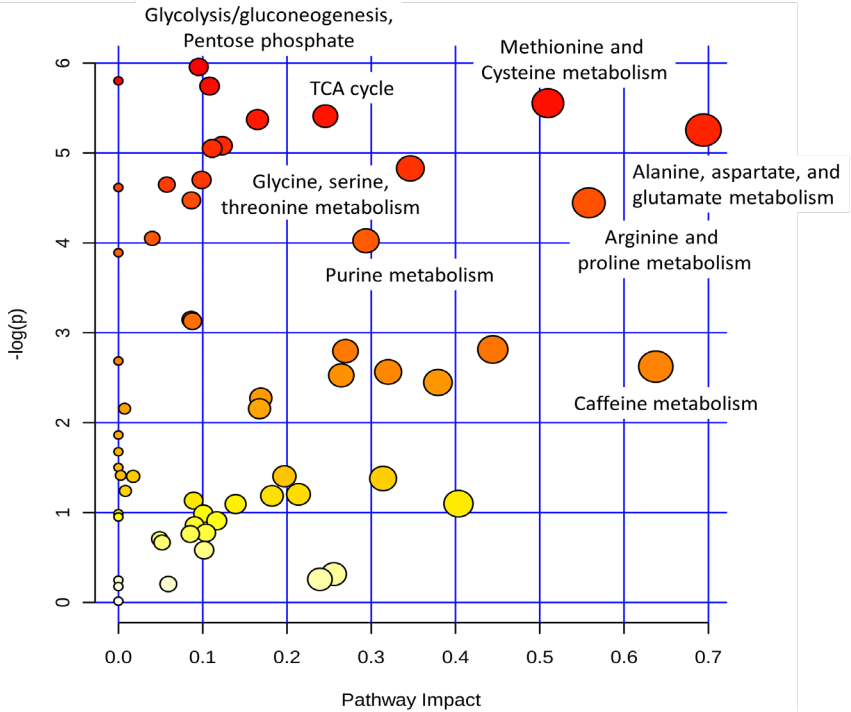


"Ablation length" dose-dependent efficacy of DMR

First-in-Human Study: Metabolomic changes

FIH Study: open-label, single-center trial

- DMR-treated
- Metabolomic analysis conducted on sub-cohort (n=14 patients) fasting and post-prandial plasma samples at **baseline and 12 wks**
- Age 51±2 years; HbA1c 10.2 ± 0.3%
- Data analyzed using Metaboanalyst software
- Systemic metabolome interrogated using gas-chromatograpy/mass spectrometry and liquid chromatography/mass spectrometry (Metabolon^{inc})



DMR treatment elicited:

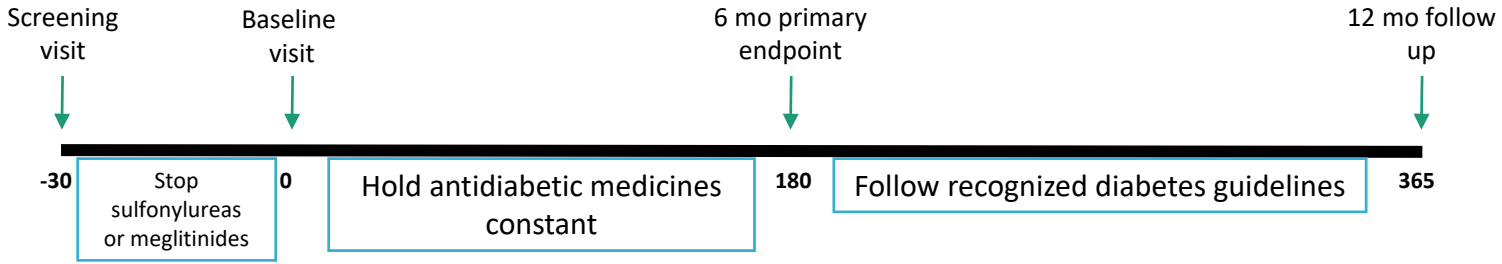
- ↓ lipotoxic stress
- ↓ gluconeogenic drive
- ↓ decreased Warburg Effect - ↓ pro-oncogenic metabolic profile
- ↑ Increased markers of improved mitochondrial function, lipid oxidation

deGravell G, et al. Poster presented at: 4th Paris NASH meeting;; Paris, France.

Revita-1: First international multicenter study

Patients with poorly controlled T2D despite > 1 oral anti-diabetic drug
No GLP-1 or insulin
Ages 28-75
HbA1c 7.5-10%
Primary endpoint: Change in HbA1c from baseline to 24 weeks
Secondary endpoints: liver enzymes & cardiometabolic parameters

Patient characteristics	N=47
Age, years (range)	55 (31-69)
Gender, n (%) male, female	30 (64); 17 (36)
Duration of type 2 diabetes, years	6 (0.1 – 12)
Weight (kg)	91 ± (13)
BMI (kg/m^2)	31.6 ± (4.3)
HbA1c (%)	8.6 ± (0.8)
Oral antidiabetic medications	
Metformin, n (%)	43 (91)
DPP-4 inhibitor, n (%)	30 (14)
SGLT-2 inhibitor, n (%)	5 (11)
Pioglitazone, n (%)	1(2)



Van Baar et al ADA 2018 (manuscript in review)

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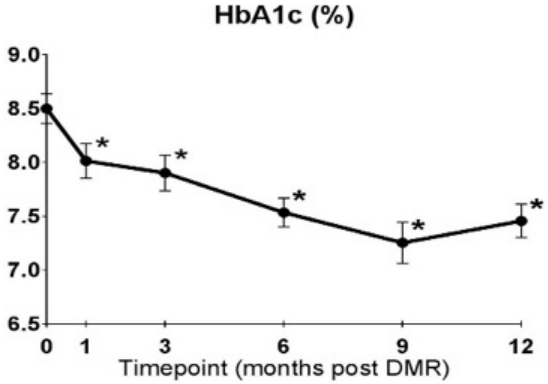
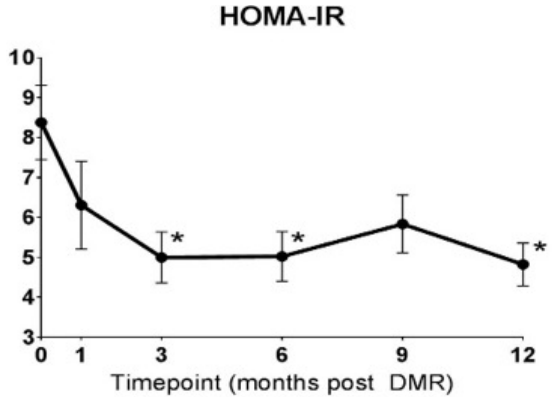
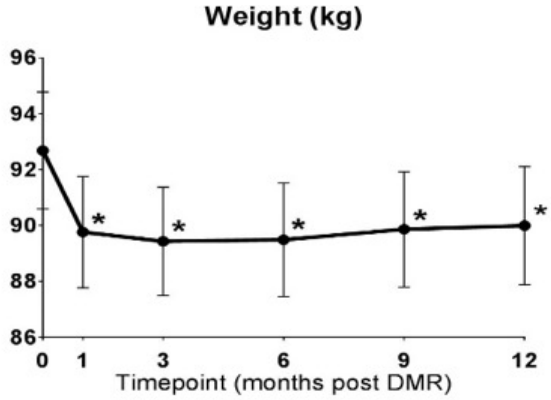
Revita-1: Impact on HBA1c and insulin resistance



Sustained HbA1c reductions in patients despite net medication reductions ($p<0.01$)



Sustained improvement in measures of insulin resistance (HOMA-IR) tie to core mechanism of action

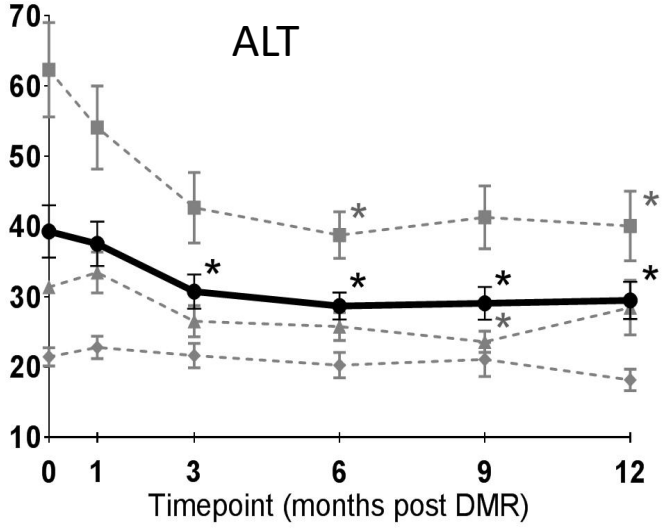


Sustained weight loss without any prescriptive lifestyle intervention program

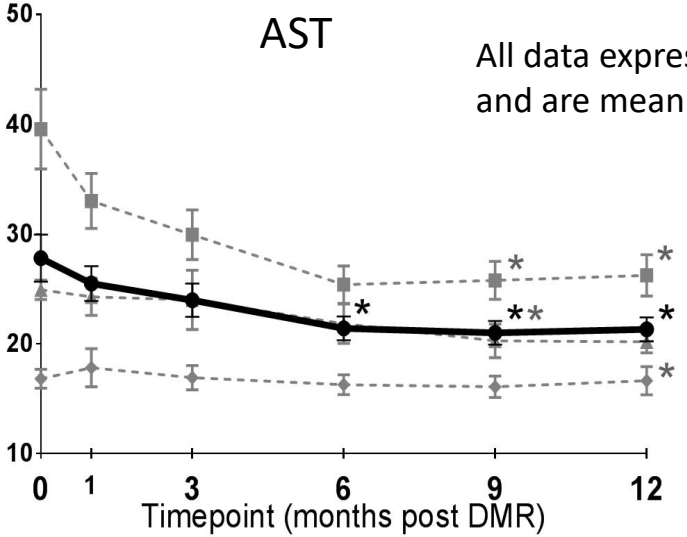
Van Baar et al ADA 2018 (manuscript in preparation)

Revita-1: Impact on liver transaminases

12 months post DMR procedure, significant improvement in transaminases:



Mean reduction: -10 ± 2 (p = 0.005)



Mean reduction: -6 ± 2 (p = 0.002)

All data expressed in U/l and are mean +/- SEM

Dotted grey lines represent ALT and AST levels divided into tertiles based on baseline levels (squares: high, triangles: middle, diamonds: low baseline).

Van Baar et al ADA 2018 (manuscript in review)

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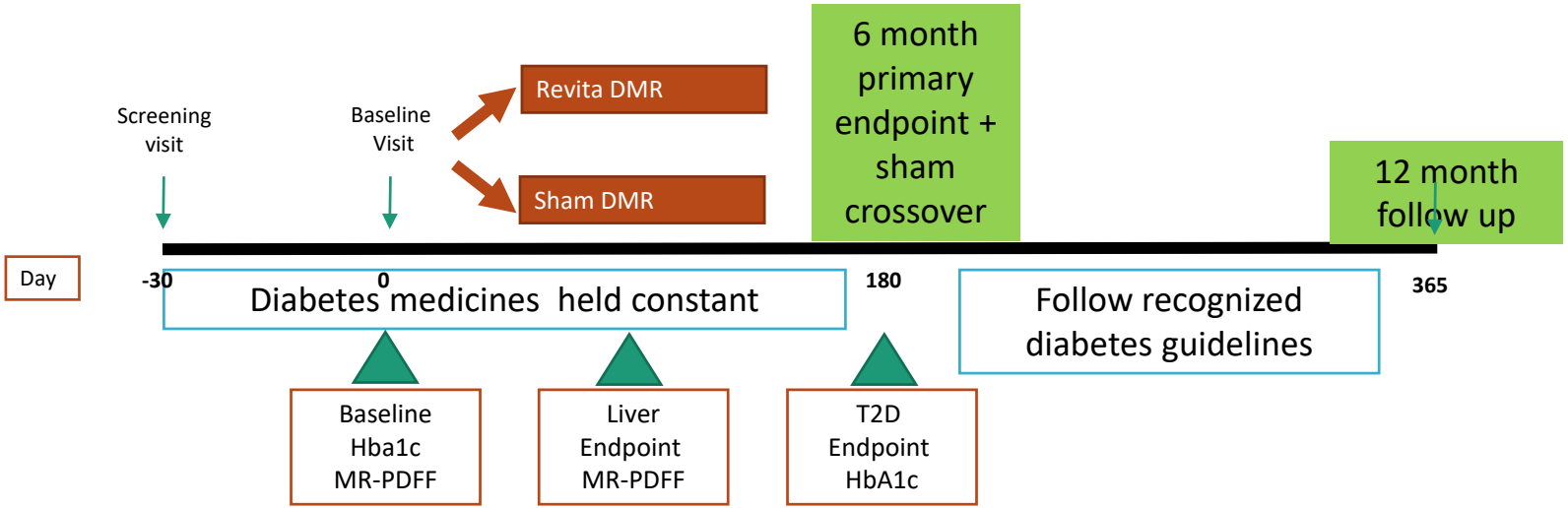
Revita-2: multicenter sham controlled study

- Patients with poorly controlled T2D despite > 1 oral anti-diabetic drug - Randomized 1:1, double blind, sham controlled
- No GLP-1 or insulin; Ages 28-75; HbA1c 7.5-10%
- Primary endpoints: Change in HbA1c at 6 months; change in liver MRI-PDFF at 3 months
- Secondary endpoints: cardiometabolic parameters and mechanistic sub-studies
- 31 open label training cases + 108 randomized and blinded cases



Revita-2: preliminary results – open label cohort

- Main sham controlled study in progress – recruitment completed and 6 month results due Q3 2019
- Preliminary 12 week metabolic and MRI data on 24 open label 'training' cases presented at WCITD 2019

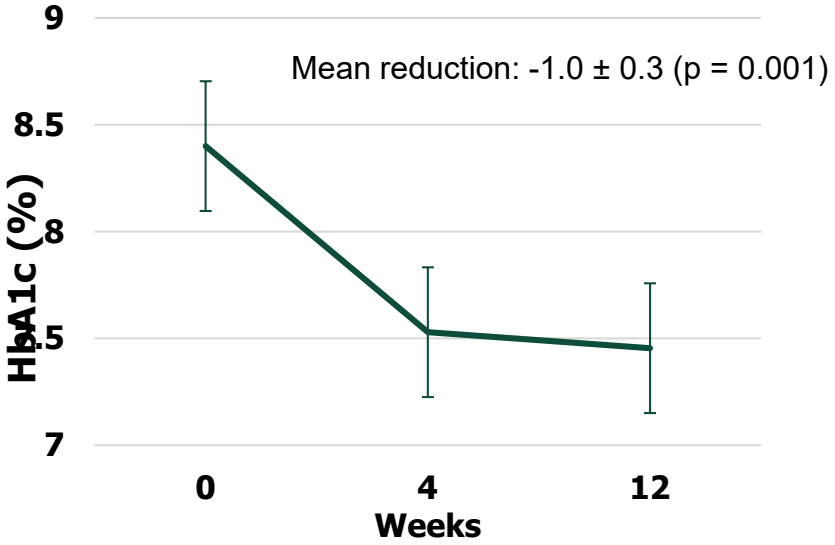
Patient characteristics	N=24
Age, years	55 (43-69)
Gender, n (%) male, female	17 (71); 7 (29)
Duration of type 2 diabetes, years (range)	8 (0.4 - 17)
Weight (kg)	89.7 ± (1.9)
BMI (kg/m^2)	31.6 ± (3.0)
HbA1c (%)	8.4 ± (0.17)
Oral antidiabetic medications	
Metformin, n (%)	23 (96)
Sulfonylurea, n (%)	15 (63)
DPP-4 inhibitor, n (%)	9 (38)
SGLT-2 inhibitor, n (%)	5 (21)

Hopkins, et al. Poster presentation WCITD New York City, April 2019

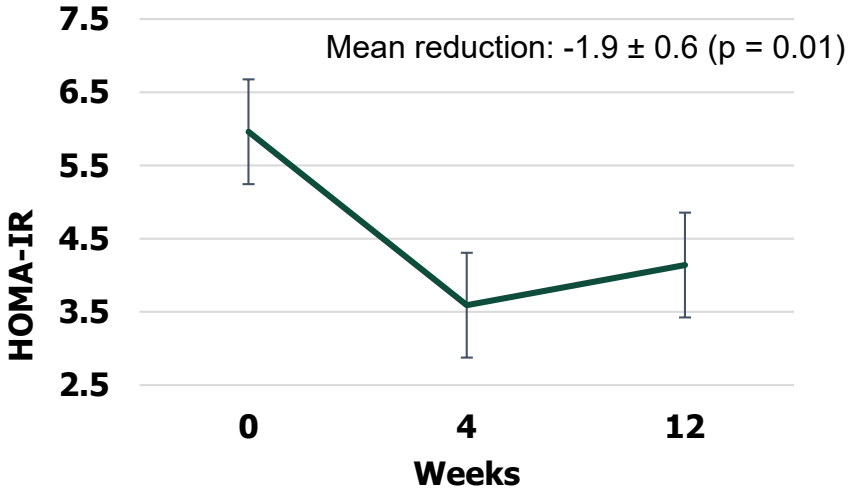
Revita-2: open label cohort

12 weeks post DMR procedure

HbA1c (%) n=24



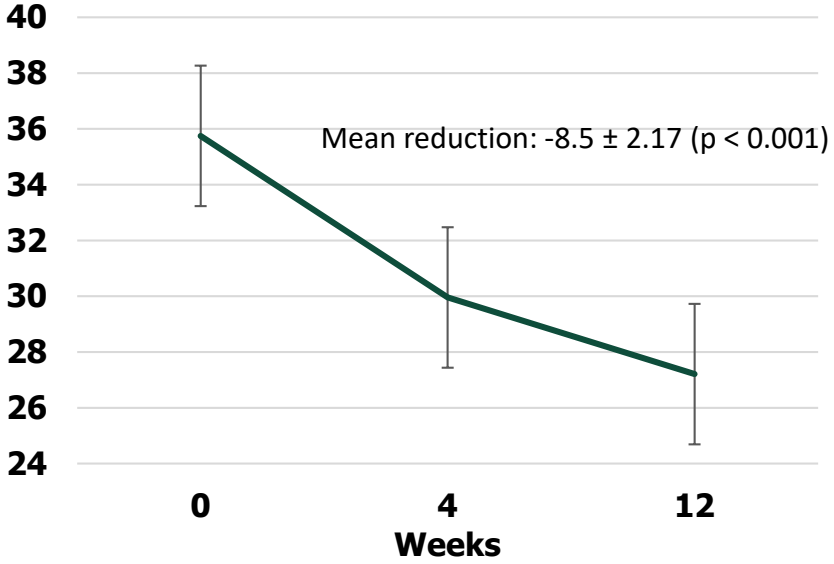
HOMA-IR n=22



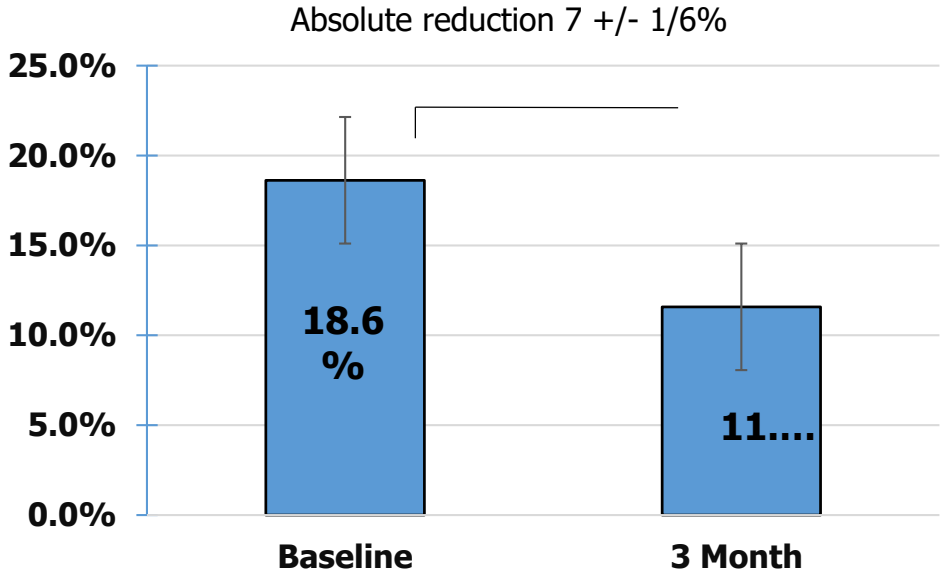
Revita-2: open label cohort

12 weeks post DMR procedure:

ALT (U/L) n=24



Reduction MRI-PDFF n=17



MRI-PDFF* data are from a subset of 17 subjects, whom had excess baseline liver fat (i.e >5%)

Other ongoing Revita clinical studies

Study	Status	Sample Size	Design	Key Questions
NASH	Initiated 4Q17	N= 14 Uncontrolled open label	Study in biopsy-confirmed NASH	Can DMR improve liver fibrosis, glycemic measures?
INSPIRE	Initiated 4Q17	N=16 Uncontrolled open label	Study in late stage insulin treated T2D	Can DMR+GLP1 allow withdrawal of insulin Rx?
DOMINO	Initiated 2Q18	N=30 Randomized Blinded	Study In women with PCOS	Can DMR improve insulin sensitivity and ovulation in women with PCOS?

Safety and Tolerability

Over 200 DMR treated subjects in FIH, Revita-1, and ongoing Revita-2 studies

No Unanticipated Adverse Device Effects (UADEs) reported

3 episodes stricture in FIH – using earlier version of catheter

Single episode of perforation since redesign – operator rather than device related

No device or procedure related deaths reported

No incidence of pancreatitis, gastro-intestinal bleeding or incidence of injury to surrounding organs

No incidence of procedure-related infection (no systemic infection, no abscess, no sepsis)

Most commonly reported AEs tended to be:

- mild in severity
- reported within the first month of the procedure.
- associated with the GI system post procedure
- infrequent hypoglycemia reported – only in presence of sulfonylurea treatment

Summary

Early Clinical Studies of Revita DMR have shown

1. Consistent improvements in glycemic control in type 2 diabetes
2. Evidence of sustained metabolic response to at least 12 months post-procedure
3. Evidence of insulin sensitizing mode if action with ↓ HOMA-IR, and consistent metabolomic signature
4. Evidence to support positive impact on liver
5. Excellent safety profile of procedure

These data support considerable potential for clinical utility, particularly in:

1. Type 2 diabetes
2. NAFLD/ NASH
3. Other insulin resistant states

Extensive further data due 2019-2020 which will further define place of DMR in clinical practice