DUODENAL MUCOSAL RESURFACING (DMR) COMBINED WITH GLP-1 RECEPTOR AGONISM MAY ELIMINATE INSULIN TREATMENT WHILE MAINTAINING GLYCEMIC CONTROL AND IMPROVING OVERALL METABOLIC HEALTH IN TYPE 2 DIABETES

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Background

Systemic hyperinsulinemia, resulting from background insulin resistance and exogenously administered insulin, contributes to impaired metabolic health in many patients with type 2 diabetes (T2D). Altered metabolic signaling from the gut is thought to play a pathophysiological role in T2D. Duodenal Mucosal Resurfacing (DMR) is an endoscopic procedure that administers hydrothermal ablation to the duodenum. It has been shown to improve glycemic control and insulin sensitivity in T2D patients on oral glucose lowering medication.

Objective

To assess feasibility and efficacy of halting daily insulin therapy in insulin treated T2D patients and instead treating with a combination of a single DMR procedure, GLP-1 agonism and lifestyle counselling.

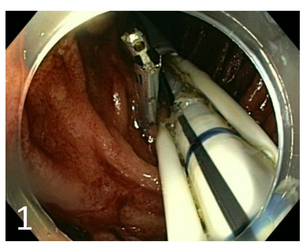
Methods

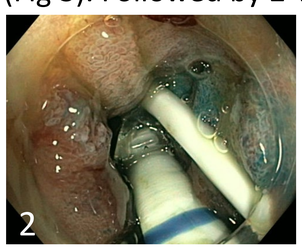
Study Single arm, single center, open label pilot study

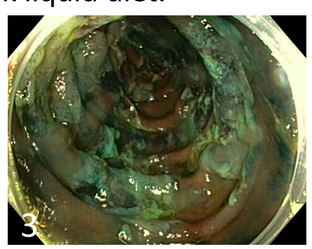
Subjects 16 T2D patients using long-acting insulin once-daily(25-75 years, HbA1c ≤64 mmol/mol; BMI 24-40kg/m^2; c-peptide ≥0.5 nmol/l)

Intervention Discontinuation of insulin, replaced by a combination of:

1. **Endoscopic DMR procedure:** catheter based, post-papillary (clip, Fig 1) duodenal mucosal lifting (Fig 2) and circumferential hydrothermal ablation over 9-10 cm (Fig 3). Followed by 2-week liquid diet.







2. **GLP-1 antagonist** liraglutide is introduced at 2 weeks after the DMR procedure with a stepwise dose increase to 1.8 mg/day.
3. **Lifestyle counseling and tailored diet** by a dedicated dietician.

Follow-up measurements (baseline and 6 months): HbA1c, Fasting Plasma Glucose [FPG], insulin, C-peptide, HOMA-IR, liver enzymes, liver MR (proton density fat fraction), mixed meal test (MMT) and DEXA-scan

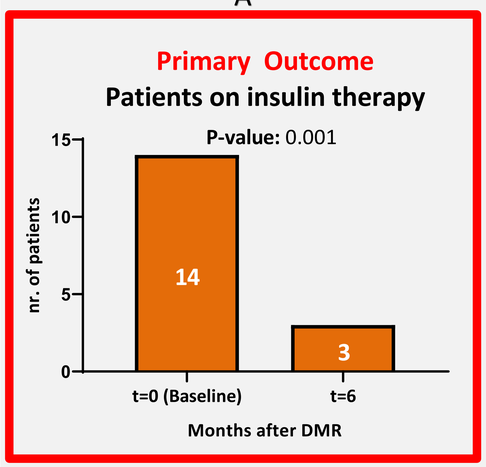
Primary endpoint **Percentage of patients free of insulin therapy** and Hba1c <59 mmol/mol at 6 months.

Results

Currently sixteen patients have initiated this combination treatment approach. Fourteen patients have reached the primary endpoint and in eleven (79%) adequate glucose regulation has been maintained despite discontinuation of insulin therapy.

In these eleven patients parameters of metabolic health (HbA1c, HOMA-IR, weight) improved significantly at 6 months follow-up (see Table). Mixed Meal Test results indicate significant decreases in postprandial glucose excursions(Figure B). Preliminary liver MR reports reduced fat fraction at 6 months(Figure C) and ALT improved significantly at 6 months follow-up(see Table).

A



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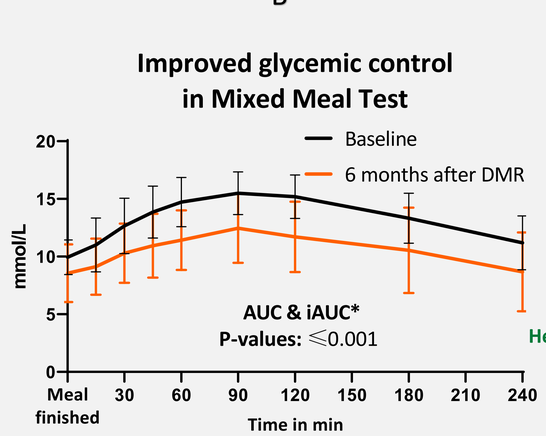

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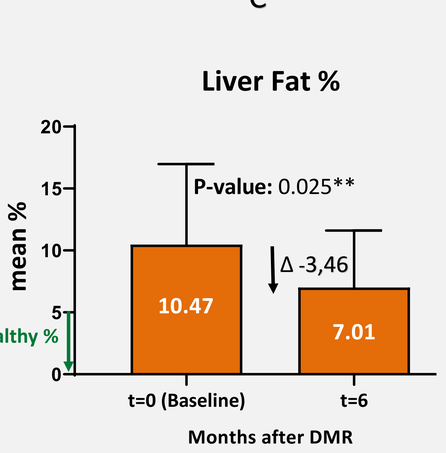

Measurement	Baseline	6 months	P-value	Δ From baseline
N	11	11		
HbA1c (SD;mmol/mol)	58 (5)	52 (6)	0.011	5.55 (5.9)
HOMA-IR (SD;Assessment of Insulin Resistance)	9.1 (5.5)	3.2 (3)	0.002	5.86 (4.5)
Weight (SD;kg)	97 (23)	90 (21)	≤ 0.001	7.62 (3.4)
Liver				
ALT (SD;IU/L)	25.2 (8)	19 (6)	0.022	5.7 (7.0)
Fat (SD;%)	10.47 (6.5)	7.01 (4.6)	0.025	3.46 (4.1)

*n=11 AUC: Area Under the Curve, iAUC: Incremental Area Under the Curve

**n=10 due to exclusion of one patient that didn't undergo the second MRI due to claustrofobia

Conclusion

Our study suggests that single endoscopic DMR, combined with GLP-1 receptor agonism (liraglutide) and lifestyle counseling, may effectively eliminate the need for insulin therapy in T2D while improving glucose regulation and, more importantly, improving overall metabolic health. This novel combination treatment offers real promise to many insulin treated patients but further controlled studies are necessary.