Single arm, single center, open label pilot study to Curve the Discontinuation of insulin, replaced by a combination of: B
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Incremental 16 T2D patients using long-acting insulin once-daily (25-75 years, that of liraglutide is introduced at 2 weeks after the DMR exclusion Area Under by a dedicated dietician. didn't Δ From DMR procedure, GLP-1 agonism and lifestyle counselling. treated T2D patients and instead treating with a combination of a single intervention Discontinuation of insulin, replaced by a dedicated 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 counselling 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.

**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/m²; c-peptide ≥0.5 nmol/l)

**Intervention** Discontinuation of insulin, replaced by a dedicated 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 a 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 counselling 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).

**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.

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