

Early clinical experience of duodenal mucosal resurfacing (DMR), a new endoscopic approach to treating type 2 diabetes



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Abstract

INTRODUCTION: Bariatric surgery improves glycemia in type 2 diabetes (T2D). Exclusion of nutrient contact with an abnormal duodenal surface may be a key mechanistic contributor, involving potential weight-independent changes in insulin sensitivity. DMR, a minimally invasive, upper endoscopic procedure involving thermal ablation of the duodenal mucosa, also appears to elicit glycemic improvements in T2D. We report the first-in-human clinical experience with DMR. **OBJECTIVES:** Assess procedural safety and glycemic measures for 6 months after a single DMR procedure in patients with T2D and HbA1c > 7.5% on at least 1 oral anti-diabetic agent. **METHODS:** Using novel balloon catheters, DMR was conducted on varying lengths of duodenum in anesthetized patients at a single center (Santiago, Chile). **RESULTS:** A total of 39 patients were treated (baseline HbA1c: 9.5%): 28 had ablation of a long-duodenal segment (LS-DMR; ~9.3 cm treated) and 11 had short-segment ablation (SS-DMR; ~3.4 cm treated). Baseline HbA1c was reduced by 1.2% at 6 months in the full cohort. More potent glycemic effects were observed among the LS-DMR cohort, who experienced a 2.5% reduction in baseline mean HbA1c at 3 months post-procedure vs 1.2% with SS-DMR (p<0.05). Excluding patients who reduced concomitant anti-diabetic medication post-procedure, LS-DMR among patients with a baseline HbA1c of 7.5-10% (n=8) lowered HbA1c from a mean of 8.8% to 7.1% at 6 months (p<0.05), accompanied by a modest weight reduction of 2.3 kg. Overall, DMR was well tolerated with minimal gastrointestinal symptoms post-procedure. Three patients experienced duodenal stenosis treated successfully by balloon dilation. **CONCLUSIONS:** To date, single procedure DMR elicits a robust improvement in glycemia in T2D with acceptable safety and tolerability. Further examination of safety, efficacy, durability and possible mechanisms is needed.

Introduction

- Interventions that prevent nutrient contact with the duodenum (i.e. bariatric surgery, intra-luminal sleeve) improve glycemic control in T2D
- Exclusion of nutrient contact with an abnormal duodenal surface may be a key mechanistic contributor, involving potential weight-independent changes in insulin sensitivity
- Duodenal mucosal resurfacing (DMR) is a minimally invasive, endoscopic procedure that potentially offers similar metabolic benefit through ablation of the duodenal mucosa surface
- This was a first-in-man, proof-of-concept study to assess procedural safety and glycemic control after endoscopic DMR

Methods

- Adults with poorly controlled T2D (HbA1c > 7.5% on at least 1 oral anti-diabetic agent) underwent ablation of a short segment (SS-DMR; <6 cm ablated) or long segment of duodenum (LS-DMR; >9 cm ablated) using novel balloon catheters (Revita™ DMR System, Fractyl Laboratories, Waltham, MA, USA)
- Procedural steps: duodenal sizing → saline expansion of sub-mucosa → hydrothermal ablation of superficial mucosa
- All procedures were performed at a single center in Santiago, Chile by trained endoscopists
- 2-week, low calorie, graduated diet for all patients post-procedure (liquids → soft → puree)
- No specific recommendation on management of anti-diabetic medication post-procedure

Results

- 44 consecutive patients were enrolled, 39 treated
 - 28 LS-DMR (mean length ablated: 9.3 cm)
 - 11 SS-DMR (mean length ablated: 3.4 cm)
- Baseline (mean): age=53.3 y; weight=84.5 kg; HbA1c=9.5%; fasting plasma glucose (FPG)=184 mg/dL
- 5 excluded patients: 4 did not receive DMR (2 failed screening endoscopy, 1 tortuous anatomy, 1 procedure duration), 1 excluded for anti-GAD +

Safety & Tolerability

- Procedure well tolerated with minimal GI symptoms
- 3 patients experienced duodenal stenosis that required endoscopic balloon dilation, with good resolution
- No GI bleeds, perforation, pancreatitis, evidence of malabsorption or hypoglycemia
- Follow up endoscopies indicate full mucosal healing by 1 month post-procedure (**Fig. 1**)



Fig. 1. Full mucosal healing is evident 1 month after DMR

Efficacy

- HbA1c reduction in full cohort: 1.2% at 6 months
- LS-DMR had more potent glycemic effects
 - 2.5% reduction in baseline mean HbA1c at 3 months post-procedure vs 1.2% with SS-DMR (p<0.05)
 - Early and sustained improvement in FPG plus improvement in post-prandial glucose (**Fig. 2 & 3**)
- Greater effects in patients on stable medications (**Fig. 4**)
- Modest weight reduction (2-4%), but no apparent correlation between degree of weight loss and glycemic improvement

Fig. 2. Mixed-meal tolerance test (long segment; n=28)

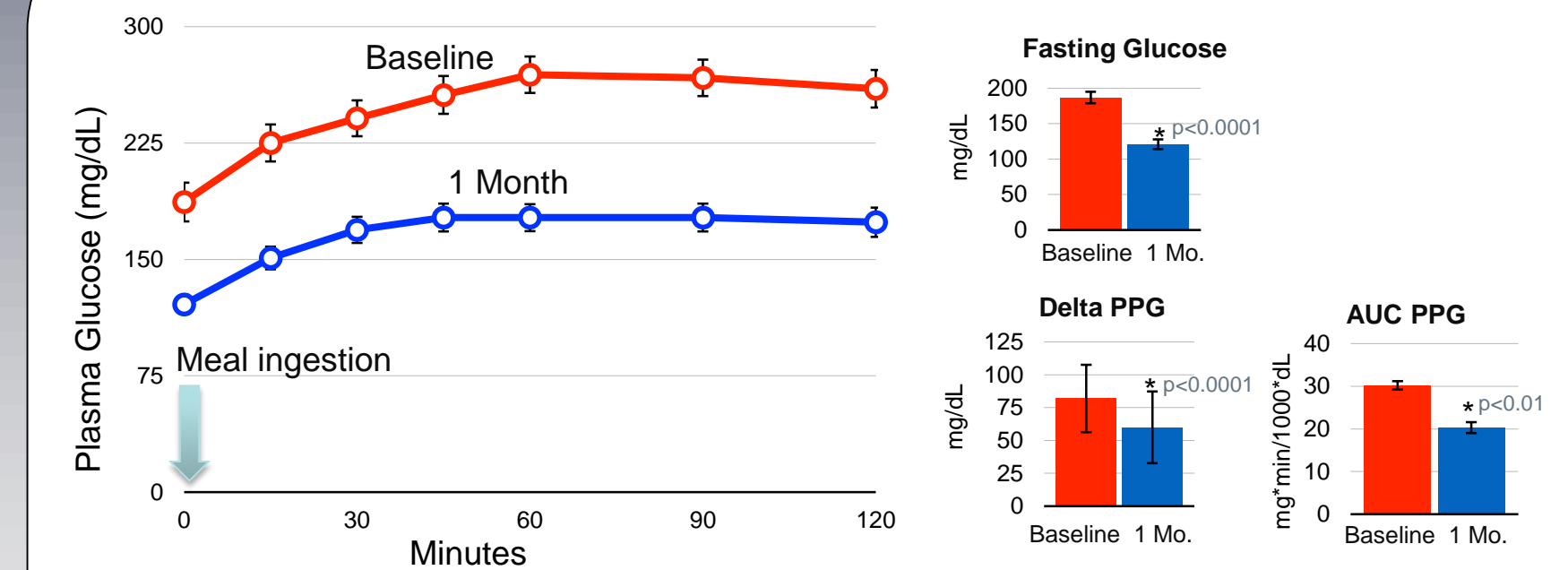


Fig. 3. Fasting plasma glucose by ablation cohort

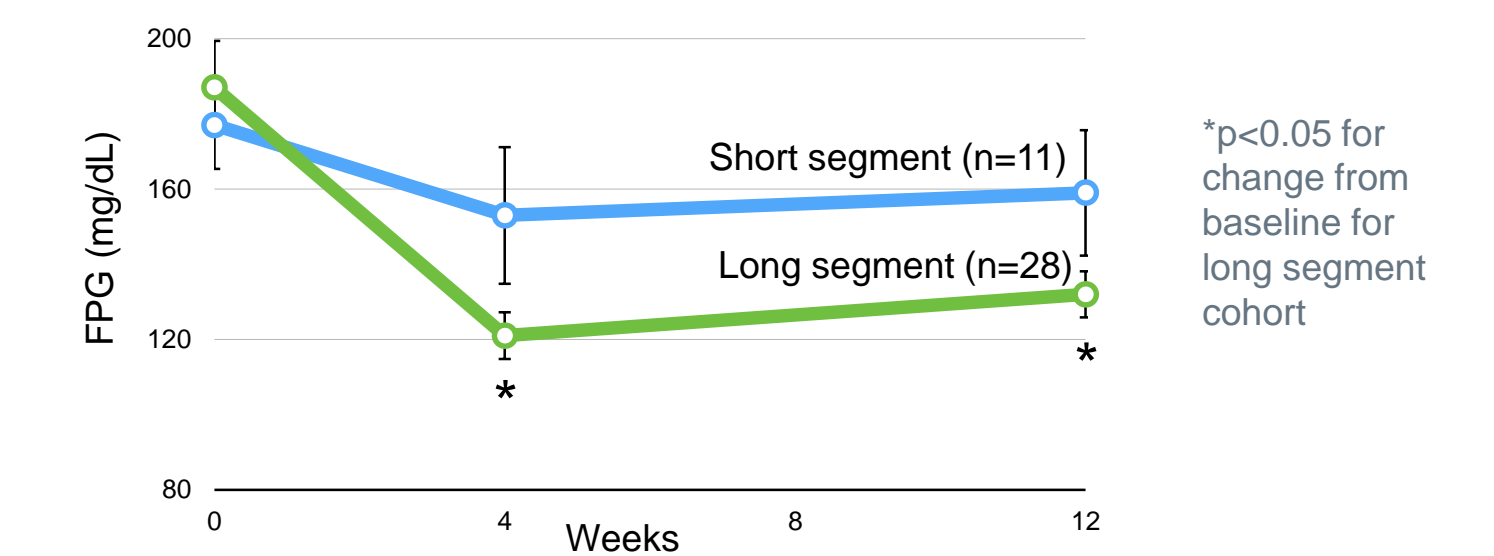
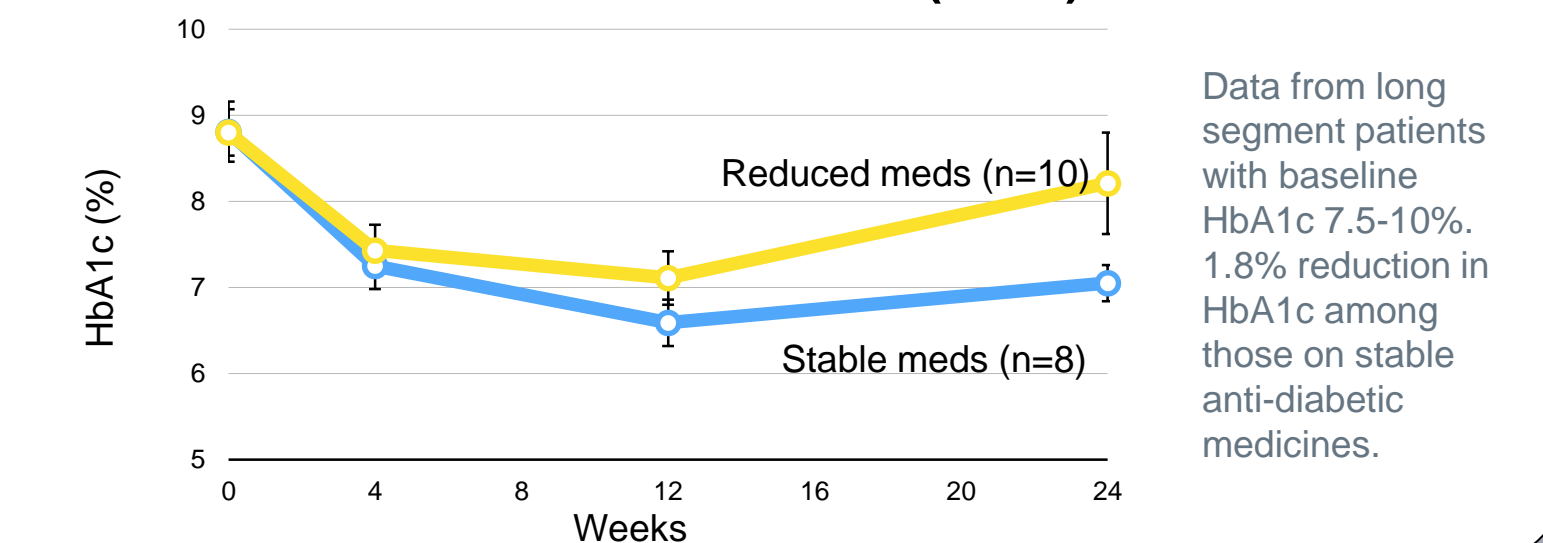


Fig. 4. Effect of changes in concomitant anti-diabetic medication use on DMR outcome (n=18)



Conclusions

- In this first-in-man study, single procedure DMR substantially improved glycemic control in patients with T2D, with acceptable safety and tolerability to date
- Upper GI procedural intervention may be a novel way to improve glycemia in T2D