Clinical and mechanistic studies of duodenal mucosal resurfacing for type 2 diabetes

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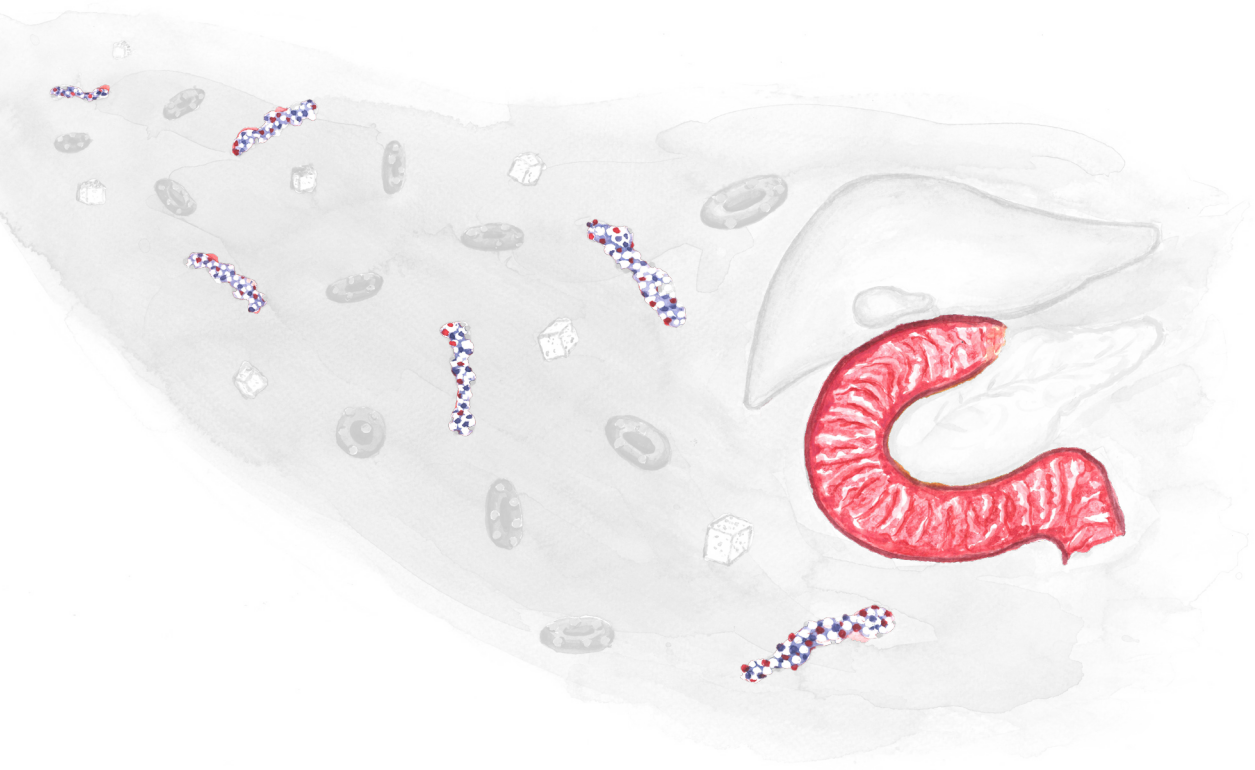

Duodenal mucosal resurfacing combined with GLP-1 receptor agonism to discontinue insulin in type 2 diabetes: a feasibility study.

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Abstract

Background and Aims

Duodenal mucosal resurfacing (DMR) is an endoscopic intervention in which the duodenal mucosa is ablated by hydrothermal energy. DMR improves glycaemic control in patients with type 2 diabetes (T2DM), most likely by altered duodenal signalling leading to insulin sensitization. We studied whether we could discontinue insulin use in T2DM patients by combining DMR with glucagon-like peptide-1 receptor agonist (GLP-1RA) and lifestyle counselling.

Methods

In this single-arm, single-center feasibility study in 16 insulin-treated patients with T2DM (haemoglobin A1c [HbA1c] ≤8.0%, basal insulin <1 U/kg/day, C-peptide ≥0.5 nmol/L), patients underwent a single DMR followed by a 2-week postprocedural diet, after which GLP-1RA (liraglutide) was introduced. Lifestyle counselling was provided per American Diabetes Association guidelines. The primary endpoint was percentage of patients without insulin with an HbA1c ≥7.5% (responders) at 6 months. Secondary endpoints were changes in multiple glycaemic and metabolic parameters and percentage of responders at 12 and 18 months, respectively.

Results

All 16 patients underwent successful DMR without procedure-related serious adverse events. At 6 months, 69% of patients were off insulin therapy with an HbA1c ≤7.5%. At 12 and 18 months 56% and 53% remained off insulin, respectively. All patients significantly improved in the glycaemic and metabolic parameters of homeostatic model assessment for insulin resistance, body mass index, weight, and liver fat fraction.

Conclusions

In this feasibility study, the combination of a single DMR and GLP-1RA, supported by lifestyle counselling, eliminated the need for insulin therapy in most patients with T2DM through 18 months post procedure, with adequate beta cell capacity, while improving glucose regulation and metabolic health in all patients. A randomized-sham controlled trial is currently initiated based on these results.

Introduction

Metabolic syndrome is a cluster of conditions associated with insulin resistance, hyperinsulinemia, and type 2 diabetes (T2DM). Pathophysiological conditions characterized by insulin resistance and hyperinsulinemia can lead to several, often overlapping, metabolic diseases, including T2DM, nonalcoholic fatty liver disease (NAFLD), and cardiovascular disease.[1]

T2DM is managed by lifestyle interventions and pharmacological agents.[2] Nevertheless, only 50% of T2DM patients achieve their treatment targets.[3] For many patients, insulin therapy remains the final treatment option to manage their hyperglycaemia. However, this approach does not treat the root phenomenon of the disease (i.e., insulin resistance), and the resulting hyperinsulinemia contributes to weight gain and further deterioration of the patient's metabolic health.[4] There are currently no prospective data of successful drug substitution to replace insulin for any duration of 24 weeks or longer.

Bariatric surgery has been found to result in metabolic improvements in T2DM patients. Patients undergoing Roux-en-Y gastric bypass surgery demonstrate major improvements in glycaemic, metabolic, and cardiovascular health, which occur virtually immediately after surgery and well before any significant weight loss is established.[5] Reintroduction of nutrients into the bypassed duodenal limb quickly returns rodents to their previous dysmetabolic state,[6,7] highlighting the importance of the duodenum in the insulin-sensitizing effect of bariatric surgery and in the pathogenesis of metabolic syndrome.

Duodenal mucosal resurfacing (DMR) is an endoscopic procedure that applies hydrothermal energy to the duodenum, leading to ablation and subsequent regeneration of the duodenal mucosa.[8] Data from human and animal model studies suggest that this is followed by an insulin-sensitizing effect that resembles the metabolic improvements that are observed after bariatric surgery. In a recent European multicenter study that examined patients with suboptimally controlled T2DM (using only oral glucose-lowering drugs), a single DMR procedure elicited substantial improvement in glycaemia, insulin resistance, and liver transaminase levels at 24 weeks, which were sustained at 12 and 24 months post procedure.[9] Moreover, this study underscored that DMR is safe as most of the post procedure adverse events (AEs) were mild and self-limiting. A recent multi-center, sham-controlled randomized study, confirmed these findings.[10] Together, these studies strongly suggest that DMR is followed by an insulin-sensitizing effect that, in lesser extent, resembles metabolic improvements observed after bariatric surgery, but trough a less-invasive procedure.
We reasoned that the insulin-sensitizing effect of DMR might be strengthened by coadministration of a glucagon-like peptide-1 receptor agonist (GLP-1RA), an

anti-diabetic drug that stimulates endogenous insulin production and protects the remaining pancreatic beta cells. Patients who replaced their insulin therapy with only a GLP-1RA had adequate glucose regulation with this single treatment in 9% of cases.[11-15] We speculated that the stimulation of endogenous insulin production by GLP-1RA combined with the insulin sensitizing effect of DMR, would achieve elimination of insulin in far more patients. Elimination of exogenous insulin therapy is highly desirable, because hyperinsulinemia is associated with hypoglycaemic events, weight gain, and further deterioration of metabolic health in patients with T2DM.[4] In accordance with the guidelines of the American Diabetes Association, this experimental treatment approach in our pilot study was supported by lifestyle counselling.[16] For this pilot study, we hypothesized that the treatment combination of DMR and GLP-1RA, supported by lifestyle counselling, constitutes a more physiological treatment of T2DM that may eliminate the need for insulin therapy while maintaining glycaemic control and improving metabolic health.

Methods

Study design

This pilot study was a single-center, single-arm, prospective, clinical study that evaluated the effect of a single DMR combined with GLP-1RA (liraglutide) and lifestyle counselling in patients with T2DM who were on insulin therapy. The study protocol was approved by the Medical Ethics Committee of the Amsterdam University Medical Center. The study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice Guidelines and the Declaration of Helsinki. An independent data safety monitoring committee established criteria for stopping the study before enrolment of the first patient and reviewed all AEs that occurred over the course of the study. The study is registered under EudraCT number 2017-00349-30 at Clinicaltrialsregister.eu.

Study population

Eligible patients were T2DM patients aged 28 to 75 years with a body mass index (BMI) of 24 to 40 kg/m^2, a maximum haemoglobin A1c (HbA1c) of 8.0% (62 mmol/mol), and adequate beta cell reserve (fasting C-peptide >0.5 nmol/L) and who were using long-acting insulin. Exclusion criteria were type 1 diabetes, a history of ketoacidosis, and use of noninsulin injectable glucose-lowering medication. The complete list of eligibility criteria can be found in Appendix 1. Written informed consent was obtained from all patients.

Intervention, study flow, and assessments

Intervention

The DMR procedure was performed with the patient under deep sedation with propofol by a single endoscopist with experience in therapeutic upper GI endoscopy. A screening gastroduodenoscopy was conducted first to ensure that there were no conditions that would preclude the procedure. The DMR procedure involved circumferential hydrothermal ablation of the duodenal mucosa using an over-the-guidewire catheter next to the endoscope, as described previously.[8, 9] Patients were instructed to follow a 2-week diet after DMR in which clear liquids were gradually replaced by solid foods. Insulin administration was discontinued immediately after DMR. All oral glucose-lowering medications were continued in the same dosage throughout the study. After the postprocedural diet, patients began self-administration of subcutaneous GLP-1RA (liraglutide, Victoza; Novo Nordisk A/S, Bagsvaerd, Denmark) once daily at a standard dosage of 0.6 mg/day that was gradually increased to 1.8mg/day, as registered for treatment of T2DM. General dietary and lifestyle advice was provided before the DMR and at each follow-up visit (Appendix 1).

Assessments and outcome measurements

At screening, baseline, and at the 3-, 6-, 9-, 12-, 15-, and 18-month follow-up visits after DMR, physical examinations (weight and blood pressure) and laboratory assessments (fasting plasma glucose, HbA1c, haematology, biochemistry, and urine microalbumin) were performed and any medication use, AEs, and/or occurrence of self-measured hypoglycaemia were recorded. Oral glucose-lowering medication was continued in the same dose during the complete follow-up. Patients were instructed to measure their glucose levels regularly and to act upon hypoglycaemia and hyperglycaemia (Appendix).

Glycaemic control and metabolic health testing

At baseline and at the 6- and 12-month follow-up, magnetic resonance imaging (model clinical 3 Tesla scanner, Achieva; Philips, Amsterdam, the Netherlands) was performed to measure the liver proton density fat fraction (PDFF). At baseline and 6-months follow-up, a mixed meal tolerance test (MMTT) was conducted to assess postprandial glucose response after ingestion of a standard liquid meal (200ml, 2.0 kcal/ml, Fresubin; Fresenius Kabi Nederland BV, Zeist, the Netherlands). Detailed information regarding these assessments can be found in the Appendix.

Study endpoints

The primary endpoint of this pilot study was the percentage of patients free of exogenous insulin therapy with adequate glycaemic control, defined as HbA1c ≤7.5% at the 6-month follow-up (*responders)*. The cut-off of 7.5% was selected to

have patients on a GLP-1RA longer instead of insulin to allow gradual glycaemic and metabolic improvements.

Secondary endpoints were the percentage of patients free of exogenous insulin therapy with adequate glycaemic control, defined as HbA1c ≤7.5% at 12- and 18-month follow-up, and changes compared with baseline in glycaemic parameters during follow-up (HbA1c, homeostatic model assessment for insulin resistance [HOMA-IR], fasting plasma glucose [FPG], and area under the curve [AUC], incremental AUC, and peak plasma glucose during the MMTT) and in metabolic parameters (BMI, alanine aminotransferase, fat free mass, and PDFF) to evaluate additional benefits of the intervention in this pilot setting.

Feasibility endpoints were DMR procedure time, number of complete DMR procedures (defined as a ≥5 sequential ablations of 2 axial cm each), and percentage of patients who used liraglutide without significant side effects.

Safety endpoints were all AEs, serious AEs (SAEs), procedure- and device-related SAEs, unanticipated adverse events, suspected unexpected serious adverse reactions, and the number of hypoglycaemic events (Appendix 1). The relationship of AEs to the study procedure and to the study drug was assessed by both endocrinologists and gastroenterologists.

Statistical Analysis

All the data were analysed using SPSS software, version 25 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA). Data are expressed as medians (interquartile ranges [IQRs]). The *complete study population* consisted of all patients in whom the treatment combination of DMR, GLP-1RA, and lifestyle counselling was initiated. In this population, we report the primary endpoint, secondary glycaemic and metabolic endpoints, and the feasibility and safety endpoints. In those patients that responded successfully to the combination treatment (*responders*), we report secondary glycaemic and metabolic endpoints. The Wilcoxon paired signed-rank test was used to evaluate the secondary endpoints. The Wilcoxon unpaired signed-rank test was used to compare the baseline values between *responders* and *non-responders*. Missing data was handled using available case analysis where missing values were approximated using the mean of the values prior and posterior of the missing value. See the Appendix for sample size calculation.

Results

Twenty-five T2DM patients were screened for this pilot study, and 16 patients fulfilled the entry criteria. Seven patients were excluded based on low C-peptide levels, and 2 patients were excluded because HbA1c values were outside the eligibility range. All 16 enrolled patients underwent a successful DMR procedure (Figure 1). Table 1 shows the patients baseline characteristics.

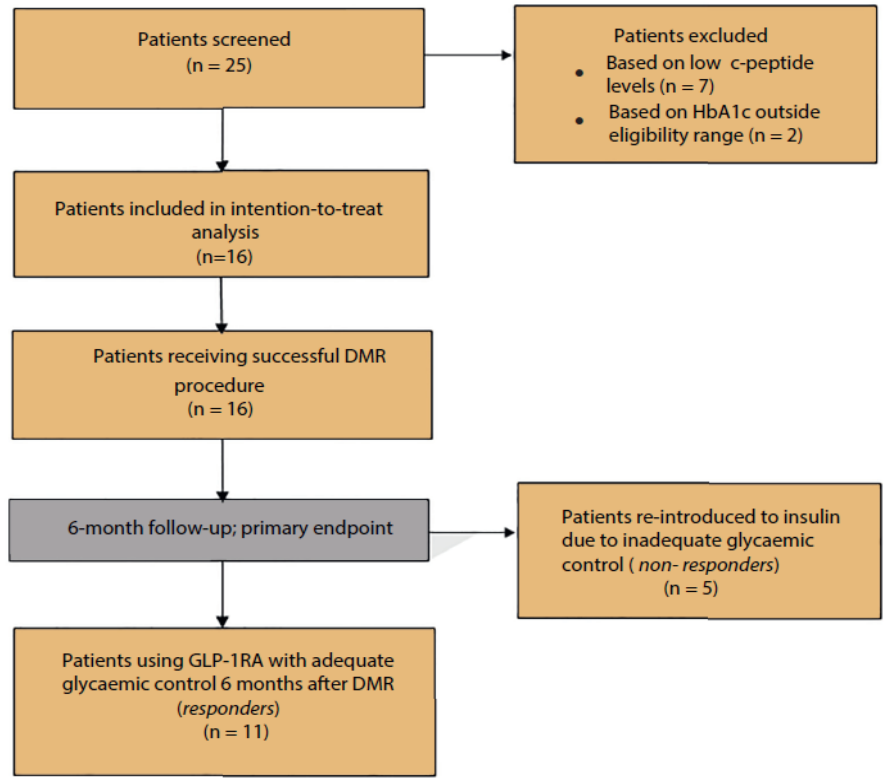

Figure 1. Enrolment flow diagram.

HbA1c, Glycated haemoglobin A1c; GLP-1RA, glucagon-like peptide-1 receptor agonist; DMR, duodenal mucosal resurfacing.

Table 1. Clinical patient characteristics at baseline (n=16)

Patient characteristics (n=16)	
Age [years]	61 (55–67)
Male gender, n (%)	10 (63%)
Duration of T2DM [years]	11 (8–15)
Weight [kg]	87.8 (80.2–99.7)
BMI [kg/m²]	28.8 (26.5–31.7)
HbA1c [%], [mmol/mol]	7.5 (7.1–7.9), 58 (54-63)
Fasting plasma glucose [mmol/L]	10.1 (8.9–12.0)
Fasting plasma insulin [pmol/L]	104 (49–178)
C-peptide [nmol/L]	0.63 (0.55–0.91)
HOMA-IR	8.4 (4.3–12.0)
Glucose-lowering medication	
Mean number of daily units of insulin	31 (16–47)
Insulin monotherapy, n (%)	2 (12.5%)
Oral glucose-lowering medications, n (%)	14 (87.5%)
Metformin, n (%)	13 (81.3%)
Empagliflozin, n (%)	1 (6.25%)

Values are median (interquartile range) or n (%). T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycated A1c; HOMA-IR, homeostatic model assessment for insulin resistance.

Efficacy

Primary endpoint

At the 6-month follow-up, 11 of 16 patients (69%) met the primary endpoint of the study: adequate glycaemic control (i.e., HbA1c ≤7.5% at 6 months) with the combination of DMR and GLP-1RA, with lifestyle support, without insulin therapy (*responders).* At 6 months, all patients administered 1.8 mg liraglutide per day and oral glucose-lowering medication remained unchanged.

At the 12-month follow-up, 9 of 16 patients (56%) were still *responders*. One patient in this responder group experienced corticosteroid-induced hyperglycaemia on prednisolone treatment for a chronic obstructive pulmonary disease/asthma exacerbation between 9 and 12 months of follow-up, which was treated with insulin. We used last observation carried forward for the time points after 9 months of follow-up. This patient did not agree to continue the study after 12 months because of the disease burden of the aforementioned disease. At 18 months follow-up, 8 out of 15 patients (53%) were *responders*. All *responders* used liraglutide throughout the study with unchanged oral glucose-lowering medication. One patient used 1.2 mg instead of 1.8 mg liraglutide because of an irregular stool pattern.

Insulin use

Five of 16 patients switched back to insulin because of HbA1c values >7.5% at 6 months. At baseline, these patients used on average 31 daily units (IQR, 16-47) of long-acting insulin. At 12 months, the 7 non-responding patients used on average 12 daily units (IQR, 10-28) of long-acting insulin. At 18 months, 2 non-responding patients were

able to phase out insulin (without liraglutide), the other 5 patients used 26 daily units (IQR, 10-41) of long-acting insulin.

Secondary glycaemic endpoints

In the complete study population, HOMA-IR values decreased significantly, from 8.4 (IQR, 4.3-12.0) at baseline to 2.5 (IQR, 1.8-3.1) at 6 months (P=0.002) and remained improved through 18 months: 3.9 (IQR, 2.0-6.0; P=0.006). FPG values improved from 10.1 mmol/L (IQR, 8.9-12.0) to 8.0 mmol/L (IQR, 6.6-9.5) at 6 months (P=0.039) and to 7.3 (IQR, 6.7-8.4) at 18 months (P=0.011). Average HbA1c values improved but were not statistically significant: 7.5% (IQR, 7.1-7.9) to 7.0% (IQR, 6.7-7.9), 7.3% (IQR, 6.6-8.2) and 7.1% (IQR, 6.6-7.5) at 6-, 12-, and 18-month follow-up, respectively (Table 2).

All glycaemic parameters derived from the MMTT at 6 months showed a significant improvement at 6 months (Figure 2). Fasting insulin concentrations improved from 104 pmol/L (IQR, 49-178) at baseline to 42 pmol/L (IQR, 26-64) at 6 months (P=0.001) and to 63 pmol/L (IQR, 34-110) at 18 months (P=0.036). In the post-hoc analysis studying the responder population, HbA1c improved from 7.5% (IQR, 7.1-7.6) at baseline to 6.7% (IQR, 6.6-7.0) at 6 months (P=0.009) (Table 2). Thereafter HbA1c did not change significantly.

Secondary metabolic endpoints

Metabolic parameters also improved significantly in the *complete study population*. Weight improved from 87.8 kg (IQR, 80.2-99.7) at baseline to 80.7 kg (IQR, 73.8-96.8) at 18 months (P=0.001). BMI decreased from 28.8 kg/m² (IQR, 26.5-31.7) at baseline to 26.4 kg/m² (23.5-30.2) at 18 months (P=0.001) (Table 2). The liver PDFF value improved in the *complete study population* from 8.1% (IQR, 4.0-13.5) at baseline to 5.6% (IQR, 2.8-10.9) at 12 months (P=0.035) (Table 2).

In the *responders*, weight and BMI both improved significantly at 6-, 12-, and 18-month follow-up compared with baseline (Table 3). Average PDFF improved from 8.1% (IQR, 5.1–13.2) at baseline to 4.6% (IQR, 2.4–11) at 6 months (P=0.028) (Figure 3), and to 6.0% (IQR, 2.7-10.9) at the 12-month follow-up, but the latter did not reach statistical significance (P=0.237). We found no significant differences in baseline characteristics between *responders* and *non-responders*.

Table 2. Overview of glycaemic and metabolic secondary endpoints.

	Baseline	6 months	*P* value	12 months	*P* value	18 months	*P* value
		Glycaemic parameters					
Patients off insulin	**0 (0%)**	**11 [69%]**		**9 [56%]**		**8 [53%]†**	
HbA1c [%]	7.5 (7.1–7.9)	7.0 (6.7-7.9)	0.208	7.1 (6.6-8.2)	0.690	7.1 (6.6-7.5)	0.208
HOMA-IR	8.4 (4.3-12.0)	2.5 (1.8–3.1)	0.006	3.8 (2.4-7.9)	0.015	3.9 (2.0-6.0)	0.006
FPG [mmol/L]	10.1 (8.9–12.0)	8.0 (6.6–9.5)	0.011	7.1 (6.6-9.5)	0.006	7.3 (6.7-8.4)	0.011
Fasting insulin [pmol/L]	104 (49-178)	42 (26-64)	0.036	71 (45-121)	0.116	63 (34-110)	0.036
Fasting c-peptide [nmol/L]	0.63 (0.55-0.91)	0.55 (0.51-0.79)	0.245	0.58 (0.39-0.70)	0.224	0.46 (0.39-0.59)	0.245
		Metabolic parameters					
Weight [kg]	87.8 (80.2-99.7)	80.1 (74.6-92.3)	0.001	80.8 (73.2-95.8)	0.001	80.7 (73.8-96.8)	0.001
BMI [kg/m²]	28.8 (26.5–31.7)	26.5 (24.3–29.8)	0.001	27.7 (23.4-30.1)	0.001	26.4 (23.5-30.2)	0.001
PDFF [%]†	8.1 (4.0–13.5)	5.3 (3.9–11.4)	0.053	5.6 (2.8-10.9)	0.035		

*Values are as median (interquartile range) or n (%). Paired Wilcoxon signed-rank tests were used to compare measurements between baseline and 6 months. *Eight of 15 patients: 1 patient did not agree to continue follow-up to 18 months. †Proton density fat fraction was known in 15 of 16 patients. HbA1c, glycated A1c; HOMA-IR, homeostatic model assessment for insulin resistance; FPG, fasting plasma glucose; BMI, body mass index; PDFF, proton density fat fraction.*

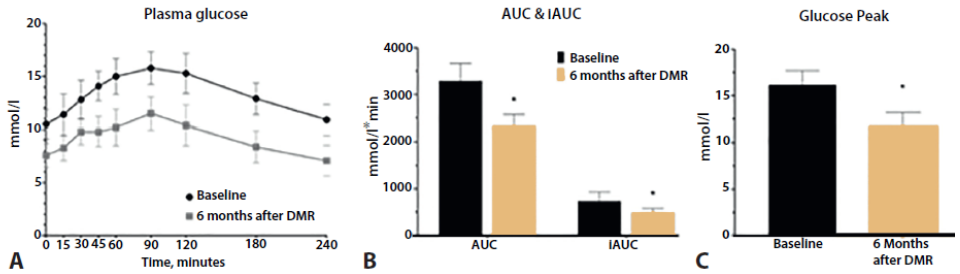

Figure 2. Glucose concentrations. (A) AUC and iAUC values. (B) Glucose peaks during mixed-meal tolerance test at baseline and at 6-month follow-up in whole population analysis. (C)

*Data represent median (interquartile range). *P<0.05. Analysis with paired Wilcoxon signed-rank test. AUC, Area under the curve; iAUC, incremental area under the curve; DMR, duodenal mucosal resurfacing.*

Procedure feasibility information

The DMR procedure was completed in all 16 patients with a minimum of 5 ablations. The median procedure time was 51 minutes (IQR, 46-56).

Safety and tolerability

None of the patients reported hypoglycaemia during follow-up. No unanticipated adverse device events were reported. Four treatment-unrelated SAEs were reported during follow-up: fibula fracture after accident with subsequent thrombosis in 1 patient, and an asthma exacerbation (treated with oral prednisolone and antibiotics) with a subsequent pneumonia with hospital admission in 1 patient.

Twenty-one procedure-related AEs were reported during 6 months of follow-up in 10 of 16 patients (Table 4). Of these, 16 were reported as "possibly" procedure-related and 5 as "probably" procedure-related; none were considered "definitely" procedure-related. Most of the 21 procedure-related AEs (95%) were graded as mild. Two AEs were treated with medication. In 6 of 16 patients, no procedure-related AEs were reported. No device-related AEs were reported.

Thirteen study drug-related AEs were reported in 11 of 16 patients. Of these, 13 were assessed as "possibly" study drug-related and 2 as "probably" study drug-related. Most of the drug-related AEs (93%) were graded as mild.

Table 3. Overview of glycaemic and metabolic secondary endpoints in responders.

	Baseline (n=16)	6 months (n=11/16)	*P* value	12 months (n=9/16)	*P* value	18 months (n=8/15)	*P* value
Glycaemic parameters							
HbA1c [%]	7.5 (7.1–7.9)	6.7 (6.6-7.0)	0.009	6.7 (6.6-7.3)	0.231	7.0 (6.6-7.2)	0.182
HOMA-IR	8.4 (4.3-12.0)	2.5 (1.6-3.1)	0.008	3.1 (1.7-5.1)	0.015	2.3 (1.5-5.3)	0.012
FPG [mmol/L]	10.1 (8.9–12.0)	7.3 (6.5-8.6)	0.004	7.1 (6.7-7.8)	0.008	7.3 (7.0-8.2)	0.012
Fasting insulin [pmol/L]	104 (49-178)	43 (26-64)	0.005	63 (33-88)	0.012	48 (31-91)	0.018
Fasting c-peptide [nmol/L]	0.59 (0.54-0.91)	0.54 (0.51-0.62)	0.508	0.58 (0.49-0.66)	0.214	0.49 (0.40-0.77)	1.000
Metabolic parameters							
Weight [kg]	87.8 (80.2-99.7)	80.6 (77.7-92.7)	0.004	79.6 (73.7-95.4)	0.011	80.3 (74.4-96.8)	0.012
BMI [kg/m²]	28.8 (26.5–31.7)	25.7 (24.2-29.9)	0.003	28.2 (22.2-30.6)	0.008	27.7 (23.2-32.3)	0.017
PDFF [%]*	8.1 (4.0–13.5)	4.4 (2.2-10.6)	0.028	6.0 (2.7-10.9)	0.237		

*Values are median (interquartile range) or n (%). Paired Wilcoxon signed-rank tests were used to compare measurements between baseline and 6 months. *Proton density fat fraction was known in 15 of 16 patients.*

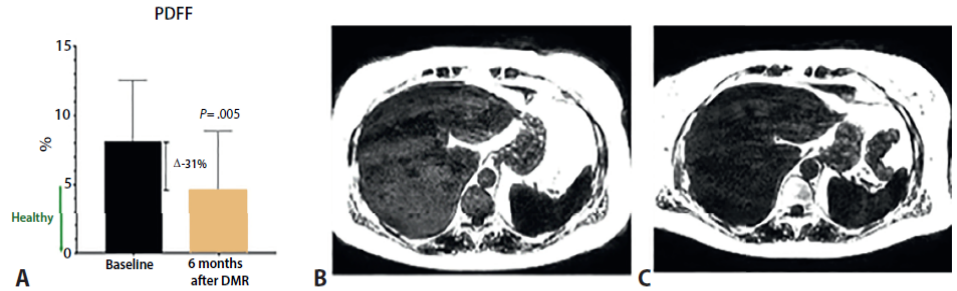

Figure 3. Magnetic resonance imaging (MRI)-based proton density fat fraction (PDFF) representing liver fat fraction in whole study population.

*Data represent median (interquartile range). A PDFF value below 5% is considered healthy. *PZ.036. Analysis with paired Wilcoxon signed-rank test. Example MRI-based PDFF images at (B) baseline and (C) 6-month follow-up with PDFF in percentage. PDFF improved from 8.1% to 4.1%. T2-weighted images: water is black, fat is white.*

Table 4. Summary of adverse events during 6-month follow-up period

Total number of adverse events (in 15/16 patients)	**65**
Procedure-related adverse events* (in 10/16 patients)	**21**
Gastrointestinal symptoms *Such as diarrhea, heartburn, abdominal pain and nausea*	17
General symptoms *Such as low energy level, orthostatic hypotension etc.*	4
Severity of procedure-related adverse events†	**21**
Mild	20 (95%)
Moderate	1 (5%)
Severe	0 (0%)
Study drug-related adverse events (in 10/16 patients)	**15**
Gastrointestinal symptoms *Such as nausea, varying stool pattern, and reflux*	11
General symptoms *Such as low energy level, dizziness and orthostatic hypotension*	4
Severity of study drug-related adverse events†	**15**
Mild	14 (93%)
Moderate	1 (7%)
Severe	0 (0%)
Not procedure-related or study drug-related adverse events* (in 8/16 patients)	**29**
Gastrointestinal symptoms *Such as nausea oropharyngeal pain and obstipation*	(10.3%)
General symptoms *Such as injuries, orthostatic hypotension, deep vein thrombosis and fatigue*	9 (31%)
Metabolic symptoms *Such as hypo- and hyperglycaemia*	1 (3.4%)
Infections *Such as pneumonia, common cold and cellulitis*	16 (55%)
Total number of serious adverse events (in 1/16 patients)	**4 (12.5%)**

**Relationship to procedure was assessed as in terms of not, possibly, probably, and definitely based on the temporal association with combination treatment and the possibility of other aetiologies. †Mild, discomfort but no disruption of daily activities; moderate, discomfort sufficient to affect daily activities; severe, discomfort rendered patient unable to perform daily activities. Two adverse events were treated with medication (paracetamol for abdominal pain after duodenal mucosal resurfacing for 4 days and a proton pump inhibitor [40 mg daily] for 6 months to treat gastroesophageal reflux symptoms that arose 4 weeks after duodenal mucosal resurfacing).*

Discussion

In this single-arm, single-center, prospective, open-label feasibility study, the combination of single DMR and GLP-1RA, supported by lifestyle counselling, successfully eliminated the need for insulin therapy in a subset of patients with T2DM. The responder rate was 69% at 6 months, 56% at 12 months, and 53% at 18 months. Although this rate shows a slow decrease, most patients were off insulin at the 18-month follow-up. Despite the complete discontinuation of insulin (median baseline dosage, 31 units), the *responding* patients experienced improved glycaemic control and significant beneficial metabolic effects. The treatment combination was associated with a favourable safety profile; patients that underwent DMR had minimal GI symptoms and required minimal or no analgesic treatment. No device-related AEs or treatment-related SAEs were reported. All patients tolerated GLP-1RA liraglutide therapy, and there were no episodes of hypoglycaemia. Below we give an overview of the results of this feasibility study. The results are encouraging and surpass our expectations, but we must proceed with caution when interpreting the results given the small sample size and the uncontrolled nature of this study.

In the complete study population, multiple glycaemic parameters improved throughout the 18-month follow-up, which indicated stable improvements of glucose control. In addition, significant decreases in AUC, incremental AUC, and peak glucose levels in widely used reliable MMTTs were observed. At 12 and 18 months, most patients were still off insulin and had acceptable HbA1c values after DMR with GLP-1RA. These results are clinically relevant, because cessation of insulin is experienced as a major advantage for patients in their daily lives. Improved glycaemic control in *responders* was more pronounced than in the complete study population, reflected by significant decreases in HbA1c (0.8%) at 6 months. The improved HbA1c levels are supported by significantly improved insulin plasma concentrations. Together, these results underscore improved insulin resistance and reduced hyperinsulinemia, which both lead to an improved metabolic health. All patients who had to return to insulin therapy used less daily insulin units as compared with the pre-DMR baseline. Interestingly, 2 patients were able to completely discontinue insulin after its reintroduction. This might be because of improved insulin sensitivity in combination with strongly motivated patients who were able to comply strictly with dietary and lifestyle guidelines.

Multiple parameters of metabolic and hepatic health improved throughout the 18-month follow-up. We observed significant reductions in BMI and body weight. Patients lost on average 8 kg of weight at 6 months, and thereafter weight stabilized. Patients did not regain weight, in contradiction to that previously observed after other interventions. The weight loss observed here is greater than expected. DMR and GLP-1RA treatment account for a weight reduction of around 3 kg as monotherapies.[9, 17, 18] The greater weight loss in our study reflects ceasing insulin therapy and the incorporation of lifestyle counselling in our study. It is important to note that lifestyle counselling did not include a hypocaloric diet.

Significant improvement in liver fat fraction was seen at 12 months in the complete study population. A relative PDFF reduction of 31% was observed, increasing the proportion of patients with healthy PDFF values (<5%) from 33% to 47% at 12 months. A reduction in transaminase levels was seen in an earlier prospective study of DMR in T2DM patients.[7] Our study, however, combined DMR with liraglutide treatment. GLP-1 analogues have been shown to reduce liver enzymes and oxidative stress and improve liver histology in murine models of nonalcoholic steatohepatis.[19] However, human trials studying this effect are scarce. In one trial, liraglutide reduced liver fat significantly by 19% (P<0.001) in patients with T2DM.[20] In our study, we found a relative reduction of 31%, so it is expected that DMR also plays a role in the improvement in liver fat fraction in our patients, but larger controlled human studies are necessary to confirm this. T2DM and NAFLD often coexist since they share the common pathway of hepatic insulin resistance and adipose tissue dysfunction, and 70% of patients with T2DM are estimated to have NAFLD.[21] NAFLD is the most common chronic liver disease in developed countries and its more severe form, nonalcoholic steatosis hepatitis (NASH), is a leading cause of end-stage liver disease and hepatocellular carcinoma.[22] In our study, we did not preselect T2DM patients for coexisting NAFLD/NASH, yet our results suggest that the combination of DMR, GLP-1RA, and lifestyle counselling may be particularly effective for treating patients with both T2DM and NAFLD, because long-term glycaemic and hepatic improvement was seen in the complete study population, especially because there are currently no registered treatment options for NAFLD.

Our results raise the question of whether there is a potential synergistic effect of DMR, GLP-1RA, and lifestyle counselling on glycaemic control and metabolic health in patients with T2DM who have suboptimal glycaemic control (HbA1c ≤8.0%) and adequate beta cell capacity. Lifestyle counselling should be the cornerstone of T2DM treatment, but its effect on HbA1c is fairly limited.[23] We provided a general lifestyle counselling without prescribing a hypocaloric diet, similar to the Revita-1 study, in which DMR was used in the treatment of T2DM patients on oral glucose-lowering medication.[9] In our opinion, the standard lifestyle counselling provided as part of this study is an unlikely explanation for the observed significant improvement in glycaemic and metabolic health in this study. Recent guidelines promote the use of GLP-1RA as an intermediate step before insulin therapy in T2DM patients, yet based on a weighted average of published studies, <10% of patients are able to eliminate insulin therapy after initiation of GLP-1RA monotherapy. In most of these studies, lifestyle counselling was part of the standard

study design.[11-15] In our study, 69% of patients were able to discontinue insulin therapy, a rate that is hard to explain by the use of GLP-1RA and standard lifestyle counselling only. The two prospective studies of DMR in T2DM patients on oral glucose-lowering medication found a mean HbA1c decrease of 0.9 to 1.2% at 6 months after DMR.[8, 9] Before we started this feasibility study, we assumed that the combination of DMR, GLP-1RA, and lifestyle counselling would allow us to withdraw insulin therapy in 40% of T2DM patients while retaining glycaemic control at 6 months. Such a 40% insulin withdrawal rate would already be twice the largest observed effect after GLP-1RA monotherapy and 4 times the weighted average of all published studies. Surprisingly, in our study, this endpoint was achieved in 69% of patients who, in addition to remaining insulin-independent, also demonstrated improved glycaemic control and metabolic health. Based on these results, we speculate that DMR and GLP-1RA have a synergistic effect on glycaemia because they address two core pathophysiological features of T2DM, insulin resistance and failure of endogenous insulin production, through complementary mechanisms of action. This is in contrast to symptomatic treatment with exogenously administered insulin, which may reduce glycaemia yet at the price of negative metabolic and cardiovascular effects, such as weight gain, dyslipidemia, and the associated feared adverse event of hypoglycaemia.[4]

The mechanism of action of DMR remains to be elucidated. Studies suggest that a Western diet induces adaptive responses in the duodenum, including mucosal hyperplasia and changes in the enteroendocrine cell population. In this regard, glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 are important mediators of effects of gut hormones on metabolic control.[24] We speculate that DMR partially reverses these adaptive responses and restores GIP/GLP-1 homeostasis in patients with T2DM who have adequate beta cell capacity, resulting in a reduction in hyperinsulinemia and insulin resistance. Further mechanistic studies are in progress.

In a subset of our study patients, the combination treatment of DMR, GLP-1RA, and lifestyle counselling failed to maintain adequate glycaemic control after the discontinuation of insulin. We speculate that these patients may have had an insufficient pancreatic beta cell reserve at baseline, which restricts the beneficial effect of GLP-1RA (i.e., increased endogenous insulin production). Under these circumstances, improved insulin sensitivity after DMR may fall short since endogenous insulin production is insufficient. This implies that to eliminate exogenous insulin, DMR is most effective at a stage of T2DM where the beta cell function is not yet largely exhausted. In our study, we found that baseline C-peptide levels (reflecting endogenous insulin production) were indeed lower in *non-responders* than in *responders* (0.54 vs. 0.63 nmol/L), and HbA1c levels were higher (8.0 vs. 7.4%), albeit not statistically significant given the small sample size of our pilot study. Our study is underpowered to identify predictors

for response, and further studies are required in this respect. A sham-controlled, randomized study in insulin-dependent T2DM patients is underway.

This feasibility study has some inherent limitations. Our sample size was too small to find predictors for effectiveness and restricts the generalizability of our findings. The study was designed to get an idea of the effect size of combining theoretically synergistic therapies. The uncontrolled nature of our study does not allow us to assess the relative contributions of DMR, GLP-1RA, and lifestyle counselling. A multicenter, sham-controlled, randomized study is expected to start enrolment in September 2020. We cannot exclude the possibility that the improvement of glycaemic and metabolic parameters were a consequence of the observed 8-kg weight reduction. However, the effects on glycaemia seen in monotherapy studies of DMR and GLP-1RA cannot be explained by weight reduction alone. Finally, it would also be interesting to observe what happens after 18 months and to investigate whether retreatment with DMR is effective.

In conclusion, in this feasibility study, DMR, combined with GLP-1RA and supported by lifestyle counselling, eliminated the need for insulin therapy in the majority of T2DM patients after 6, 12, and 18 months, while improving their glycaemic and metabolic health. Given the limited size and uncontrolled nature of this study, randomized sham-controlled studies are required to confirm its findings.

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Appendix. Supporting information

Complete list of eligibility criteria

Inclusion criteria:

1. Diagnosed with type 2 diabetes
2. 28-75 years of age
3. Treatment with long-acting insulin ≤5 years
4. Daily long-acting insulin dose ≤1 U/kg
5. Body mass index ≥24 and ≤40 kg/m2
6. HbA1c ≤8.0% (64 mmol/mol)
7. Fasting C-peptide ≤0.5 nmol/L (1.5 ng/mL)
8. Willing to comply with study requirements and able to understand and comply with informed consent
9. Signed informed consent form

Exclusion criteria:

1. Diagnosed with type 1 diabetes or with a history of ketoacidosis
2. Fasting C-peptide <.5 nmol/L (<1.5 ng/mL)
3. Current use of multiple daily doses of insulin or insulin pump
4. Current use of a sulfonylurea derivate, GLP-1 analogue, DPP4 inhibitor, or meglitinide
5. A positive anti-GAD test, as an indication of type 1 diabetes mellitus or latent autoimmune diabetes of the adult with progressive beta cell loss.
6. Previous GI surgery that could affect the ability to treat the duodenum, such as subjects who have had a Billroth II, Roux-en-Y gastric bypass, or other similar procedures or conditions
7. History of chronic or acute pancreatitis
8. Known active hepatitis or active liver disease
9. Symptomatic gallstones or kidney stones, acute cholecystitis, or history of duodenal inflammatory diseases, including Crohn's disease and celiac disease
10. History of coagulopathy or upper GI bleeding conditions, such as ulcers, gastric varices, strictures, and congenital or acquired intestinal telangiectasia
11. Use of anticoagulation therapy (such as phenprocoumon and acenocoumarol) and novel oral anticoagulants (such as rivaroxaban, apixaban, edoxaban, and dabigatran) that cannot be discontinued for 7 days before and 14 days after the procedure
12. Use of P2Y12 inhibitors (clopidogrel, prasugrel, and ticagrelor) that cannot be discontinued for 14 days before and 14 days after the procedure; aspirin use was allowed
13. Unable to discontinue nonsteroidal anti-inflammatory drugs during treatment through 4-week post procedure phase
14. Taking corticosteroids or drugs known to affect GI motility (eg, metoclopramide)

Intervention, study flow, and assessments

Study population

Patients with T2DM were recruited via advertisements in the Dutch Diabetes Association magazine and by diabetes nurses in primary care facilities.

Dietary counselling

A specialized dietician instructed all patients to adhere to a personal tailored energy and carbohydrate restricted and, if necessary, protein and fibre enriched diet. Based on the patients' preference, daily routine, and body mass index, dietary advice plan A or B was chosen (see below). The diet plan could be adjusted based on the patients' needs, body weight, and preferences during the study. Patients were stimulated to exercise for a minimum of 30 minutes per day, following the national guidelines for a healthy lifestyle. Examples of exercising were walking, cycling, swimming, jogging, or dancing. During the first month after DMR, subjects were called weekly to remind them and support them to adhere to the diet and lifestyle advice. During the regular outpatient clinic follow-up visits at 1, 3, and 6 months after DMR, patients were also seen by the dietician to discuss their progress in terms of dietary and exercise compliance.

Dietary advice plan A
Calories: According to Harris and Benedict equation, no extra calories
Carbohydrates: 30% to 40%, low in refined sugars
Proteins: >20% (1.0 g/kg)
Fat: 20% to 35%, <10% saturated fat

Dietary advice plan B
Calories: According to Harris and Benedict equation + 20% extra calories
Carbohydrates: <50%, low in refined sugars
Proteins: 10% to 20% (0.8-1.0 g/kg)
Fat: 20% to 35%, <10% saturated fat

Monitoring of glycaemia

Subjects were instructed to measure their fasting glucose levels daily and to measure glucose levels in case of complaints (eg, sweating, shaking, mood changes, nausea, feeling unwell, dizziness, etc). From the DMR up to 4 weeks post DMR, subjects measured their fasting glucose levels daily. From baseline up to DMR, and from 4 weeks post DMR up to 18 months post DMR, patients were instructed to measure their fasting glucose levels twice weekly. Glucose levels of ≥4 mmol/L, ≤15 mmol/L fasting, and ≤20 mmol/L nonfasting were acceptable, and no action was required. Glucose

levels of <4 mmol/L were considered unacceptable; if these occurred, subjects were instructed to consume a sugar-containing beverage or snack. If the subject had unacceptable low glucose levels on 3 consecutive days, the subject was instructed to call the clinic to evaluate the dose of their glucose-lowering medication. In case of 3 consecutive days of unacceptable glucose levels of >15 mmol/L fasting or >20 mmol/L nonfasting, subjects were instructed to call the clinic to increase the dose of GLP-1RA (if possible) or to switch back to treatment with insulin; in the latter case, GLP-1RA was discontinued. Telephone consultations were scheduled at 7, 14, 21, and 42 days after the DMR procedure to provide nutritional and lifestyle counselling, to record any AEs, and to evaluate self-monitored blood glucose levels.

Glycaemic control and metabolic health testing

PDFF values were calculated by assessing the areas under the peaks using jMRUI software and calculating the T2 decay to define the fat-to-water ratio, as previously described.[1] MMTT was conducted to assess the postprandial glucose response. Participants ingested a liquid meal (200mL, 2.o kcal/ml, Fresubin®; Fresenius Kabi Nederland B.V.) within ten minutes. Thereafter, blood samples were drawn at 0 minutes (fasting) and at 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the liquid meal to measure plasma glucose concentrations.[2] The AUC reflects the total increase in blood glucose during the MMTT, whereas the incremental AUC reflects the increase in blood glucose relative to baseline values.

Safety endpoints

The safety endpoints were all AEs, SAEs, procedure- and device-related SAEs, unexpected adverse events, suspected unexpected serious adverse reactions, and the number of hypoglycaemic events (blood glucose levels <3.1 mmol/L or requiring third-party assistance). AEs were defined as any undesirable experience from screening up until 6 months post DMR, whether or not the experience was considered to be related to the DMR (device or procedure) or the GLP-1RA liraglutide (study drug). AEs were graded as mild, moderate, or severe. The relationships to the device, procedure, and study drug were assessed in terms of "not", "unlikely", "possibly", "probably", and "definitely" (see Table 4).

Sample size calculation

We expected that without DMR, at most 8.8% of patients would remain insulin-independent, based on the weighted average of multiple studies that investigated the percentage of patients on GLP-1RA with adequate glucose regulation without insulin.[3-7]. Assuming that 40% of previously insulin-dependent T2DM patients could be free of insulin therapy 6 months after the DMR procedure with concomitant GLP-1RA treatment and lifestyle counselling support, the required sample size, with a power of

80% and alpha of 0.025 (one-sided), was 16 patients.

Subgroup analysis responders versus nonresponders

In the nonresponder group, the baseline HbA1c values were slightly higher than those of the *responder group*, but this difference was not statistically significant: 8.0% (IQR, 7.3-8.3) vs. 7.4% (IQR, 7.1-7.6). Baseline C-peptide levels were slightly lower in the nonresponder group than in the *responder group*, but this difference was also not statistically significant: 0.54 nmol/L (IQR, 0.36-0.92) vs. 0.63 nmol/L (IQR, 0.58-0.91).

References of supplementary material

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