Title: Investigation of the mechanism of action of duodenal mucosal resurfacing. The *DOMINO* experimental medicine study.

Authors: Vasha Kaur [1]*, Georgios K. Dimitriadis [2]*, Belen Pérez-Pevida [1], Davinder Singh Bansi [3], Channa Jayasena [1], Danielle Bate [4], Rhian Houghton [1], Barbara Fielding [6], Danai Balfoussia [7], Lisa Webber [7], Yun Miao [1], Frederick Mears [1], Nicola Jackson [6], Lucy Coppin [6], Jeremiah Perez [8], Megan Williams [8], Brett Johnson [1], Margot Umpleby [6], Harpal Randeva [4, 5]*, Alexander Dimitri Miras [1]*.

* equally contributing authors

Affiliations

1. Department of Metabolism, Digestion and Reproduction, Imperial College London, UK
2. Department of Endocrinology, King's College Hospital NHS Foundation Trust, Denmark Hill, SE5 9RS, UK
3. Department of Gastroenterology, Imperial College Healthcare NHS Trust, UK
4. Warwickshire Institute for Diabetes, Endocrinology & Metabolism, University Hospitals Coventry & Warwickshire, UK
5. Department of Experimental & Translational Medicine, Warwick Medical School, UK.
6. Department of Nutritional Sciences, University of Surrey, UK
7. Department of Gynaecology, Imperial College Healthcare NHS Trust, UK
8. Biostatistics, Avania Clinical, US

Corresponding author

Dr Alexander Miras
Senior Clinical Lecturer in Endocrinology
Department of Metabolism, Digestion and Reproduction
Hammersmith Hospital
Imperial College London
W12 0NN, UK
Email: a.miras@nhs.net
Mobile: +44 (0) 7958377674

Abstract

Background: Duodenal mucosal resurfacing (DMR) is a novel day-case endoscopic intervention which results in weight loss-independent reductions in HbA1c in patient with type 2 diabetes mellitus (T2DM). We hypothesized that DMR works by increasing insulin sensitivity and we aimed to investigate the mechanism of action of DMR through longitudinal metabolic phenotyping in humans

Methods: Thirty-two insulin-resistant women with polycystic ovary syndrome (PCOS) and obesity were randomised in a double-blinded manner to DMR or sham endoscopy. They underwent measurements of insulin sensitivity using euglycaemic hyperinsulinaemic clamps, insulin secretion using oral glucose tolerance tests and reproductive function using weekly reproductive hormone profiles and ovarian ultrasonography for 6 months post-intervention.

Results: A small increase in total body insulin sensitivity measured by the clamp was observed in both groups at week 12. An increase in insulin sensitivity, as measured by HOMA-IR, was observed in both groups at week 24. There was an increase in the number of menses (median 2 DMR, 0.5 sham). There were no significant differences between the two groups in these outcomes or insulin secretion.

Conclusions: These findings suggest that DMR does not work by increasing insulin sensitivity in euglycaemic, insulin resistant women with PCOS. The procedure may exert its effects only in the context of hyperglycaemia or pathologically hyperplastic, insulin-desensitised duodenal mucosa. Future studies could examine the effect of DMR in people with T2DM in whom an insulin sensitising effect might be more pronounced, but also explore the reduction of intestinal glucose absorption as an alternative mechanism of action.

Keywords: insulin, resistance, polycystic ovarian syndrome, endoscopic, ovulation, small intestine.

Abbreviations - DMR: duodenal mucosal resurfacing

1.0 Introduction

The management of type 2 diabetes mellitus (T2DM) has improved dramatically in the last decade through the use of modern glucose-lowering pharmacotherapy. Despite this, only 40% of people with T2DM in England and Wales meet the UK National Institute for Health and Care Excellence defined treatment targets for glucose control, blood pressure and blood cholesterol [3].

In contrast, bariatric or metabolic surgery, and in particular the Roux-en-Y gastric bypass (RYGB), is substantially more effective than intensive medical care for the treatment of hyperglycaemia of T2DM (e.g. [4]). The effects of surgery are so profound that 50% of people achieve "diabetes remission", i.e. euglycaemia in the absence of glucose-lowering medications ([4]). Manipulations in the anatomy of the gut in RYGB underpin changes in the physiology of appetite and glucose regulation. These exciting discoveries have led to the recognition of the intestine as a potent endocrine organ.

However, the majority of people with T2DM do not wish to undergo a major gastrointestinal procedure as even laparoscopic surgery is not without risk [5]. It is a treatment with high upfront costs which many healthcare systems cannot afford [6]. Overall, there is a large gap in treatment efficacy between lifestyle / pharmacotherapy and surgical interventions for T2DM.

Endoscopic interventions could address this gap and unmet clinical need.
The duodenal mucosal resurfacing (DMR) intervention is a novel therapy for the treatment of T2DM. It involves the hydrothermal ablation of up to 14 cm of the duodenal mucosa through a specially designed endoscopic catheter [9-11]. The procedure is performed under general anaesthesia, patients are discharged home the same day and it does not involve the implantation of a foreign body. Thus, it is associated with only transient gastro-intestinal side effects and a low incidence of complications [9-11]. The evolving evidence from cohort studies and 1 RCT has demonstrated that it induces reductions of glycated haemoglobin of 0.5-1.4% by 3-6 months in the absence of clinically significant weight loss [9-11]. It is this intriguing weight loss-independent effect on glycaemia that generates a number of hypotheses regarding its mechanisms of action which remains elusive.

The aim of this study was to investigate the mechanism of action of DMR in a cohort of insulin resistant women with polycystic ovary syndrome (PCOS), obesity and oligomenorrhea. We chose this model of insulin resistance as it avoids the practical complexities, heterogeneity and confounding variables present in people with T2DM. We hypothesized that an intervention combining DMR with lifestyle intervention would improve insulin sensitivity more than lifestyle intervention alone. In this population, the improvements in insulin sensitivity would translate to increased number of menses.

2.0 Methods

2.1 Study Design

This was a mechanistic study conducted using a multicentre prospective randomised double-blinded sham-controlled design. It was conducted at two academic clinical centres in the UK, Imperial College London and University Hospitals Coventry and Warwickshire. Thirty female participants were recruited and randomised, using a computer software algorithm at a 1:1 ratio to receive lifestyle modification with DMR or a sham endoscopic procedure. Following randomisation, all participants were followed-up for 6 months (Figure 1). The full protocol is included as a supplementary file.

2.2 Inclusion and Exclusion Criteria

Key inclusion criteria for the study were women of reproductive potential, aged between 18 and 50 years, with a body mass index (BMI) ≥30 kg/m^2, a diagnosis of PCOS based on the National Institute of Health criteria [12], insulin resistance defined as HOMA-IR ≥3.0 and/or blood glucose level 7.8-10.9 mmol/L after a 2-hour OGTT, and <6 reported menses in the 12 months prior to screening. Key exclusion criteria were a diagnosis of Type 1 or Type 2 diabetes, use of medications affecting insulin sensitivity or reproductive function at screening or 2 months prior.

2.3 Study Interventions

Participants were invited to a screening visit to be assessed for eligibility. Following inclusion in the study, participants were asked to take Medroxyprogesterone 10mg once a day for 10 days to induce a menstrual bleed before the baseline visit to enable all women to be studied at the early follicular phase of their menstrual cycle.

2.4 DMR and sham procedure

All the procedures were performed under general anaesthesia at Imperial College London by a single endoscopist (DSB).

All participants were assessed for technical feasibility of DMR at a screening gastro-duodenoscopy prior to randomisation, to assess for precluding conditions such as duodenitis, duodenal ulcers, varices, strictures or telangiectasia. A clip was placed distal to the papilla and a guidewire was passed into the duodenum. The sealed randomisation envelope was then opened by the endoscopist to reveal the allocation. Participants and the rest of the research team were blinded to the assigned allocation.

Participants allocated to the DMR arm received the DMR procedure using the Fractyl Revita System (Fractyl, Lexington) as detailed previously [9 11]. In brief, the DMR procedure was performed endoscopically using a single-use catheter with a terminal balloon and three needles spaced at 120° around the balloon's circumference. This was passed over the guidewire into the duodenum and distal to the papilla. Vacuum was used to draw the

intestinal mucosa onto the needle ports and saline was then injected into the submucosal space to facilitate the circumferential lift of the mucosal tissue, effectively separating it from the underlying duodenal layers. The balloon was then inflated with hot water (heated to 90°C) to thermally ablate the lifted mucosa under endoscopic and fluoroscopic guidance. The submucosal lift and circumferential hydrothermal ablation are then repeated for a length of 10 – 14cm, from the post-papillary duodenum up to the ligament of Treitz. The sham procedure consisted of placing the DMR catheter in the stomach of the patient and leaving it in place for 45 minutes before removing it. All procedures were carried out as day-case.

Following the interventions, participants in both arms of the study were instructed to consume a low-calorie liquid diet (1200 kcal/day, containing 16% protein, 49% carbohydrate and 35% fat) for 14 days using 125 ml Fortisip Compact Protein (Nutricia, Wiltshire).

For the 6 months thereafter, participants received standard NHS behavioural modification ("tier 3 intervention") that included advice on healthy eating behaviour and increased physical activity by a dietician specialising in obesity in accordance with the UK National Institute of Clinical and Care Excellence guidance.

2.5 Metabolic measurements

2.5.1 Hyperinsulinaemic euglycaemic clamp

Participants underwent the gold-standard assessment of insulin sensitivity using a two-phase euglycaemic hyperinsulinaemic clamp ("clamp") incorporating use of a stable isotope ([6, 6-$^{2}H_{2}$] labelled-glucose) at baseline and 3 months after intervention as previously described [13]. At 17.00 on the evening prior to their visit, participants were instructed to have a standardised meal of 400mls of Ensure Plus and were then allowed a liquid diet until 21.00. They were then instructed to fast for 12 hours prior to their visit at the Imperial National Institute for Health Research (NIHR) Clinical Research Facility (CRF). and only allowed clear fluids.

The rate of 20% glucose infusion during time points +210 to +240 minutes was used as a measure of total body insulin sensitivity. Glucose isotopic enrichment was measured by gas chromatography mass spectrometry using a 7890A Gas Chromatograph coupled to a 5975C MSD (Agilent Technologies, Wokingham, Berks, UK) at the Stable Isotope Laboratory in the Faculty of Health and Medical Science, University of Surrey. Plasma glucose was measured on the ARCHITECT c8200 platform using a hexokinase method. The rate of glucose appearance (Ra), which is a marker of hepatic insulin sensitivity, and disappearance (Rd) from plasma, which is a marker of peripheral insulin sensitivity, were calculated using non-steady-state equations proposed by Steele and modified for stable isotopes[14].

2.5.2 Oral Glucose Tolerance Test (OGTT)

Participants in both arms of the study were assessed with a 3-hour OGTT at screening, 2 weeks and 3 months after intervention. Participants were instructed to fast for 12 hours prior to

attending for their OGTT. An intravenous cannula was placed in the antecubital vein of the patient. Participants were instructed to consume 75g of glucose powder dissolved in 300ml water at time point 0. Blood samples were obtained at time points -30, 0, +15, +30, +60, +120, and +180 minute, centrifuged immediately and stored at -80 °C until analysis.

2.5.3 Surrogate indices of insulin sensitivity and secretion

The following indices were used as surrogate measures of insulin sensitivity and insulin secretion:

(i) Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) = Fasting plasma glucose (mmol/L) x fasting serum insulin (mU/ml) / 22.5

(ii) Matsuda Index = 10 000 / [(Fasting plasma glucose x Fasting serum insulin) x (Mean plasma glucose $_{0\text{-}120}$ x Mean serum insulin $_{0\text{-}120}$)]$^{1/2}$, where the mean glucose and mean insulin values were derived from plasma glucose and serum insulin levels at 0, +15, +30, +60 and +120 minutes of the OGTT,

(iii) Oral disposition index (ODI) = (Insulin AUC $_{0\text{-}120}$ / Glucose AUC $_{0\text{-}120}$) x Matsuda Index, where AUC $_{0\text{-}120}$ refers to the area under the curve (AUC) from time point 0 to +120 during the OGTT.

2.6 Reproductive measurements

The number of reported menses was captured using an online data collection platform (SurveyGizmo, Boulder, Colorado) for the 6 months after intervention. Ovulation was also formally assessed with pelvic ultrasound scans and reproductive hormone profiles performed weekly between weeks 12 to 24 after intervention. The ultrasonographer was blinded to treatment allocation. During each scan, the following parameters were measured: endometrial thickness (in millimetres), mean ovarian volume (in cubic centimetres), mean follicle number, and maximum diameter of largest follicle in each ovary (in millimetres). Ovulation was defined as a rise in serum progesterone >10 nmol/L together with suggestive radiological features of visualization of a dominant follicle with subsequent appearance of a corpus luteum [15]. The reproductive hormone panel included the measurement of serum progesterone, oestradiol, luteinising hormone, follicle stimulating hormone, sex hormone binding globulin, testosterone, DHEAS, and androstenedione.

2.7 Primary outcomes

The three co-primary outcomes included the change from baseline in:

- Total body insulin sensitivity at 12 weeks as assessed by the clamp
- Insulin sensitivity at 24 weeks as assessed by HOMA-IR
- The number of menses in the 24 weeks post-procedure.

2.8 Secondary and exploratory outcomes

These are detailed in the statistical analysis plan (appendix).

2.9 Statistical Analyses

These were conducted by two senior biostatisticians (JP, MW) and detailed in the statistical analysis plan (appendix).

In brief, normality assessment was performed, and all statistical tests were conducted accordingly. The primary analysis for the change from baseline to Week 12 in total insulin sensitivity, derived from the clamp, was performed in the mITT population using an Analysis of Covariance (ANCOVA) model with terms for baseline total insulin sensitivity and treatment. The primary analysis for change from baseline to Week 24 in insulin sensitivity as assessed by HOMA-IR was carried out using Mixed Model Repeated Measures in the mITT population. The primary analysis for the number of menses during the first 24 weeks after randomization was performed in the mITT population comparing treatment groups with an ANCOVA model on rank of measured number of menses over 24 weeks with terms for rank of number of reported number of menses in the 12 months before randomisation and treatment. For each primary endpoint corresponding analyses was also conducted in the per protocol analysis population.

For Analysis data sets, statistical analyses and associated output were generated using SAS version 9.3 or later, SPSS Software version 24 or later or Prism version 6.0 or later.

2.10 Study oversight

The study was funded through the Fractyl® investigator-initiated study programme and sponsored by Imperial College London. The study was approved by the London-Dulwich Research Ethics Committee (Reference number 17/LO/1095), registered on the ISRCTN registry (ISRCTN76278694) and conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The sponsor and funder had no role in the accrual or analysis of the data or in the preparation of the manuscript.

3.0 Results

3.1 Study patients

In total, 32 participants were randomised to receive either DMR or sham procedures from May 2018 to February 2019 (Figure 1, Supplemental File). Two participants were excluded from the ITT/mITT analysis due to technical difficulty intubating the duodenum and accidental unblinding of the research team during endoscopy. Both participants were replaced. Two participants were excluded from the ITT/mITT analysis due to major protocol deviations (laboratory assessment incomplete due to poor intravenous access and poor adherence to the dietary intervention). Both were included in the PP analysis.

Across the entire cohort, the mean age was 31.1 ± 6.1 years, and the mean BMI was 42.5 ± 5.6 kg.m^2 (Table 1). The mean HOMA-IR was 6.2 ± 3.1 and HbA1c 38.7 ± 4.6 mmol/mol.

3.2 Procedural information

Sixteen patients underwent the DMR procedure during this study. One participant was replaced due to technical difficulty intubating the duodenum which precluded the procedure. DMR was feasible in all other participants and the required length of ablation was consistently achieved. The total length of duodenum ablated was 11.3 ± 1.8 cm and the duration of the procedure was 82.4 ± 49.2 minutes.

3.3 Primary endpoints

A small increase in total body insulin sensitivity as measured by the glucose infusion rate during clamp was observed in both groups at week 12, but there was no significant difference between the groups (Table 2). An increase in insulin sensitivity as measured by HOMA-IR was observed in both groups at week 24, but there was no significant difference between the groups. There was an increase in the number of menses over a 6-month period by a median of 2 in the DMR group and 0.5 in the sham group, but there was no significant difference between the groups (Table 1, Supplemental file).

3.4 Secondary and exploratory outcomes

The rate of glucose appearance during the hyperinsulinaemic euglycaemic clamp (a measure of hepatic insulin sensitivity) and rate of glucose disappearance (a marker of peripheral insulin sensitivity) were not significantly different either between or within the groups at baseline and 3-months post-intervention (Figure 2).

No significant difference was observed at the OGTT between or within the groups in terms of glucose and insulin excursions at baseline, 2 weeks after and 3 months after the intervention (Figure 3 and Table 3).

Participants in both groups lost small amounts of weight of approximately 4kg at 2 weeks and 2kg at 3 months, but there was no significant difference between groups at any time point (Table S1). Comparison of the participants' liver and lipid profiles did not reveal any significant differences between or within groups at any time point (Table S1).

In terms of reproductive outcomes, the participants in the DMR group reported a median of 1 menstrual periods in the 6 months pre-procedure compared to 3 menstrual periods in the 6 months post-procedure. In the sham group, the participants reported a median of 1.5 menstrual periods pre-procedure and 2 post-procedure. Participants in the DMR group had more clinical and ultrasonographic ovulatory events compared to the sham group (2.2 $\pm$ 3.3 vs 1.5 $\pm$ 1.2), although this difference did not reach statistical significance. Biochemically, the

reproductive profiles of the participants in both groups did not change significantly either between or within the groups (Table S2, Supplemental file).

3.5 Adverse events

In total there were 22 procedure-related adverse events in the DMR group, 29 in the sham group, and 2 significant adverse events observed during the study (Table S3, Supplemental File). The most common adverse event observed was abdominal pain which was self-limiting in all cases. One patient in the DMR group was admitted to hospital with cholecystitis 4 months following the procedure. This was though not to be related to the procedure due to its timing. One patient in the sham group developed breathlessness due to a mucous plug and was admitted for observation overnight.

4.0 Discussion

In this experimental medicine study, we demonstrated that the addition of the DMR to lifestyle modification does not result in superior improvements in insulin sensitivity in women with PCOS and insulin resistance over a 6-month follow-up period compared to a sham procedure and lifestyle intervention alone. This was the first attempt to determine the elusive mechanism of action of this novel intervention in humans using state-of-the-art metabolic methodologies.

Contrary to our hypothesis, we did not observe an effect of the DMR on hepatic insulin sensitivity at 12 weeks. Instead, there was a slight increase in total body insulin sensitivity as measured by the clamp probably as the result of the small degree of weight loss. The rationale underlying the hypothesis that insulin sensitivity is the predominant mechanism of action of the DMR was supported by evidence from human and animal studies. They have demonstrated that procedures including the duodenal-jejunal bypass operation and the duodenal-jejunal bypass liner, in which food bypasses the proximal intestine, cause caloric restriction and weight-loss independent reductions in fasting glucose and markers of hepatic insulin sensitivity [17-19]. Indeed, the DMR is associated with reductions in HOMA-IR, a surrogate marker of hepatic insulin sensitivity, in humans with T2DM at 3 and 6 months after intervention [9 11]. The mechanisms underlying these observations are thought to involve altered glucose-sensing in the mid- and distal jejunum [20 21] triggering neural or hormonal signals that reduce hepatic glucose output or the reduction in secretion of putative insulin "desensitising" factors from the duodenum and proximal jejunum [22].

There are a number of potential explanations for our findings. The duodenum and its mucosa can be pathological in the context of T2DM, insulin resistance and hyperglycaemia [23 24], but not necessarily in other insulin resistance states like PCOS or fatty liver disease. PCOS is considered an early manifestation of the spectrum of metabolic disorders characterised by insulin resistance. It might be the case that duodenal pathology only becomes apparent in more advanced stages of this continuum when hyperglycaemia ensues. Thus, selecting the

duodenal mucosa as a therapeutic target may only be effective in T2DM and not in other insulin resistant, but still euglycaemic, states. Consistent with this explanation, (i) duodenal mucosal abrasion does not improve glycaemia in Sprague-Dawley rats without diabetes and hyperglycaemia [10] and (ii) we did not observe any improvements in fasting and post-prandial glucose excursions or glycated haemoglobin in our cohort which was in its majority euglycaemic. Even in the context of established T2DM, there is substantial variability in response to the DMR [9 11] suggesting that pathology of the intestinal mucosa might not be a universal finding in this cohort. It should be noted that the evidence for link between a pathological mucosa and a dysmetabolic state is stronger in animal models than humans. These unanswered questions can be addressed by obtaining human duodenal biopsies and correlating histological findings with metabolic profiles in people with and without hyperglycaemia.

As hypothesized, we did not observe an increase in indices of insulin secretion after the DMR. The enhanced secretion of glucagon-like peptide-1 that drives, at least in part, insulin secretion after the RYGB is thought to be due to the rapid delivery of less digested nutrients to the L-cells of the ileum [29]. After the DMR we did not expect an increase in gastric emptying or intestinal motility, and it is unlikely that the length of mucosa ablated is enough to affect protein or fat absorption.

Our findings are strengthened by key aspects of the study design. These include (i) the multi-centre double-blinded sham-controlled randomised approach, (ii) the standardisation of the intervention which was performed by a single endoscopist, (iii) the use of the gold-standard method of measuring insulin sensitivity through euglycaemic hyperinsulinaemic clamps with stable isotopes, (v) the selection of a homogenous cohort of women with severe PCOS and insulin resistance, (vi) the longitudinal deep metabolic and reproductive phenotyping of participants both early and at 6 months after the two interventions and (vii) the conduct of the baseline measurements at the same phase of the menstrual cycle in all participants and standardisation of caloric intake before the metabolic measurements.

The limitations of the study include the relatively short follow-up, small sample size to detect differences in clinical outcomes and especially those with substantial variability like ovulation, and the use of HOMA-IR instead of clamps to measure insulin sensitivity at the 6-month time point. This was an experimental medicine study powered to detect differences in insulin sensitivity and not a clinical trial. The randomised sham-controlled double-blinded design was only used to increase scientific vigour.

In conclusion this study demonstrated that the DMR intervention does not increase insulin sensitivity in insulin resistant women with PCOS. Future studies could examine the effect of DMR in people with T2DM in whom an insulin sensitising effect might be more pronounced, but also explore intestinal glucose absorption as an alternative mechanism of action. Experimental medicine studies interrogating the elusive metabolic biology of the intestine are

key to the optimisation of current therapies but also development of novel non-surgical metabolic interventions. **Acknowledgments**

This manuscript presents independent research funded by Fractyl's investigator-initiated research programme and supported by the Imperial National Institute for Health Research (NIHR) Clinical Research Facility (CRF). The views expressed are those of the authors and not necessarily those of Fractyl, the NHS, the NIHR or the Department of Health. The Section of Endocrinology and Investigative Medicine is funded by grants from the MRC, BBSRC, NIHR and is supported by the NIHR Biomedical Research Centre Funding Scheme.

Funding: This research funded by Fractyl's investigator-initiated research programme. The funder had no role in the study design, collection, analysis and interpretation of data, writing of the report or in the decision to submit the article for publication.

Author contributions

The conception and design of the study: ADM, HR.
Acquisition of data, or analysis and interpretation of data: VK, GKD, BPP, DSB, CJ, DB, RH, BF, DB, LW, YM, FM, NJ, LC, JP, MG, BJ, MU, HR, ADM.
Drafting the article, revising it critically for important intellectual content: VK, GKD, HR, ADM.
Final approval of the version to be submitted: VK, GKD, BPP, DSB, CJ, DB, RH, BF, DB, LW, YM, FM, NJ, LC, JP, MG, BJ, MU, HR, ADM.

Conflicts of interest: DSB is a proctor for Apollo Endosurgery and has received funding from Fractyl to attend educational meetings. VK has received funding from Fractyl to attend educational meetings. All other authors do not report any relevant conflicts of interest.

Data sharing statement

Data are archived at the Imperial NIHR Clinical Research Facility. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

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Figures

Figure 1: Study design and interventions

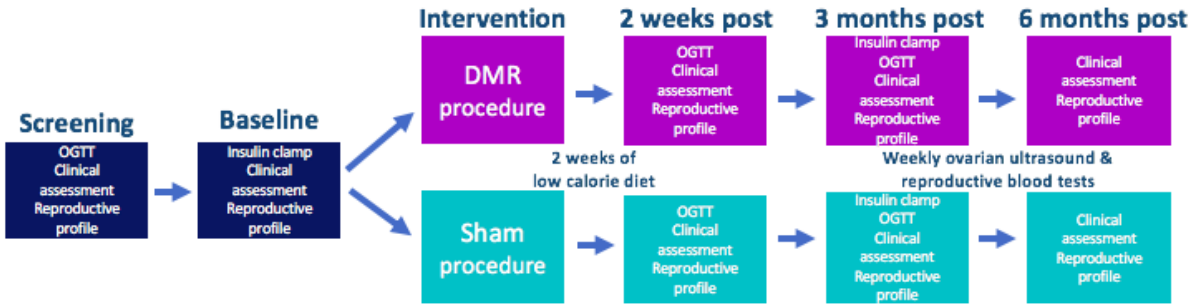

Figure 2: Graph A and B denotes the rate of glucose appearance (Ra) during the low insulin infusion rate phase of the euglycaemic hyperinsulinaemic clamp for the DMR and sham groups respectively. Graph C and D denotes the rate of glucose disappearance (Rd) during the high insulin infusion rate phase of the euglycaemic hyperinsulinaemic clamp for the DMR and sham groups respectively. Each line represents the change within an individual participant.

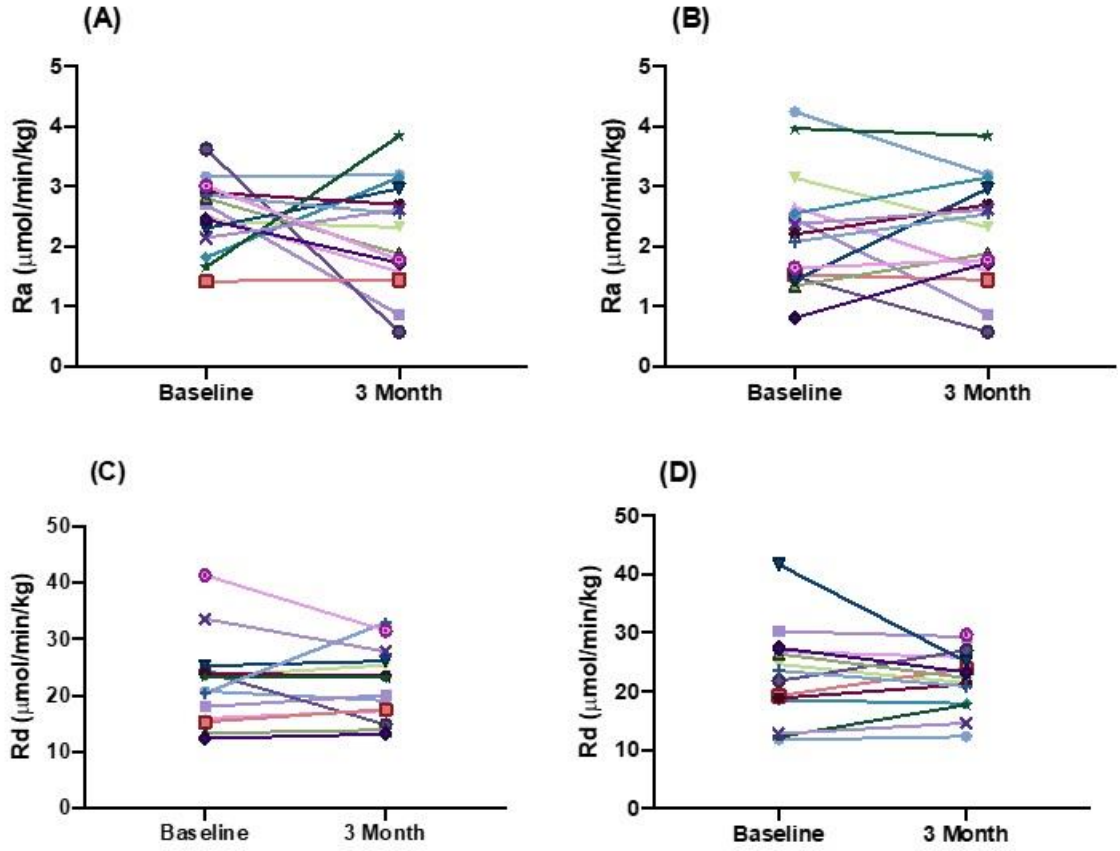

Figure 3: Glucose (Graphs A, B and C) and insulin (Graphs D, E and F) concentrations during the oral glucose tolerance test for the Duodenal Mucosal Resurfacing (DMR, n=15) and SHAM (n=15) group. Data presented as Mean ± SD.

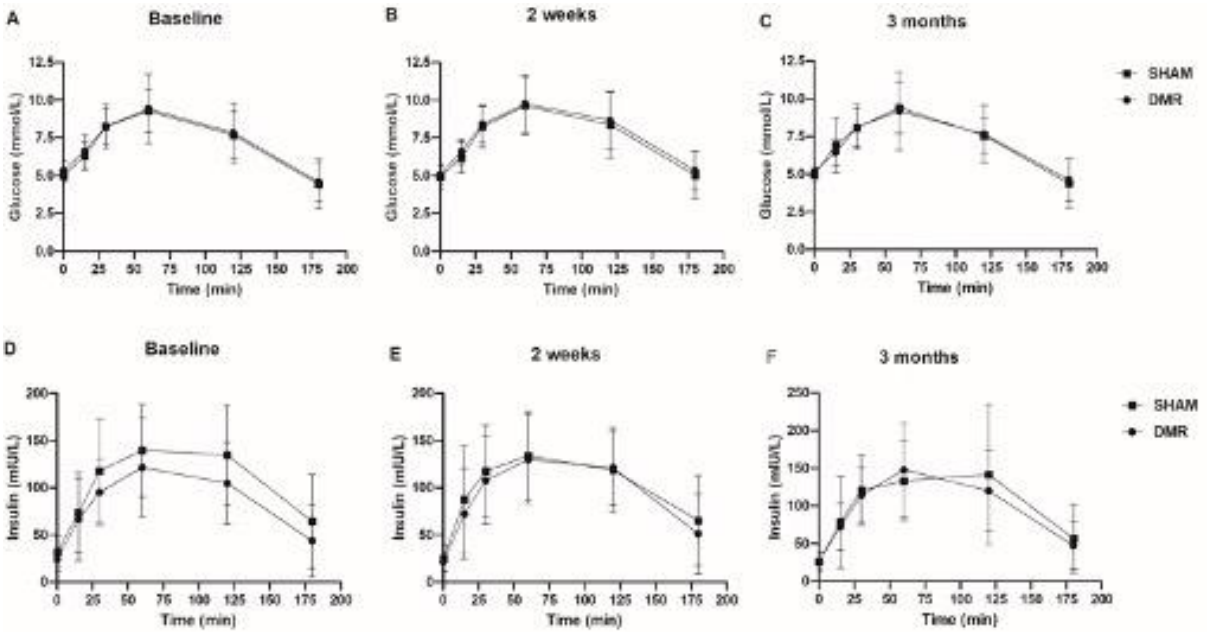

Table 1. Baseline Characteristics

	DMR Group (n=15)	**Sham group (n=15)**
Age (years)	30.6 ± 5.2	31.6 ± 6.9
Ethnic origin		
White %, n	60% (9/15)	60% (9/15)
Black %, n	0% (0/15)	6.7% (1/15)
Asian %, n	26.7% (4/15)	13.3% (2/15)
Mixed/Other %, n	13.3% (2/15)	20% (3/15)
Weight (kg)	107.8 ± 19.0	121.2 ± 12.6
Body Mass Index (kg/m^2)	40.2 ± 6.6	44.7 ± 3.4
Body fat (%)	43.9 ± 3.5	46.1 ± 2.1
Waist / Hip ratio	0.9 ± 0.1	0.9 ± 0.1
Markers of fecundity		
Number of menses in preceding 12 months	2 [0,6]	3 [2,4]
Participants with parity %, n	20% (3/15)	33.3% (5/15)
Participants with prior miscarriage %, n	26.7% (4/15)	20% (3/15)
Pre-existing Medical Conditions		
Sleep Apnoea %, n	6.7% (1/15)	6.7% (1/15)
Hypertension %, n	20.0% (3/15)	33.3% (5/15)
Hypercholesterolaemia %, n	33.3% (5/15)	6.7% (1/15)
Non-diabetic hyperglycaemia %, n	26.7% (4/15)	13.3% (2/15)
Glycaemic profile		
HbA1c (mmol/mol)	39.7 ± 3.7	37.7 ± 5.3
Fasting glucose (mmol/L)	5.5 ± 0.7	5.1 ± 0.6
Fasting insulin (mIU/L)	22.0 ± 8.4	27.7 ± 13.9
HOMA-IR	6.2 ± 3.4	6.2 ± 2.9
Oral Disposition Index	27.2 ± 10.0	28.9 ± 9.1
Liver Profile		
ALT (U/L)	32.9 ± 20.8	35.2 ± 22.0
AST (U/L)	30.5 ± 10.9	26.6 ± 8.2
AST/ ALT	1.1 ± 0.6	1.0 ± 0.5
ALP (U/L)	73.7 ± 17.6	82.4 ± 17.7
GGT (U/L)	39.1 ± 48.2	27.60 ± 9.7
Lipid Profile		
Total cholesterol (mmol/L)	5.3 ± 1.0	4.9 ± 0.8
HDL (mmol/L)	1.1 ± 0.2	1.1 ± 0.2
LDL (mmol/L)	3.4 ± 0.7	3.2 ± 0.6
Non-HDL (mmol/L)	4.2 ± 0.9	3.8 ± 0.7
Triglyceride (mmol/L)	1.7 ± 0.8	1.2 ± 0.4
Reproductive hormone profile		
LH (U/L)	5.7 ± 3.7	6.7 ± 3.0
FSH (U/L)	4.0 ± 1.4	5.3 ± 3.0

SHBG (nmol/L)	21.9 ± 8.1	28.1 ± 7.0
Progesterone (nmol/L)	4.8 ± 10.2	2.7 ± 6.2
Testosterone (nmol/L)	1.9 ± 0.9	2.5 ± 1.5
Oestradiol (nmol/L)	259.1 ± 155.6	252.5 ± 144.1
DHEAS (µmol/L)	6.4 ± 3.6	5.19 ± 4.1
Androstenedione (nmol/L)	6.4 ± 2.4	6.0 ± 2.2

Data presented as mean ± SD or median [interquartile range]. Percentages with n used where stated. Modified intension to treat population. HOMA-IR: homeostatic model assessment of insulin resistance, ALT: alanine aminotransferase, AST: Aspartate aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, HDL: high density lipoprotein, LDL: Low density lipoprotein, LH: luteinising hormone, FSH: follicle-stimulating hormone, SHBG: sex-hormone-binding globulin, DHEAS: dehydroepiandrosterone sulphate.

Table 2. Measurements of Insulin Sensitivity

	DMR Group (n=14)	Sham group (n=14)	p-value
HOMA-IR			
Pre-intervention	6.2 ± 3.4	6.2 ± 2.9	0.48
Week 2	4.0 ± 1.3	3.9 ± 1.6	0.41
Week 12	5.1 ± 2.2	4.7 ± 2.5	0.31
Week 24	5.5 ± 2.4	5.0 ± 3.1	0.30
Euglycaemic Hyperinsulinaemic Clamp Glucose Infusion Rate (mg/min/kg)			
Total Body Insulin Sensitivity			
Pre-intervention	5.2 ± 1.7	5.3 ± 2.1	0.45
Week 12	5.4 ± 1.6	5.6 ± 1.4	0.37
Hepatic Insulin Sensitivity			
Pre-intervention	1.4 ± 0.4	1.4 ± 0.5	0.40
Week 12	1.4 ± 0.4	1.5 ± 0.4	0.36
Peripheral Insulin Sensitivity			
Pre-intervention	3.9 ± 1.4	3.90 ± 1.76	0.47
Week 12	4.0 ± 1.4	4.11 ± 1.04	0.40
Rate of glucose appearance (µmol/min/kg) Basal stage (prior to insulin infusion)			
Pre-intervention	8.8 ± 1.1	8.5 ± 0.7	0.16
Week 12	9.0 ± 1.1	8.4 ± 0.9	0.14
Rate of glucose appearance (µmol/min/kg) (Low-dose insulin infusion stage)			
Pre-intervention	2.5 ± 0.6	2.3 ± 1.0	0.20
Week 12	2.6± 1.0	2.2 ± 0.9	0.23
Rate of glucose disappearance (µmol/min/kg) (High-dose insulin infusion stage)			
Pre-intervention	22.3 ± 7.5	22.6 ± 8.1	0.47
Week 12	22.0 ± 6.1	22.2 ± 5.0	0.38

Data presented as mean ± SD. HOMA-IR: homeostatic model assessment of insulin resistance. Analyses was conducted using analysis of co-variance (ANCOVA) and Mixed Model Repeated Measures on the modified intension to treat population. N=14 for both groups as 1 patient was lost to follow-up in the DMR group and a 1 patient had poor IV access and was unable to complete the clamp study.

Table 3: Measurements of Glucose Tolerance and Insulin Secretion

	DMR Group (n=15)	Sham group (n=15)	p-value
Oral Disposition Index			
Baseline	27.5 ± 10.3	28.9 ± 9.1	0.36
Week 2	29.5 ± 12.2	31.7 ± 10.0	0.35
Week 12	28.7 ± 9.2	31.1 ± 9.1	0.28
Glucose AUC (mmol/L.min)			
Baseline	1350.8 ± 275.6	1328.8 ± 184.5	0.40
Week 2	1445.4 ± 226.1	1402.3 ± 253.9	0.33
Week 12	1331.5 ± 252.9	1331.3 ± 151.6	0.41
Glucose Incremental AUC (mmol/L.min)			
Baseline	405.7 ± 198.3	443.8 ± 186.0	0.30
Week 2	538.5 ± 170.2	533.2 ± 203.2	0.30
Week 12	418.1 ± 223.2	452.6 ± 131.2	0.42
Insulin AUC (mIU/L.min)			
Baseline	16385.0 ± 6044.8	20710.3 ± 7002.2	0.05
Week 2	18393.5 ± 6466.4	20100.17 ± 6141.2	0.21
Week 12	19148.8 ± 6385.0	20010.27 ± 9012.9	0.41
Insulin incremental AUC (mIU/L.min)			
Baseline	12065.3 ± 4614.4	15907.3 ± 6401.9	0.04
Week 2	14595.6 ± 6016.0	15695.2 ± 4835.2	0.21
Week 12	14398.5 ± 5551.7	15399.7 ± 9267.3	0.41

Data presented as mean ± SD. AUC: area under the curve. Analyses was conducted using analysis of co-variance (ANCOVA) and Mixed Model Repeated Measures on the modified intension to treat population).