

Review

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Duodenal mucosa resurfacing: the endoscopic silver bullet against metabolic disorders?

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Abstract

With the backset of the epidemic surge of type 2 diabetes (T2D), obesity, and metabolic dysfunction-associated steatotic liver disease (MASLD), the key role of jejunal mucosa in the development of metabolic disorders, beyond its normal function in nutrient absorption, has become increasingly appreciated. In humans, compared to non-diabetic controls, diabetic patients have jejunal mucosa hypertrophy, hyperplasia of enteroendocrine cells, and increased numbers of enteroendocrine cells and enterocytes. Moreover, functional changes have also been observed, including variations in glucose transporters, enteric nerves, and intestinal microbiota composition. Duodenal mucosa resurfacing (DMR) starts with the assumption that resurfacing the mucosal interface will reset and correct any abnormal signaling from the duodenal mucosa and will, therefore, result in improved pancreatic endocrine function and glucose tolerance owing to restored normal mucosal surface. The endoscopic technique of DMR involves the hydrothermal ablation of the more superficial duodenal mucosal layers. Data reviewed indicate that DMR is a safe and well-tolerated procedure, with favorable outcomes on glucose homeostasis among those with T2D, body weight among those with obesity, and liver tests among those with MASLD. Additional studies are therefore urgently needed to ascertain, among the various surgical, endoscopic and medical choices, the best precision medicine option to fit the individual patient with T2D, obesity, and MASLD.

Keywords: BMI, C-peptide, HbA1c, metabolic dysfunction-associated steatotic liver disease, obesity, type 2 diabetes



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INTRODUCTION

Common metabolic diseases, comprising type 2 diabetes (T2D), arterial hypertension, obesity, hypercholesterolemia, and metabolic dysfunction-associated steatotic liver disease (MASLD), have become a health challenge over the last thirty years, accounting for a substantial burden of disability-adjusted life years (DALYs) and deaths globally^[1]. In 2021, arterial hypertension had the greatest burden, while T2D conferred much greater disability than MASLD^[1]. India, China, and the United States have the highest absolute burden, and the Oceania Islands exhibit the highest relative burden^[1]. The onus of T2D and obesity has increased at an accelerated rate, while the growth of arterial hypertension and hypercholesterolemia is slowing, and MASLD is stable over time^[1]. These worrying figures call for prompt action directed at the root causes of this burdening epidemic.

Which is the target we should hit to fight metabolic disorders? In other words, which is the anatomic site of the most important regulator of metabolic function in the human body? Probably most people would respond: the liver^[2]. Endocrinologists would say the pancreas^[3]; nephrologists would answer the kidneys^[4]. The most experienced clinicians would say the skeletal muscle or the visceral adipose tissue^[5]. However, three categories of medical scholars would probably respond the duodenum: metabolic surgeons, the gastroenterologists practicing endoscopy, and the physio-pharmacologists^[6-8].

Accumulating evidence suggests that the duodenum is a major player in normal metabolism and systemic metabolic dysfunction. Anatomical and functional changes, collectively representing maladaptation of the duodenal mucosa, may result from chronic exposure to unhealthy nutrient loads of fat and sugars. These eventually culminate in the development of insulin resistance, which is the common denominator of the metabolic syndrome and its constituent features^[5,9]. In 2016, Rajagopalan *et al.* published the first proof-of-concept study demonstrating that hydrothermal ablation of the duodenal mucosa elicited a clinically significant improvement in metabolic control among subjects with decompensated T2D^[10]. Two years later, Semaglutide, a synthetic analog of the human glucagon-like protein-1 (GLP-1), was licensed for use to treat T2D and certain types of obesity and overweight associated with T2D, arterial hypertension, dyslipidemia, obstructive sleep apnea, or a history of cardiovascular disease^[11]. Interestingly, the GLP-1 hormone is produced by the intestinal epithelial endocrine L cells in response to a meal and acts as a master regulator of glucose homeostasis and appetite^[12,13]. Collectively, these data clearly demonstrate the key role played by the intestinal mucosa in metabolic homeostasis.

With this intriguing landscape, the present narrative review aims to provide a critical perspective on duodenal mucosa resurfacing (DMR) as an accessible option to treat the increasing burden of metabolic disorders. To this end, we describe the DMR technique, its findings, the putative mechanisms of action, and the research agenda. Relevant articles were identified in the PubMed database accessed on November 28th, 2024, using the keyword - duodenal mucosa resurfacing [Title/Abstract].

PRINCIPLE AND TECHNIQUE OF DMR

Ablation, a common treatment modality for various medical conditions such as Barrett's esophagus, atrial fibrillation, liver tumors, benign prostatic hyperplasia, dermatologic conditions, and heavy uterine bleeding, involves a stem cell-mediated healing response that follows the physical removal of superficial abnormal tissue, eventually restoring normal tissue^[9,14].

The rationale for DMR is supported by studies in humans showing that, compared to non-diabetic controls, diabetic patients have mucosa hypertrophy in the upper GI tracts, with hyperplasia of enteroendocrine cells, and increased numbers of enteroendocrine cells and enterocytes^[9,15]. DMR assumes that resurfacing the

mucosal interface will reset and correct any abnormal signaling arising from the duodenal mucosa and will, therefore, result in improved function of pancreatic β cells and amelioration of glucose homeostasis owing to restored normal mucosal surface^[16].

The technique has been detailed elsewhere^[17]. In short, the procedure is carried out under deep sedation with propofol^[18] or general anesthesia^[19] and involves the expansion of the submucosal layer with saline, and hydrothermal ablation of the more superficial layers. To this end, a polyethylene terephthalate balloon catheter is introduced intraduodenally, and mucosal is circumferentially lifted along the length of the post-papillary duodenum. After removal of the initial catheter, a 2-cm-long balloon on the catheter is introduced and inflated with hot water for circumferential ablation of the duodenal mucosa. Under duodenoscopic inspection, repeated 10-s circumferential thermal ablations are supplied at 90 °C to achieve the mucosal ablation of the desired length^[17].

FINDINGS

Since 2016, when Rajagopalan *et al.* published their pioneering study in humans^[10], several other studies have been conducted on DMR addressing relevant metabolic endpoints. These are summarized in Table 1^[10,18,20-30]. Collectively, data indicate that the procedure is safe and, particularly when combined with GLP-1Ras and lifestyle counseling, effective in achieving improved metabolic control in selected T2D patients. This is accomplished irrespective of whether the weight loss - ranging in the various studies from 2^[22] to ~2.3 kg^[21] up to an average of 8 kg^[22] - is maintained in the long term because of intensive dietary intervention^[21-23,27], and when combined with certain glucose-lowering medications, it enabled insulin discontinuation in up to 86% patients^[31]. This figure is in the same order of magnitude reported by a recent study including 156 subjects who initiated a GLP-1 RA (receptor agonist) and, at 24 months, 81% of whom discontinued prandial insulin, while 38.6% discontinued basal insulin as well, suggesting that insulin requirement at the baseline was the only significant predictor of prandial insulin discontinuation^[32].

Moreover, improved cardiometabolic health is also accompanied by improved surrogate indices of development and fibrotic progression of MASLD^[20], although these hepatic benefits are critically dependent on concurrent lifestyle counseling and are not obtained unless lifestyle changes are implemented^[23].

However, the paucity of data on unselected patient populations with T2D of various duration and severity, and the relatively invasive DMR technique call for carefully designed and conducted randomized controlled trials. These should not be sponsored but rather investigator-driven to ascertain the true entity of the cardiometabolic and liver benefit compared to sham DMR^[27] or to simple lifestyle intervention without DMR. Additionally, the major endpoints - improved glucose homeostasis, remission of T2D, development and progression of MASLD, and control of body weight - should be based on solid long-term outcomes such as assessment of major adverse cardiovascular events, development and progression of diabetic kidney disease, cirrhosis, hepatocellular carcinoma, and survival. Finally, assessment of cost-benefit ratio and patient satisfaction may complete the research agenda.

PUTATIVE MECHANISMS OF ACTION

Exposure to nutrients is essential for maintaining the histological and functional integrity of the intestinal mucosa. A study conducted among 30 individuals who had undergone percutaneous endoscopic gastrostomy (PEG) following a prolonged period of fasting^[33] found several changes that were reversible after refeeding. These included atrophy of duodenal mucosa in 10% of cases, significantly shorter median villi length compared to controls, ultrastructural changes comprising focal shortening, bending, and disrupted enterocyte microvilli, cytoplasmatic autophagic vacuoles, dilation and vesiculation of the smooth

Table 1. Overview of published studies, ordered chronologically, assessing the safety and efficacy of DMR in humans

Author, year	Method	Findings	Comment
Rajagopalan <i>et al.</i> , 2016 ^[10]	Phase I, first-in-human, open-label, single-arm, nonrandomized design performed at a single center 39 T2D patients (HbA _{1c} 9.5%; BMI 31 kg/m ²) were enrolled (28 had LS; 9.3 cm treated; and 11 had SS; 3.4 cm treated)	DMR was well tolerated and in 3 patients post-DMR duodenal stenosis was successfully dilated with balloon HbA _{1c} was reduced by 1.2% at 6 months in the full cohort ($P < 0.001$), while the LS cohort had a 2.5% reduction in mean HbA _{1c} at 3 months post-DMR vs. 1.2% in the SS group ($P < 0.05$) Among LS subjects with decompensated T2D and on stable antidiabetic treatment post-DMR, HbA _{1c} was reduced by 1.8% at 6 months ($P < 0.01$)	DMR is safe, tolerable, and significantly reduces hyperglycemia
Van Baar <i>et al.</i> , 2019 ^[20]	Open-label, single-arm study 85 adults with T2D duration < 10 years, BMI 24-40 kg/m ² , and HbA _{1c} ranging from 7.5% to 12.0%, treated with ≥ 1 oral antidiabetic medication and FCP > 1 ng/mL were enrolled Main exclusion criteria: T1D or diabetic ketoacidosis, use of insulin or GLP-1RA	DMR was not associated with any complications. Six months after the DMR, the following parameters were significantly reduced compared to the baseline: HbA _{1c} ; FPG; ALT and AST ($P < 0.001$). Mean FIB-4 was also markedly decreased	DMR induces metabolic and hepatic benefits among T2D patients
Van Baar <i>et al.</i> , 2020 ^[21]	International multicenter, open-label study recruiting 46 T2D patients with BMI 24-40 Kg/m ² , HbA _{1c} 7.5%-10.0% on oral antidiabetic treatment who were submitted to DMR Glucose-lowering medication was kept stable for ≥ 24 weeks after the DMR procedure	37 out of 46 patients underwent complete DMR and 36 were analyzed. DMR-related AEs were reported by 24 patients. 6 and 12 months after DMR, HbA _{1c} , FPG, HOMA-IR, body weight, and liver enzymes were significantly decreased. Variations of HbA _{1c} were not correlated with weight loss	DMR is a safe endoscopic technique that induces long-lasting improvement of glucose homeostasis and liver enzymes irrespective of weight loss in subjects with inadequately controlled T2D under oral antidiabetics
Van Baar <i>et al.</i> , 2021 ^[22]	Single-arm, mono-center feasibility study enrolling 16 insulin-treated T2D subjects with HbA _{1c} $\leq 8.0\%$, basal insulin < 1 U/kg/day, FCP ≥ 0.5 nmol/L submitted to a single DMR followed by a 2-week postprocedural diet, after which liraglutide was initiated together with lifestyle counseling Primary endpoint: % of patients without insulin with an HbA _{1c} $\leq 7.5\%$ (responders) at 6 months Secondary endpoints: variations in glyco-metabolic control and proportion of long-term responders (12 and 18 months)	DMR was successful without any serious Aes At 6, 12, and 18 months, 69%, 56%, and 53% of patients were off insulin therapy, respectively All patients had significant improvements in HOMA-IR, BMI, and LFF	Combining a single DMR session with GLP-1RA and lifestyle counseling permitted the elimination of insulin therapy in most T2D patients, and improved glyco-metabolic homeostasis in all subjects
Hadeifi <i>et al.</i> , 2021 ^[23]	Single-center, open-label pilot study Out of 14 subjects with biopsy-proven NASH who were submitted to DMR followed by a 2-week postprocedural diet, without lifestyle changes, 11 were enrolled	12 months after DMR, no cases of NASH resolution, improved NAS score, nor weight loss were observed However, marginally improved fibrosis with no NASH worsening was observed in 3 individuals Serious procedure-related AEs were observed in 2 out of 14 subjects	DMR without lifestyle changes does not induce NASH resolution and improves liver fibrosis to a marginal extent at 1 year
Van Baar <i>et al.</i> , 2022 ^[24]	REVITA-1 was a prospective, single-arm, open-label, multicenter study of DMR in T2D subjects with HbA _{1c} 7.5%-10.0% on oral antidiabetic treatment	No DMR-related serious AEs, or hypoglycemic episodes were registered Compared to the baseline value, mean $\pm$ SD HbA _{1c} levels were significantly reduced at 6 months and maintained 24 months after DMR, while in > 50% of subjects, antidiabetic treatment was either	In T2D subjects, DMR is a safe procedure and induces long-lasting increased IS and related metabolic variables through 2 years after treatment

		diminished or unaltered	
		ALT modestly decreased ($P = 0.048$), and HDL and TG/HDL ratio decreased during 24 months of follow-up	
Meiring <i>et al.</i> , 2022 ^[18]	In this single-center, single-arm, prospective, open-label clinical study, 16 adults with T2D, BMI 24-40 kg/m ² , HbA1c $\leq 8.0\%$, and FCP > 0.5 nmol/l were submitted to DMR followed by discontinuation of exogenous insulin administration. Patients followed a postprocedural diet to allow duodenal mucosa regeneration for 2 weeks, after which self-administration of subcutaneous liraglutide was initiated	Six months after replacing exogenous insulin with DMR plus GLP-1RA, VAT, postprandial TG, and insulin concentrations, TC, LDL, microalbuminuria, daytime BP, and ASCVD 10-year risk score all decreased significantly	Replacing insulin therapy with the association of DMR and GLP-1RA improves cardiometabolic health among T2D patients
Meiring <i>et al.</i> , 2022 ^[25]	Fecal samples from the 16 patients enrolled in the previous single-center, single-arm, prospective, open-label clinical study ^[18] were submitted to Illumina shotgun sequencing at baseline and 3 months after DMR to assess α - and β -diversity (respectively indicating gut microbiota richness and changed microbiota composition) of the gut microbiota and analyze the correlations with variations in HbA1c, BMI, and liver MRI-PDFF	HbA1c was negatively correlated with α diversity ($P = 0.011$), while changes in PDFF correlated significantly with β diversity ($P = 0.036$) 3 months after the combined intervention was initiated. However, no changes in the diversity of gut microbiota were observed 3 months after DMR	Changes in the diversity of gut microbiota diversity are associated with metabolic improvements after DMR associated with GLP1-RA treatment in T2D
Meiring <i>et al.</i> , 2022 ^[26]	In this single-center, single-arm, prospective, open-label, pilot clinical study, the effect of DMR associated with GLP1-RA on postprandial BA was assessed among 16 insulin-treated T2D, with mixed meal tests at the baseline and 6 months after DMR	The combined DMR + GLP1-RA treatment enabled the discontinuation of insulin treatment in 11/16 (69%) subjects while improving glyco-metabolic function Increased postprandial unconjugated BA values (all $P < 0.05$), overall increased secondary BA response ($P = 0.036$), and a higher 12 α -hydroxylated: non-12 α -hydroxylated ratio were found ($P < 0.001$), while total BA concentrations did not vary and postprandial FGF19 and C4 concentrations decreased after DMR (both $P < 0.01$)	Combined treatment with DMR + GLP1-RA modulates the postprandial BA responses probably because of variations in the microbiome, ileal BA uptake, and decreased IR
Mingrone <i>et al.</i> , 2022 ^[27]	This randomized, double-blind, sham-controlled trial conducted across nine sites in Europe and two in Brazil) is called REVITA-2. 109 patients from Europe or Brazil were randomized 1:1 either to DMR ($n = 56$) or to sham procedure ($n = 52$). The median BMI was 31.5 kg/m ² in the DMR group and 30.7 kg/m ² in the sham group; the median baseline HbA1c was 8.7% in the DMR group vs. 10.4% in the sham group. The median T2D duration was 10.0 and 9.1 years among patients submitted to DMR or sham procedure, respectively. 85.5% in the DMR group vs. 82.7% in the sham group had > 5% LFC detected with MRI-PDFF Persistent hyperglycemia was a reason for rescue medication with increasing doses of oral medications and/or insulin according to clinical practice guidelines	In the European population, DMR was associated with a greater improvement than sham procedure in both primary endpoints (HbA1c and LFC), as well as in secondary measures of IS and BMI	DMR is safe and, compared to the sham procedure, significantly improves glycemic control and LFC in European patients
Chuang <i>et al.</i> , 2023 ^[28]	Meta-analysis of 2 published studies totaling 67 participants with histologically-proven NAFLD/NASH or liver MRI-PDFF > 5%	Compared to the baseline, the mean difference of MRI-PDFF, HbA1c, and HOMA-IR after DMR was -2.22%, -0.32%, and 0.15%, respectively	DMR induces a statistically non-significant trend in reduced LFC and improved glucose homeostasis
Fonseca <i>et al.</i> , 2023 ^[29]	Open-label phase study recruiting 9 subjects aged 60 years, 66.7% males, HbA1c 8.5%, C-peptide 1.7 ng/mL, with background glucose-lowering agents, weight 96 kg, diabetes duration 13 years; long-acting insulin dose 33 U/day	Safety: no DMR-related AEs. 48-week median change from baseline; HbA1c -1.5%, FPG -82 mg/dL, body weight -9.3%. All (7/7) patients reduced insulin dose, and 2 patients totally discontinued insulin	DMR is safe, induces metabolic benefits, and reduces treatment burden
Busch <i>et al.</i> , 2024 ^[30]	Post-hoc analysis of 28 patients on noninsulin glucose-lowering medications from REVITA-1, a multicenter open-label study, and from the open-	Compared to the baseline value, statistically significant decreases in BMI, HbA1c, FPG, FI, IS, and FCP	DMR improves IS and secretion

label phase of the Revita-2 double-blind, randomized, were observed both 3 and 6 months
sham-controlled study with HbA1c 7.6%-10.4% and after DMR
BMI 24 to 40 kg/m²

Aes: Adverse events; ALT: alanine transaminase; ASCVD: atherosclerotic cardiovascular disease; AST: aspartate transaminase; BA: bile acids; BMI: body mass index; BP: blood pressure; C4: 7- α -hydroxy-4-cholesten-3-one; FCP: fasting C-peptide; FI: fasting insulin; FPG: fasting plasma glucose; GI: gastrointestinal; HbA1c: glycosylated hemoglobin; FGF-29: fibroblast growth factor 19; GLP1-RA: glucagon-like peptide 1 receptor agonist; HDL: high-density lipoprotein; HOMA- homeostasis model of insulin resistance; IR: insulin resistance; IS: insulin sensitivity; LFF: liver fat fraction; LFC: liver fat content; LS: long duodenal segment ablated; MI: Matsuda Index; MRI-PDFF: magnetic resonance imaging-proton density fat fraction; RCTs- randomized controlled trials; SS: short duodenal segment ablated; T1D: type 1 diabetes; TC: total cholesterol; TG: triglycerides; VAT: visceral adipose tissue; VLDL: very low density lipoproteins; NASH: non-alcoholic steatohepatitis.

endoplasmic reticulum, and dilated spaces among cells with detached basement membrane^[33]. Collectively, these observations substantiate the notion that prolonged fasting has the potential to induce malabsorption through a variety of structural and functional alterations of the proximal small bowel.

Contrasting with the effects of prolonged fasting, obesogenic high-fat diets induce hyperplasia of proximal intestinal mucosa in rodents^[15]. Consistently, mouse or human duodenum-derived organoids demonstrate increased self-renewal, differentiation, and growth response after exposure to increasing amounts of nutrients such as lipids and glucose^[15]. It is important to highlight that, in the context of these mucosal hyperplastic changes, a decreased number of enteroendocrine cells indicates the potential for perturbed hormonal secretion in the context of experimental prediabetes associated with an obesogenic diet^[34].

These profiles conflict with findings of the distal gut, which, under the same high-fat diets, becomes hypoplastic owing to depressed stemness^[15] and pinpoint the notion that the mucosa of the small intestine plays a major role in regulating metabolic function under normal and pathological conditions opening avenues to novel approaches to treat metabolic disorders.

Further to the above summarized histological changes, functional changes should also be considered. These comprise altered hormonal secretion and changes in the intestinal transporters of nutrients.

The three principal gastrointestinal hormones that regulate glucose blood levels in a direct or indirect manner by modulating appetite, gastric emptying, the hepatic release of glucose, and the pancreatic secretion of insulin and glucagon secretion comprise cholecystokinin (CCK), GLP-1, and the glucose-dependent insulinotropic peptide (GIP)^[7].

In response to a meal, CCK promotes satiety by inhibiting gastric emptying, activating duodenal vagal afferents, and initiating the digestive phase. It triggers gallbladder emptying, stimulates the release of pancreatic enzymes and insulin, inhibits glucagon secretion, and decreases hepatic glucose production^[35].

GLP-1 is involved in glucose homeostasis by stimulating insulin and inhibiting glucagon secretion in a nutrient-dependent manner; similar to CCK, GLP-1 also acts locally via the vagal route to regulate glucose metabolism through a gut-brain metabolic axis^[36]. For example, experimental inhibition of vagal GLP-1 receptor signaling will result in increased appetite and postprandial glycemic values associated with blunted pancreatic insulin release^[36].

Together with CCK and GLP-1, duodenal nutrient sensing stimulates the release of GIP, whose action will lead to increased pancreatic secretion of insulin and glucagon^[7].

As regards transporters, approximately fourfold increased levels of duodenal sodium-glucose co-transporter-1 (SGLT1), glucose transporter 2 (GLUT-2), and glucose transporter 5 (GLUT-5) have been identified among individuals with either T2D or other metabolic disorders^[7].

Finally, additional mechanisms potentially contributing to improved insulin sensitivity comprise altered postprandial bile acid (BA) responses and changes in the microbiome^[18]. However, additional long-term studies are eagerly needed to either confirm or dispute these putative pathomechanisms.

SUMMARY AND RESEARCH AGENDA

Contemporary changes in food availability and characteristics, coupled with sedentary behavior, have contributed to the global epidemic of insulin resistance obesity, T2D, and MASLD, which are projected to become major drivers of morbidity and mortality in the years to come^[37]. These alarming considerations have prompted renewed interest in the physiology of metabolic homeostasis, eventually valorizing into a consistent endoscopic approach those lessons coming from bariatric surgery and from experiments on duodenal mucosa health status in relation to prolonged fasting and overfeeding^[38]. A robust line of research, both in experimental and clinical studies, has consistently pinpointed histological and functional changes in the duodenum, which may play a major pathogenic role in T2D^[39]. This important information provides a conceptual and comprehensive reading frame that helps to manipulate - for clinically meaningful purposes - the balance of insulin sensitivity *vs.* insulin resistance, hunger or satiety, energy dissipation *vs.* accumulation, and risks of hypoglycemia *vs.* protection from hyperglycemia^[40].

In this rapidly evolving scenario, DMR needs to find a placement among not only the various available endoscopic bariatric and metabolic therapies^[17,41-43] but also among bariatric surgery^[44] and medical treatment^[45,46]. Importantly, the independent role of DMR should be demonstrated after the confounding factors (such as improved diet and lifestyle habits) are controlled for^[47]. Although these might create ethical issues, comparative studies should ideally be conducted to confront DMR alone with medical treatment with GLP1-RAs. Additionally, the specific effect of DMR on the modulation of the various Sodium and Glucose transporters such as SGLT-1, GLUT-2, and GLUT-5 should be defined as this is relevant for precision medicine approaches^[48].

Recently, recellularization via electroporation therapy (ReCET), a novel endoscopic procedure that induces cellular apoptosis and subsequent reepithelization with electroporation to eliminate exogenous insulin treatment of T2D combined with a glucagon-like peptide-1 receptor agonist, has been assessed. Fourteen adults aged 28-75 years, with BMI 24-40 kg/m², HBA1c $\leq$ 64 mmol/mol, and C-peptide $\geq$ 0.2 nmol/L were submitted to a single 1-h ReCET session, followed by insulin discontinuation and initiation of semaglutide. ReCET was technically successful in 100% of cases, without any device-related severe adverse events (Aes) or severe hypoglycemia. One year after the procedure, 86% of patients remained off exogenous insulin therapy, with major ameliorations in glycometabolic balance. Collectively, these results suggest that ReCET is a feasible and safe option and, combined with semaglutide, promises to improve metabolic health while replacing insulin therapy in selected T2D subjects^[49].

Additional studies are urgently needed to ascertain, among the various surgical, endoscopic and medical choices, the best precision medicine option to fit the individual patient with obesity, T2D, and MASLD.

DECLARATIONS

Authors' contributions

Conceived the idea of this study and drafted the first manuscript: Lonardo A

Made substantial contributions to editing the first manuscript, as well as data analysis and interpretation: Singal AK

Revised the manuscript based on reviewers' concerns: Lonardo A, Singal AK

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Lonardo A is an Editor-in-Chief and Singal AK is an Editorial Board member of the journal *Metabolism and Target Organ Damage*. Lonardo A and Singal AK were not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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