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REVIEW ARTICLE

A look at duodenal mucosal resurfacing: Rationale for targeting the duodenum in type 2 diabetes

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Abstract

Affecting 5%–10% of the world population, type 2 diabetes (T2DM) is firmly established as one of the major health burdens of modern society. People with T2DM require long-term therapies to reduce blood glucose, an approach that can mitigate the vascular complications. However, fewer than half of those living with T2DM reach their glycaemic targets despite the availability of multiple oral and injectable medications. Adherence and access to medications are major barriers contributing to suboptimal diabetes treatment. The gastrointestinal tract has recently emerged as a target for treating T2DM and altering the underlying disease course. Preclinical and clinical analyses have elucidated changes in the mucosal layer of the duodenum potentially caused by dietary excess and obesity, which seem to be prevalent among individuals with metabolic disease. Supporting these findings, gastric bypass, a surgical procedure which removes the duodenum from the intestinal nutrient flow, has remarkable effects that improve, and often cause remission of, diabetes. From this perspective, we explore the rationale for targeting the duodenum with duodenal mucosal resurfacing (DMR). We examine the underlying physiology of the duodenum and its emerging role in T2DM pathogenesis, the rationale for targeting the duodenum by DMR as a potential treatment for T2DM, and current data surrounding DMR. Importantly, DMR has been demonstrated to change mucosal abnormalities common in those with obesity and diabetes. Given the multifactorial aetiology of T2DM, understanding proximate contributors to disease pathogenesis opens the door to rethinking therapeutic approaches to T2DM, from symptom management toward disease modification.

KEYWORDS

bariatric surgery, diabetes complications, endocrine therapy, glycaemic control, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) has become an increasingly pervasive problem for the healthcare system, currently affecting more than 530 million adults worldwide, with associated care expenditures exceeding twice the cost of individuals without diabetes.[1,2] The current prevalence of T2DM in the United States is ~10%, with similar rates in Europe, China and India.[3] It is projected that T2DM will affect over 780 million people by 2045, equating to one in eight adults living with this metabolic disease.[3] Furthermore, an increasing number of children, teens, and young adults are developing T2DM, increasing the risk of diabetes-associated morbidity and mortality across a broader segment of the population.[3]

Type 2 diabetes is a progressive, multiorgan disease in which morbidity and mortality are largely driven by micro- and macrovascular complications resulting from metabolic dysregulation, insulin resistance and chronic hyperglycaemia. Diabetes is the leading cause of blindness, end-stage kidney disease and lower extremity amputation in the United States.[4] T2DM also increases the risk of macrovascular disease, where the risk of heart disease or stroke in persons with T2DM is approximately twofold greater compared to the general population.[5] Additionally, diabetes increases the burden of nonvascular complications including cancer, infections, liver disease, mental health disorders, and pulmonary disorders, as well as Alzheimer's disease and related conditions. Collectively, the myriad complications and comorbidities associated with T2DM contribute to decreased work productivity, quality of life, and overall life expectancy for affected patients.[4,6,7]

The 2022 American Diabetes Association/European Association for the Study of Diabetes consensus report on the Management of Hyperglycaemia in Type 2 Diabetes emphasizes a broad, multi-modal approach to achieve sustained glycaemic control and mitigate the development of diabetic complications.[8] Lowering blood glucose and treating common comorbidities, such as hypertension and dyslipidaemia, provides preventive benefits that maintain patient health. Unfortunately, T2DM is a progressive condition in many patients. This presents a challenge to effective prevention, with T2DM often requiring escalating medication use. All currently available glucose-lowering therapies are directed at specific physiological targets that promote acute lowering of blood glucose. None of these medications reverse the underlying pathophysiology causing diabetes and hence must be taken continuously to provide sustained benefit. Indeed, despite significant advances in therapeutics over recent decades, it is estimated that fewer than half of all persons living with T2DM achieve and sustain their individualized glycaemic goal.[9]

A long-standing therapeutic goal in diabetes medicine has been the development of treatment approaches that directly target disease pathogenesis. DeFronzo and others have delineated the evolution of our understanding of multiorgan dysregulation leading to impaired glucose homeostasis in T2DM.[10–13] The organs and pathogenesis of the 'triumvirate' (liver and muscle insulin resistance, increased gluconeogenesis, and β-cell failure) have expanded to the 'ominous octet', inclusive of accelerated adipose lipolysis, intestinal incretin deficiency and peripheral tissue resistance, α-cell driven hyperglucagonaemia, increased nephrogenic glucose reabsorption, and brain insulin resistance.[10] Further, the 'egregious eleven' has added the colon and microbiome, immune system, stomach, and small intestine to the expanded list of organs contributing to the pathophysiology of T2DM.[13] Of note, few therapies have directly targeted the small intestine and duodenum.[14]

In recent years, the glucoregulatory role of the duodenum has been further elucidated and studies have shown that alterations in the morphology and function of the duodenal mucosa may play an important role in the pathogenesis of metabolic disease and T2DM. These findings suggest that the duodenum is a novel and accessible target organ for glucose lowering. Targeting the duodenum has the potential for fundamental disease modification and long-term efficacy. Here we review the role of the duodenum as a nutrient sensor and endocrine organ in metabolism, discuss the underlying pathogenesis implicating the duodenum in metabolic disease, and summarize the evidence for duodenal mucosal resurfacing (DMR) as an investigational procedure for T2DM that directly targets the duodenum.

2 | THE ROLE OF THE DUODENUM IN METABOLIC REGULATION

Attention has shifted to the proximal gastrointestinal (GI) tract as a potential therapeutic target for the treatment of T2DM, in part because of the long history of demonstrated beneficial metabolic effects of duodenal gastric bypass surgery. In this procedure, the bulk of the stomach, the duodenum and the upper jejunum are removed from the flow of ingested nutrients, which are routed through a small gastric pouch directly into the mid-jejunum. Patients with this procedure lose an average of 30% of their pre-surgical weight, but also have remarkable changes in glucose homeostasis that precede significant weight loss. Following gastric bypass, patients have rapid passage of nutrients into the small intestine as well as large, transient peaks in blood glucose likely driven by heightened insulin and glucagon-like peptide-1 (GLP-1) responses. In addition, there are dramatic improvements in glucose regulation among patients who had antecedent diabetes. Pories et al.[15] reported that gastric bypass restored glucose, insulin, and glycated haemoglobin (HbA1c) to normal levels in 91% of patients with T2DM, which was maintained up to 14 years post-surgery. Interestingly, marked improvements in glucose metabolism and insulin sensitivity occur within days post-bypass, prior to any significant weight loss, and appear to be independent of caloric intake.[15,16] However, several studies have reported a loss of the improved glycaemic control when nutrients are reintroduced into the gastro-duodenal remnant, a reversal of the positive postoperative changes independent of reduced food intake and weight loss.[17] In aggregate, these findings support the role of the duodenum in metabolic regulation and highlight its potential as a therapeutic target for T2DM.

Discoveries recounted in bypass literature and the clinical successes of GLP-1 receptor agonists have led to scientific interest in delineating further the role of the duodenum and small intestine in

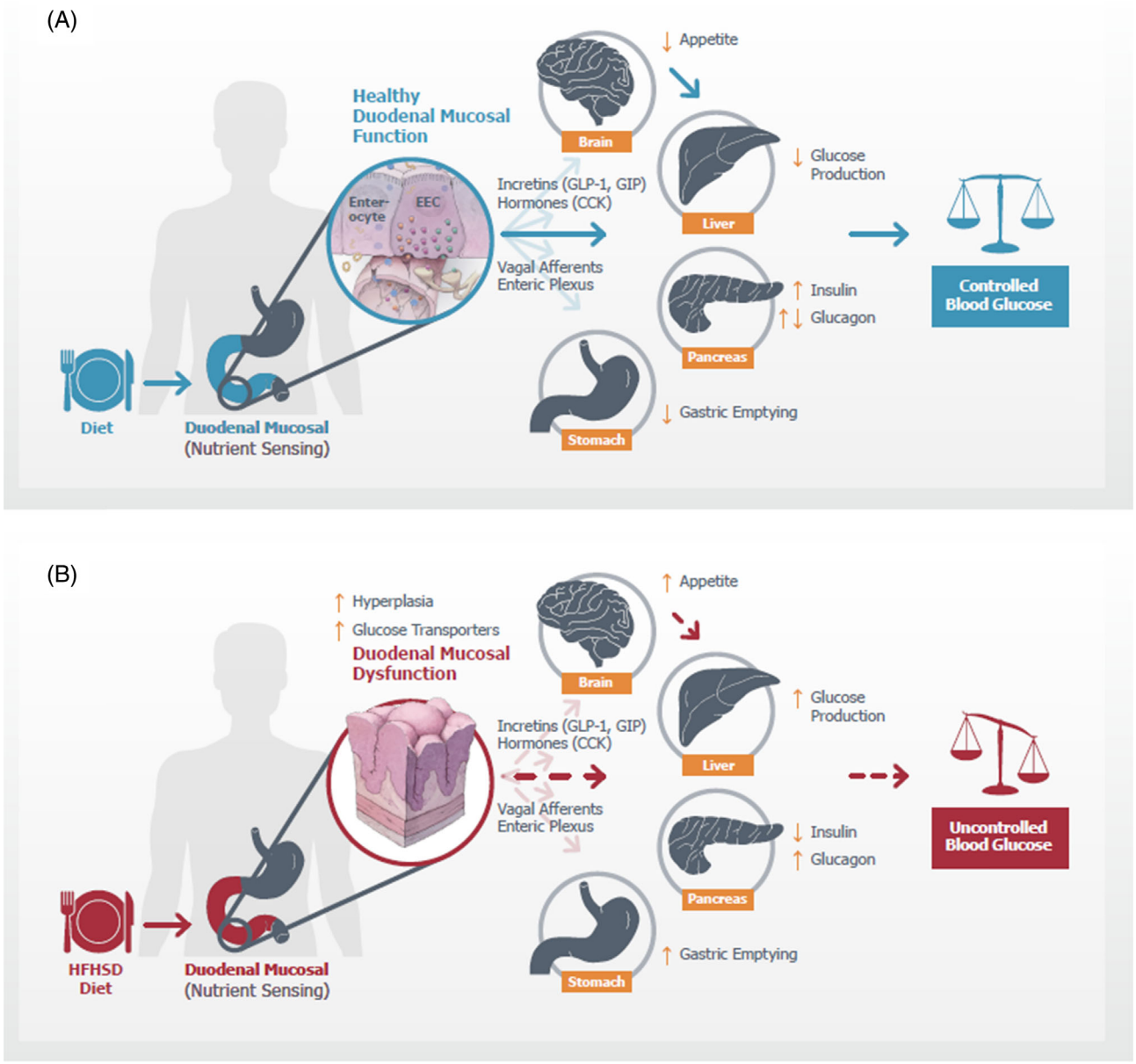

FIGURE 1 The role of the duodenum in metabolic regulation and potential contribution to metabolic disease. Duodenal nutrient absorption and sensing via mucosal enterocytes and enteroendocrine cells (EECs) can regulate the response of downstream organs through neural and hormonal signalling. This nutrient-induced signalling response choreograph appetite, hepatic glucose production, insulin and glucagon production, and gastric emptying in an effort to maintain glycaemia (A). Disrupted nutrient sensing and signalling associated with obesity and type 2 diabetes mellitus may be due to morphological and/or functional mucosal alterations (e.g., hyperplasia, increased expression of glucose transporters), which can contribute to impaired glucose homeostasis (B). CCK, cholecystokinin; GIP, glucose-dependent insulinotropic hormone; GLP-1, glucagon-like peptide 1; HFHSD, high-fat and high-sugar diet.

metabolism. It is now well understood that the duodenum plays a key role in maintaining glucose homeostasis through nutrient sensing and hormonal and neuronal signalling, which impact the metabolic response of downstream organs including the GI tract, pancreas, liver and brain (Figure 1A).[18–23] Ingested nutrients interact with duodenal mucosal enterocytes and enteroendocrine cells (EECs) to directly or indirectly mediate gastric emptying, appetite, hepatic glucose production, and pancreatic insulin and glucagon secretion, all potentially contributing to the regulation of glycaemia[18–21,23] (Figure 1A). Lipid and glucose uptake by duodenal enterocytes and EECs trigger the release of cholecystokinin (CCK), GLP-1, and glucose-dependent insulinotropic hormone (GIP), which can act as endocrine or paracrine mediators of metabolic processes (Figure 1A).

Cholecystokinin promotes gallbladder contraction and pancreatic enzyme release, and reduces gastric emptying, while CCK-mediated paracrine activation of duodenal vagal afferents decreases food intake and hepatic glucose production.[23,24] It is well known that GLP-1 stimulates pancreatic insulin and inhibits glucagon secretion in a nutrient-

dependent manner as an important mechanism for regulating glucose homeostasis.[18] Like CCK, GLP-1 also acts locally on vagal afferents innervating the intestinal mucosa or hepatoportal vein to stimulate a gut–brain metabolic axis responsible for regulating glucose tolerance.[23] When vagal GLP-1 receptor signalling is inhibited experimentally, meal size and postprandial glycaemia are increased while pancreatic insulin release is blunted.[23] In addition to CCK and GLP-1, duodenal nutrient sensing stimulates the release of GIP, which increases insulin and glucagon secretion by pancreatic β and α cells.[18] Lastly, the duodenal enteric plexus projects neurons directly into the pancreas and may regulate islet function and glycaemic control.[20,21]

In aggregate, the compelling clinical evidence for metabolic improvement post-bypass, combined with preclinical mechanism-of-action studies, support a role for the duodenum in nutrient sensing and metabolic regulation. This model, connecting meal digestion with nutrient disposition, suggests the duodenal mucosa is a plausible site for interventions to potentially arrest the T2DM pathogenic process.

3 | THE ROLE OF THE DUODENUM IN THE PATHOGENESIS OF METABOLIC DISEASE

Among the many factors associated with the development of T2DM, obesity and increased caloric intake are fundamental for disease development.[25–27] Increasing evidence from the past two decades suggests that diet-induced duodenal morphological and functional adaptations may occur in the setting of metabolic diseases like T2DM, and contribute to early pathogenesis through disruption of intestinal nutrient sensing and impaired glucose homeostasis (Figure 1B).[28–33] Studies in rodents have identified a link between increased caloric intake, and altered small intestinal mucosal morphology.[29,34,35] Aliluev et al.[29] have demonstrated in a murine model of obesity and prediabetes that a high-fat and high-sugar diet induces duodenal villus hyperplasia. Notably, this mucosal change was associated with increased enterocyte and decreased EEC numbers, indicative of the potential for enhanced nutrient absorption with altered hormonal secretion in the setting of diet-induced obesity and prediabetes.[29] Similarly, Enriquez et al.[36] showed that adaptive changes in mucosal cells that promote lipid absorptive capacity can occur within days of high-fat diet exposure, underscoring the potential for early small intestinal adaptation to contribute to metabolic disease pathogenesis.

Consistent with preclinical analyses, studies in patients with obesity, hyperglycaemia, and T2DM have documented small intestinal and duodenal alterations associated with metabolic disease.[28,30,31,33] Small intestinal cell mass is increased in patients with obesity and chronic hyperglycaemia and correlated significantly with HbA1c levels above 42.08 mmol/mol (6.0%).[31] In addition to increased intestinal cell mass, alterations in the expression and function of duodenal mucosal glucose transporters have been associated with metabolic disease.[28,30,33] Duodenal levels of sodium-glucose cotransporter-1 (SGLT1), glucose transporter 2 (GLUT-2), and glucose transporter 5 (GLUT-5) are increased approximately fourfold in patients with metabolic disease or T2DM.[28,30,33] Duodenal SGLT1 and GLUT-5 transporter levels are known to correlate with increased postprandial glucose concentration, insulin resistance, and hyperinsulinaemia in patients with metabolic disease.[28,33] Fiorentino et al.[33] reported that increased duodenal expression of SGLT1 occurs in individuals with high postprandial glucose levels and impaired glucose tolerance, suggesting that altered glucose transporter expression may be an early feature of developing T2DM. Lastly, Dyer et al.[30] evaluated the absorptive capacity of the duodenal mucosa and noted that the rate of glucose uptake was significantly increased in patients with T2DM.

In aggregate, preclinical and clinical studies provide evidence supporting the role of the duodenum in the pathogenesis of metabolic diseases including T2DM. Experimental findings demonstrate morphological and functional mucosal maladaptation and suggest mechanisms that may contribute to the pathogenesis of T2DM through increased absorption of dietary fat and sugar and altered duodenal nutrient sensing (Figure 1B). Additional studies are warranted to further elucidate the role of the duodenum in T2DM.

4 | DMR PROCEDURE AND MECHANISM OF ACTION

Duodenal mucosal resurfacing is a therapeutic approach that has been developed to directly target the duodenal mucosal dysfunction thought to contribute to the pathogenesis of metabolic diseases, including T2DM. DMR is an endoscopic procedure that uses hydrothermal energy to ablate dysfunctional duodenal mucosa, allowing for re-epithelialization.[37–39] The procedure is carried out in two main steps by an advanced endoscopist, using an endoscope and specialized catheter from just below the duodenal papilla to the Treitz flexure (Figure 2).[39] The endoscopist uses the catheter to perform circumferential saline injections into the duodenal submucosa to create a thermal barrier, or 'lift', to protect the deeper structures of the duodenum (e.g., musculature) during ablation (Figure 2A)[39–41] Subsequently, hydrothermal ablation is performed by circulating heated water through the catheter's balloon, allowing heat energy to penetrate the duodenal mucosa (Figure 2B).[39,41] Full duodenal mucosal regrowth with minimal fibrosis and no inflammation is observed 3 months after the procedure.[39]

The aim of DMR is to restore the normal physiology of the duodenum and thereby improve downstream metabolic regulation and glycaemic control in people with T2DM.[38,42–45] The mechanism of action of DMR is thought to be driven by stimulating the removal of morphologically and or functionally impaired duodenal mucosa and the subsequent regeneration of normal duodenal epithelium.[28–30,33,37–39,46,47] Preclinical DMR proof-of-concept studies in rodents support the concept that removal of the duodenal mucosa improves glycaemia.[39] Yang et al.[48] demonstrated improvements in blood glucose, insulin sensitivity, and weight loss stabilization out to 30 days after DMR with photodynamic therapy in murine high-fat diet models. Likewise, in the Goto-Kakizaki rat, a model of insulin-resistant T2DM, duodenal abrasion compared to sham control significantly reduced glycaemia during an oral glucose tolerance test at 60 ± 12 h

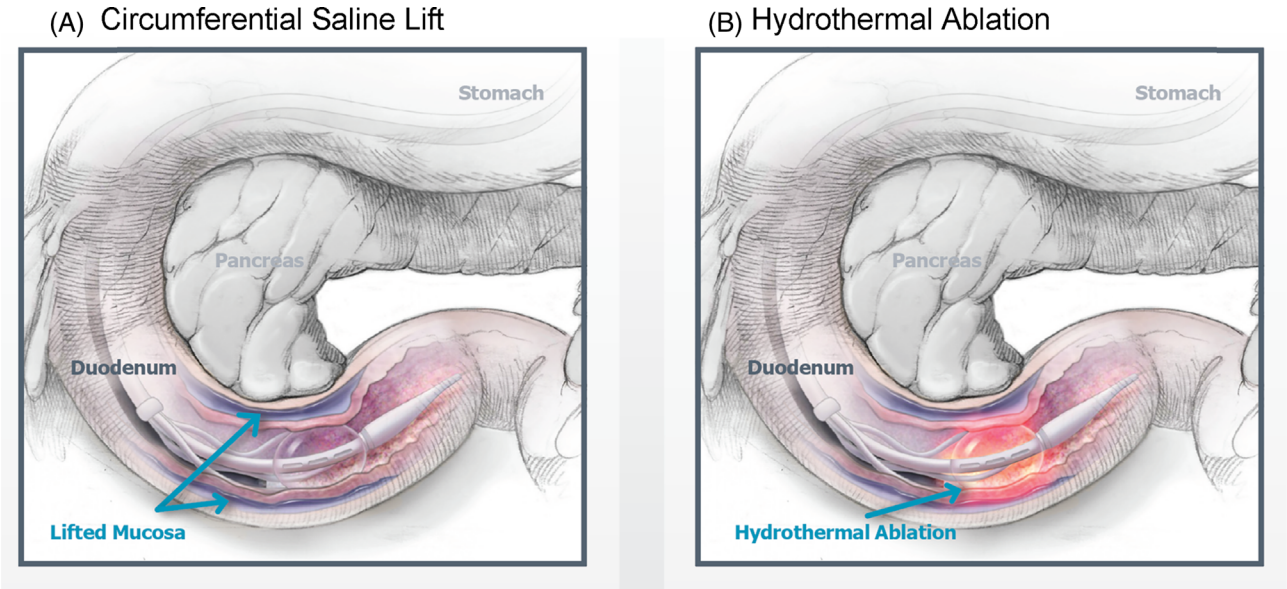

FIGURE 2 Description of the duodenal mucosal resurfacing (DMR) procedure. The DMR procedure is carried out in two main steps: circumferential saline lift (A) and hydrothermal ablation (B). Circumferential saline injections into the duodenal submucosa are performed to create a thermal barrier, or 'lift', to protect the deeper structures of the duodenum (e.g., musculature) prior to hydrothermal ablation (A). Subsequently, hydrothermal ablation is performed by circulating heated water through the catheter's balloon allowing heat energy to penetrate the dysfunctional duodenal mucosa (B).

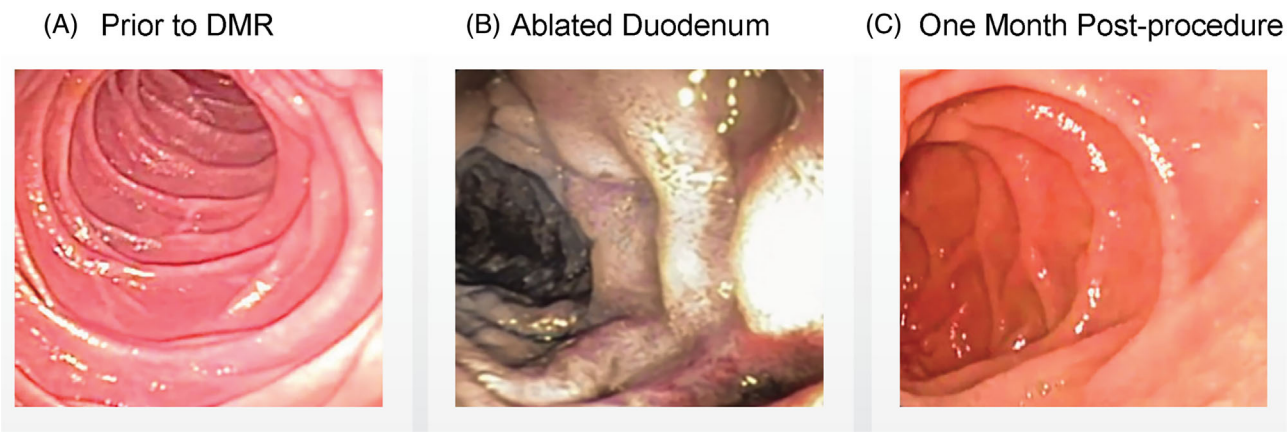

FIGURE 3 Endoscopic visualization of duodenal mucosa before and after duodenal mucosal resurfacing (DMR). (A–C) depicts the duodenal mucosal before the DMR procedure, immediately after, and 1 month post-procedure. Endoscopic visualization of the duodenal mucosa 1 month post DMR demonstrates re-epithelialization and a normal mucosal appearance (C). Adapted with permission from Rajagopalan et al[38*] and Haidry et al.[39**]. *'(A and C) Used with permission of the American Diabetes Association; from Endoscopic Duodenal Mucosal Resurfacing for the Treatment of Type 2 Diabetes: 6-Month Interim Analysis From the First-in-Human Proof-of-Concept Study; Rajagopalan H, Cherrington AD, Thompson CC, et al.; volume 39; issue 12 (2016); permission conveyed through Copyright Clearance Center, Inc.' **'This photograph was published in Gastrointestinal Endoscopy; Volume 90; Haidry RJ, van Baar AC, Galvao Neto MP, et al.; Duodenal mucosal resurfacing: proof-of-concept, procedural development, and initial implementation in the clinical setting; Pages 673–681.e2; Copyright Elsevier (2019)'.

post-procedure.[39] The early onset of the impact of abrasion on glycaemia suggests that mechanistic disruption of the duodenal mucosa may initially alter local neuronal signalling and/or aberrant nutrient sensing. Of note, there are no current data reporting on gut hormone expression and release with DMR.

Endoscopic evaluations of DMR from first-in-human (FIH) studies indicate that the duodenal mucosa at 4 weeks post-procedure appears normal (Figure 3), and histological analyses demonstrate that mucosal regeneration post-DMR is complete by Week 12.[38,39] Metabolic improvements, including reductions in fasting plasma glucose (FPG), were apparent within 1 week of the procedure, suggesting that, in humans, removal of the duodenal mucosa in T2DM may also initially alter local neuronal pathways and aberrant nutrient sensing.[38] Analyses of ablated mucosa in a porcine model demonstrated that

TABLE 1 Summary of published duodenal mucosal resurfacing clinical trials.

Title	Clinicaltrials.gov	Study Design	Primary Outcome	Years of Study	No. enrolled	Primary results
Evaluation of the fractyl duodenal remodelling system for the treatment of type 2 diabetes[38]	NCT01927562	First-in-human, single-arm, prospective, open-label, proof-of-concept (initial projected follow-up 3 years)	Procedural safety and glycaemic indices (6-month interim analyses)	2013–2014	44 (ITT)	6-month interim safety and efficacy analyses: Safety ($n = 40$): most common AE was postprocedural abdominal pain (8/40), resolved within 48 h; duodenal stenosis (3/40) 2–6 weeks post-procedure, effectively treated by balloon dilation Efficacy analysis ($n = 39$): HbA1c was reduced by 1.2 ± 0.3% at 6 months from baseline of 9.6 ± 1.4%
Evaluation of duodenal mucosal resurfacing for the treatment of type 2 diabetes[42,43]	NCT02413567	International multicenter, single-arm, prospective, 2-year open-label study, with glycaemic outcomes assessed at 24 weeks, 12 months and 2 years	Mean reduction in HbA1c at 24 weeks; durability at 12 and 24 months	2015–2017	49	24-month outcomes: Safety ($n = 46$ ITT population): No procedural SAEs were reported, with two of the 46 patients (4.3%) experiencing procedural AEs (these being one case of mild constipation and one case of mild vitamin B12 deficiency and general malaise). Seven non-device and procedure-related SAEs were reported from 6 to 24 months after DMR procedure: dyspnoea, lung adenocarcinoma, arteriosclerosis, severe back pain pilonidal cyst, bradycardia, and joint dislocation. Efficacy ($n = 36$ per-protocol population): HbA1c reduced by 0.9± 0.9% at 6 months from baseline (8.5%; $p < 0.001$), 0.8 ± 1.2% at 12 months from baseline ($p = 0.001$), and 0.8 ± 1.3% 24 months from baseline ($p = 0.034$). FPG was reduced 6, 12 and 24 months from baseline (198.4 mg/dL): −37.3 ± 47.8 mg/dL ($p < 0.001$), −43.8 ± 44.5 mg/dL ($p < 0.001$), and −34.7 ± 36.0 mg/dL ($p < 0.001$)
Evaluation of the effect of duodenal mucosal resurfacing (DMR) using the Revita system in the treatment of type 2 diabetes (T2D)[44]	NCT02879383	International multicentre, double-blind, superiority randomized controlled trial	Safety, change from baseline in HbA1c at 24 weeks, and liver MRI-PDFF at 12 weeks	2017–2019	108	Safety ($N = 109$): Safety data were reported by region. In the European population ($n = 76$), no device/procedure-related SAEs were reported; in the Brazilian population ($n = 33$) there were two ($n = 11$, 11.8%) reported device/procedure-related SAEs (haematochezia and jejunal perforation). In the European population, there were 23 AEs of special interest reported in the European population. It is not reported how many AEs

TABLE 1 (Continued)

Title	Clinicaltrials.gov	Study Design	Primary Outcome	Years of Study	No. enrolled	Primary results
						of special interest were observed in the Brazilian population. There was not an increased occurrence of hypoglycaemia with DMR compared to sham. Glycaemic efficacy: In the overall mITT population (DMR $N = 56$; sham $n = 52$) the median change in HbA1c from baseline to 6 months post procedure for those who received DMR was −10.4 mmol/mol, versus −7.1 mmol/mol for those who received the sham procedure ($p = 0.147$; treatment difference −3.3 mmol/mol). (In the European mITT population) the median change in HbA1c from baseline to 6 months post procedure for those who received DMR was −6.6 mmol/mol, versus −3.3 mmol/mol for those who received the sham procedure ($p = 0.033$; treatment difference −3.3 mmol/mol). Data for the median change in HbA1c from baseline to 6 months post procedure in the Brazilian population is noted as not significantly different between the DMR and sham arms. Liver outcomes: For patients with a baseline liver MRI-PDFF >5.0% (DMR $n = 48$; sham $n = 43$), the median absolute change in liver MRI-PDFF 12 weeks after baseline was −5.4% (5.6%) in the DMR group and −2.9% (6.2%) in the sham group ($p = 0.096$; treatment difference −2.5%)

Abbreviations: AE, adverse event; DMR, duodenal mucosal resurfacing; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; ITT, intention to treat; mITT, modified intention to treat; MRI-PDFF, magnetic resonance imaging proton density fat fraction; SAE, severe adverse event.

post-DMR mucosal crypts are relatively intact with epithelial stem cells present, although to a lesser extent than in sham controls.[37] These data suggest that it is possible for crypt stem cells to drive cellular repopulation of a normal mucosa post-procedure. More evidence is needed to delineate the phenotype of mucosal stem cells in T2DM and determine the role of DMR in augmenting enterocyte and EEC progenitor cells.

The early clinical trials in subjects with T2DM shed further light on the mechanism of action of DMR, and support the potential of duodenal mucosal ablation and re-epithelialization as a means of broad improvement in metabolic parameters including FPG, HbA1c, liver fat, liver transaminases, insulin sensitivity, and body weight.[37,41,42,45] In a subset of subjects with T2DM from the FIH study ($n = 14$), metabolomics analyses suggested changes in fasting and postprandial carbohydrate and lipid metabolites, including reductions in the lactate to pyruvate ratio and 2-hydroxybutyrate, 3 months post-DMR.[45,49] In another uncontrolled study, DMR-induced improvements in metabolic, hepatic and glycaemic parameters persisted through 2 years post-procedure.[42] These findings indicate that the changes in the duodenal mucosa post-procedure are reflected in systemic metabolism and that this regulation is durable.[42] Additional research is needed to further characterize the potential mechanisms linking mucosal changes and glycaemic control. Prominent among the candidate mediators are neural, incretin and hormonal responses.

5 | DMR CLINICAL FINDINGS IN T2DM

To date, DMR has been approved for medical use in Europe (Revita System, CE Mark) and is intended as an adjunct to diet and exercise to improve glycaemic control in T2DM patients whose diabetes is inadequately controlled and to reduce liver fat in patients with T2DM and non-alcoholic fatty liver disease (NAFLD).[50] In the United States, DMR is currently for investigational use only and is being evaluated in a pivotal randomized controlled trial for patients with T2DM who are inadequately controlled on insulin therapy (Revita System, Revitalize 1, NCT04419779). To date, the safety and efficacy of DMR have been assessed across three published sponsored clinical trials in patients with T2DM. Here, we provide an overview and summary of findings from each trial (Table 1).

The FIH proof-of-concept, single-arm, single-centre clinical trial was designed to evaluate procedural safety and improvement in glycaemic parameters in 44 patients with T2DM with an HbA1c of 58 mmol/mol - 108mmol/mol (7.5%–12%) on one or more glucose-lowering agent (GLA; NCT01927562).[38] In the 39 patients included in the efficacy analysis, reductions in FPG and HbA1c were observed 1 week and 1 month post-procedure, respectively.[38] HbA1c was shown to have improved by 13.1 ± 3 mmol/mol (1.2% ± 0.3%) at 6 months from a baseline of 81 mmol/mol ± 15.3 mmol/mol (9.6% ± 1.4%) in the complete cohort ($p < 0.001$). When evaluating patients who had received either shorter or longer duodenal ablation lengths (<6 cm vs. ≥9 cm), FPG and HbA1c declined to a greater extent, with HbA1c falling by 27.3 mmol/mol ± 2.2 mmol.mol (2.5% ± 0.2%) versus 13.1 mmol/mol ± 5.5 mmol/mol (1.2% ± 0.5%) at 3 months post-procedure in long- compared to short-ablation treatment groups, respectively ($p < 0.05$).[38] These data indicate that DMR may have a specific 'dose response', with more potent glycaemic efficacy associated with longer length of duodenal ablation. Mixed meal tolerance test (MMTT) assessments imply that observed glycaemic improvements may be driven by the ability of DMR to foster improvements in predominantly fasting glycaemia.[38] Mechanistically, these data suggest that DMR could reduce hepatic gluconeogenesis, which is known to be a central contributor to hyperglycaemia in T2DM.[51]

First-in-human safety analyses in 40 patients reveal that the DMR procedure was well tolerated, with no instances of intestinal bleeding, pancreatitis, perforations, severe hypoglycaemia, or malabsorption reported.[38] The most common adverse event (AE) was abdominal pain (8/40, 20% of patients), resolving within 48 h post-procedure. Three patients experienced duodenal stenosis 2–6 weeks post-procedure, with all cases effectively treated by balloon dilation with no recurrence.[38,39] Haidry et al.[39] attribute the stenosis cases to insufficient submucosal lift.

The proof-of concept FIH trial demonstrated the potential of DMR as a therapy to improve glycaemic control in T2DM patients and supports duodenal dysfunction as a therapeutic target for metabolic disease. Efficacy results suggest that there is a positive relationship between the length of the duodenum treated and glycaemic control. The interpretation of efficacy findings may be confounded as GLAs could be adjusted during the follow-up period. Overall safety analyses indicate that DMR is well tolerated, with AEs similar in nature to upper endoscopic procedures (e.g., transient abdominal pain). Haidry et al. and Rajagopalan et al. indicate that DMR catheter and procedural improvements have been instituted to improve procedural safety and reduce further stenosis risk (e.g., moving from a dual to integrated catheter system, performing submucosal lift and ablations in immediate succession).[38,39]

Following the FIH trial, DMR safety and efficacy were assessed in an international, multicentre, prospective, open-label single-arm study in 46 T2DM patients (intention-to-treat [ITT] population) with HbA1c levels of 58 mmol/mol - 86 mmol/mol (7.5%–10%), who were on stable oral GLAs and not on insulin at the time of enrolment (Revita 1, NCT02413567).[43,45] In the per-protocol population ($N = 36$), glycaemic indices were significantly reduced post-procedure, with mean HbA1c declining by 9.8 mmol/mol ± 2.2 mmol/mol (0.9% ± 0.2%) from a baseline of 70 mmol/mol ± 8.7 mmol/mol (8.6% ± 0.8%) at 6 months ($p < 0.001$).[43] At 6-month post-procedure, FPG reduced by 1.7 mmol/L ± 0.5 mmol/L (30.6 ± 9 mg/dL) from a baseline value of 10.7 mmol/L ± 2.7 mmol/L (193 ± 49 mg/dL) ($p < 0.001$).[43] Likewise, homeostatic model assessment of insulin resistance index (HOMA-IR) was improved, showing post-DMR reductions of 2.9 ± 1.1 from a baseline of 8.0 ± 5.7 at 6 months. Other metabolic and hepatic parameters, such as weight and liver transaminase levels, significantly improved in T2DM patients after treatment with DMR ($p < 0.05$).[42,43] Efficacy improvements in HbA1c, FPG, weight, and alanine transaminase remained significantly improved at 12 and 24 months post-procedure.[42,43]

The DMR procedure was well tolerated by patients, with no unanticipated adverse device events reported in the ITT population ($N = 46$).[43] DMR-related AEs occurred in 52% of patients, with diarrhoea, abdominal pain, nausea, and oropharyngeal pain most commonly observed.[43] The severity of DMR-related AEs was considered mild in 81% of cases.[43] No device- or procedure-related severe AEs (SAEs) were reported in long-term safety assessments between 6 and 24 months post-procedure. During this follow-up timeframe, two patients reported mild treatment-emergent AEs considered possibly related to study procedure (one patient with constipation, one patient with malaise and vitamin B_{12} deficiency).[42]

In this open-label clinical trial, treatment with DMR resulted in improvements in glycaemic, hepatic and metabolic indices of disease in patients with T2DM. This study furthers FIH findings by demonstrating the durability of DMR efficacy in patients receiving an ablation length covering the majority of the post-papillary duodenum (~9–10 cm).[43] Importantly, medication utilization in this trial was standardized and the glycaemic improvements occurred despite one third of patients stopping insulin prior to study entry. Van Baar et al.[43] speculate that HbA1c equilibrium may not have been effectively reached in those insulin-treated patients, contributing to a possible underestimation of the observed post-procedure HbA1c reduction. HOMA-IR analyses indicate that DMR may also improve insulin resistance, which may contribute to its proposed mechanism of action as insulin resistance is a known core pathogenic contributor to T2DM.[52] The DMR post-procedural and long-term safety findings in the open-label trial are encouraging, with more than 80% of cases considered mild and with no reports of stenosis.[42,43]

The third sponsored and first double-blind, multicentre randomized controlled trial of DMR evaluated safety and efficacy, inclusive of HbA1c and hepatic steatosis reduction, as co-primary endpoints in 109 T2DM participants with and without NAFLD on ≥1 GLA (Revita 2, NCT02879383).[44] DMR procedures were carried out using the integrated, single catheter system and sham procedures consisted of placing the DMR catheter within the duodenum for 30 minutes without activation.[44] In the overall modified ITT (mITT) population ($n = 56$ DMR, $n = 52$ sham), the median HbA1c decreased by 10.4 (18.6) mmol/mol in the DMR-treated group compared to 7.1 (16.4) mmol/mol in the sham-treated group at 24 weeks post-procedure ($p = 0.147$). In participants ($n = 48$ DMR, $n = 43$ sham) with a baseline liver magnetic resonance imaging proton density fat fraction (MRI-PDFF) >5% (indicative of NAFLD), DMR reduced absolute median MRI-PDFF by 5.4% (5.6%) compared to 2.9% (6.2%) in the sham cohort at 12 weeks post-procedure ($p = 0.096$).[44,53]

A prespecified statistical analysis showed heterogeneity in the Revita 2 trial, such that data from European and Brazilian centres could not be pooled due to nonuniformity. Thus, efficacy analyses were further stratified into these two aforementioned regional cohorts.[44] In the European mITT population ($n = 39$ DMR, $n = 36$ sham), treatment with DMR reduced HbA1c by 6.6 (17.5) mmol/mol compared to 3.3 (10.9) mmol/mol in the sham arm ($p = 0.033$).[44] Further, 26% of participants achieved an HbA1c of <53 mmol/mol at 24 weeks post-DMR procedure compared to 9% for the sham control cohort ($p = 0.031$).[44] In the Brazilian mITT population ($n = 17$ DMR, $n = 15$ sham) primary analysis, no statistical differences in HbA1c reduction or liver MRI-PDFF between DMR and sham cohorts were identified.[44]

In the European mITT population, the median relative liver MRI-PDFF at 12 weeks post-procedure was reduced from baseline by 32% (21%) versus 17% (26%) in participants treated with DMR compared to sham, respectively ($p = 0.020$).[44] Improvements in weight, FPG, and HOMA-IR were also noted 24 weeks post-DMR treatment compared to sham, with weight loss reaching statistical significance (2.4 [2.8] kg vs. 1.4 [2.4] kg; $p = 0.012$).[44] Matsuda index, a post-hoc analysis representing both hepatic and peripheral insulin sensitivity, was also improved post-DMR procedure compared to sham (1.2 ± 2.7 vs. 0.2 ± 1.5; $p = 0.035$).[44,54] In the Brazilian mITT population, weight, FPG, and HOMA-IR were not statistically different between treatment arms.[44]

Safety analyses were carried out in all participants in whom DMR or sham treatment were attempted ($N = 56$ DMR, $N = 53$ sham).[44] On follow-up endoscopic visualization, the duodenal mucosa post-procedure appeared healed and normal ($n = 49$).[44] There were no reports of malabsorption, anaemia, pancreatitis, biliary-related complications, or infection through 24 weeks of follow-up post-DMR procedure.[44] Consistent with prior studies, most AEs were considered transient and mild in nature, with abdominal pain, diarrhoea, hyperglycaemia, hypoglycaemia, nasopharyngitis and headache most frequently reported (≥5%).[44]

When assessed by region, there were no device- or procedure-related SAEs or unanticipated adverse device effects in the European population through 24 weeks of post-procedure follow-up ($n = 39$ DMR, $n = 37$ sham).[44] In the Brazilian population ($n = 17$ DMR, $n = 16$ sham), two patients experienced SAEs related to the DMR procedure. One SAE was a case of haematochezia attributed to external haemorrhoids and judged as possibly related to the DMR procedure. The second SAE was a perforation of the jejunum, documented as due to manipulation of the endoscope used during the DMR procedure. The perforation was surgically repaired, with no further sequela noted.[44]

Despite statistically defined heterogeneity between the Brazilian and European study populations, Mingrone et al. demonstrated glycaemic and metabolic improvements consistent with prior open-label DMR trials.[38,39,42–44] The authors ascribe the data nonuniformity to potentially more intensive GLA and lifestyle modification approaches during enrolment in the Brazilian population.[44] This is evidenced by comparing the Brazilian and European sham arm HbA1c improvements (−17.5 vs. −3.3 mmol/mol). Additionally, weight loss was nearly double in the Brazilian versus European populations.[44] Despite the large sham effect size, Brazilian participants receiving DMR did show glycaemic improvement, although this was not statistically significant, in the mITT analysis.[44]

The authors recognize the overlap that often exists between metabolic diseases such as T2DM and NAFLD. In Revita 2, 85% of T2DM patients had fatty liver disease, as evidenced by MRI-PDFF, which is consistent with previous reports.[44,55] In the European population, more DMR-treated participants reached an MRI-PDFF reduction of ≥30%,

which is known to be indicative of histological improvements in nonalcoholic steatohepatitis, the most severe form of NAFLD.[44] Based on these findings and previous reports of improvements in liver transaminases post-DMR procedure, Mingrone et al. assert that DMR may have potential as a therapy in patients with T2DM and NAFLD overlap.[42–44] HOMA-IR and Matsuda index findings were consistent with the demonstrated improvements in insulin resistance reported in previous DMR studies in patients with T2DM.[42–44] Given the consistent improvements in non-invasive assessments of insulin resistance observed, hyperinsulinaemia-euglycaemic clamp analyses are warranted to better elucidate DMR's insulin-sensitizing mechanism of action. Safety through 24 weeks of follow-up is supportive of a favourable DMR safety profile and consistent with FIH and Revita 1 findings.[38,39,42–44]

Several factors need to be taken into consideration when evaluating the results from the Revita 2 DMR trial. Heterogeneity between study populations, small sample size, and lack of stratification of baseline characteristics for secondary outcomes are study limitations. Differences in baseline medication usage (e.g., insulin concentration and number of medications) and an inability to effectively evaluate medication adherence may have confounded results.[44] In addition, no trials evaluating safety and/or efficacy of DMR have demonstrated cardioprotective benefits from DMR.

6 | ADDITIONAL MINIMALLY INVASIVE APPROACHES TARGETING THE DUODENUM

Currently, there are ongoing efforts to evaluate other interventions targeting the GI tract for the treatment of T2DM in addition to DMR. Alternative ablative interventions are being investigated, such as submucosal laser ablation targeting the submucosal nerve plexus.[56] Other minimally invasive interventions have been studied, such as the duodenal-jejunal bypass liner (DJBL) (EndoBarrier, GI Dynamics, Boston, MA, USA). The DJBL was designed to mimic the mechanisms of invasive Roux-en-Y bypass by excluding the duodenum and upper jejunum from digestive processes with an impermeable 60-cm fluoropolymer sleeve. A 2018 meta-analysis assessing the outcomes in patients treated with the DJBL showed that, on average, patients treated with the DJBL experienced an HbA1c reduction of 1.3% compared to baseline ($p < 0.0001$).[57] However, CE mark approval for the EndoBarrier was not renewed in 2017.[58] Non-invasive oral therapies are also being developed which target the GI tract to treat T2DM. One such therapy is Glyscend Therapeutic's GLY-200, a mucin-complexing polymer enhancing the duodenal mucus barrier to mimic the effects of bariatric surgery. Oral polymeric duodenal exclusion therapy was shown to mimic the biomarkers of Roux-en-Y bypass surgery in the FIH study of GLY-200.[59]

7 | CONCLUSION

Type 2 diabetes and its treatment impacts all levels of health and healthcare. Current standard of care involves regular use of multiple glucose-lowering medications, but overall, fewer than half of patients with T2DM meet their therapeutic target. Difficulty maintaining the sometimes burdensome treatment regimens and lack of disease-modifying therapies contributes to less-than-optimal treatment outcomes and subsequent end-organ complications of hyperglycaemia.

Recent efforts to understand more proximate causes of dysglycaemia have focused on the duodenum as the first enteric location for nutrient sensing and the initiation of downstream metabolic signalling. Mounting evidence from preclinical and clinical studies has shown that duodenal dysfunction is associated with metabolic disease and thus may be an important root-cause target for T2DM.

Duodenal mucosal resurfacing trials to date in people with T2DM have demonstrated that hydrothermal ablation and subsequent re-epithelialization of duodenum can durably improve glycaemic, hepatic and metabolic indices of disease. Further studies in larger, multicentre, randomized controlled trials are warranted to expand the understanding of the safety and efficacy of DMR in T2DM. The Revitalize 1 pivotal trial evaluating DMR in insulin-treated patients with T2DM is currently underway (NCT04419779).

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CONFLICT OF INTEREST STATEMENT

Jonah Hoyt has no relevant disclosures to declare. Emily Cozzi is an employee and shareholder of Fractyl Health, Inc. David D'Alessio has served as a consultant for Eli Lilly, Structure Therapeutics, Sun Pharmaceuticals, Fractyl. Chris Thompson consults for Apollo Endosurgery, Boston Scientific, Medtronic, Enterasense Ltd., EnVision Endoscopy, Fractyl, Fujifilm, GI Dynamics, GI Windows, Lumendi, Olympus, USGI Medical, Xenter, Endoquest Robotics, is a shareholder of Fractyl Health, Inc., has received research support from Apollo Endosurgery, Boston Scientific, ERBE, Fujifilm, GI Dynamics, Lumedi Olympus, USGI Medical, serves on advisory boards for Fractyl, Fujifilm, USGI Medical, Xenter and Endoquest Robotics, is a founder of, board member of and receives ownership interest from Enterasense Ltd., EnVision Endoscopy and GI Windows, is on a Speaker's Bureau for Boston Scientific, Fujifilm and Olympus, and receives royalty payments from GI Windows, EndoSim and Enterasense Ltd. Vanita Aroda has served as a consultant for Applied Therapeutics, Fractyl, Mediflix, Novo Nordisk, Pfizer and Sanofi, and has research contracts with Applied Therapeutics, Eli Lilly, Fractyl, Novo Nordisk and Sanofi. Vanita Aroda's spouse was an employee of Janssen and is an employee of Aditum Bio.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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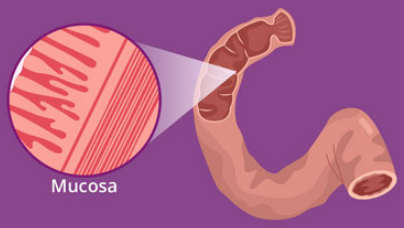
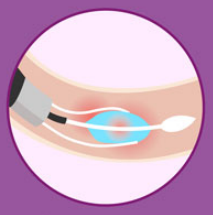
Duodenal Mucosal Resurfacing (DMR): A Treatment Approach for Type 2 Diabetes Mellitus

Recent studies have shown that functional and morphological changes in the duodenal mucosa are implicated in the pathogenesis of type 2 diabetes mellitus (T2DM)

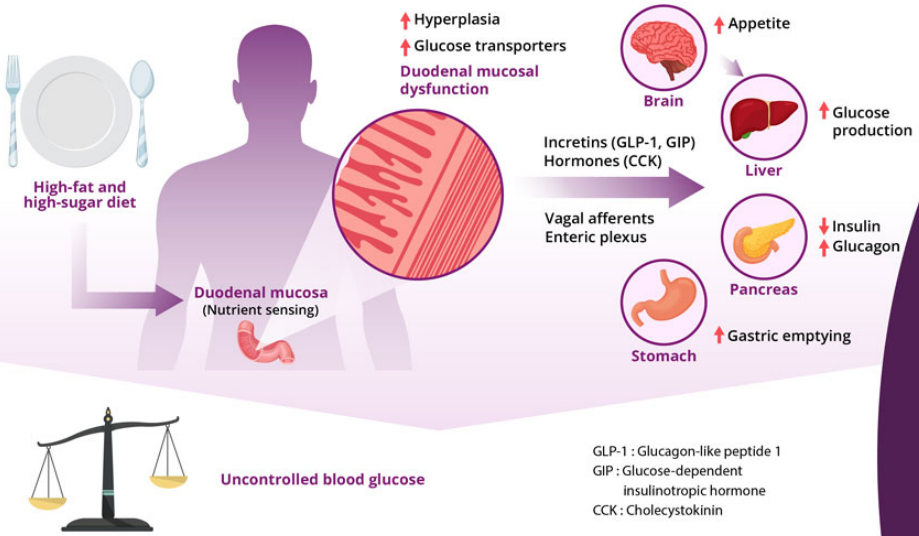


This review summarizes the role of the duodenum in glucose homeostasis and early data on the effects of DMR on glycemia in adults with type 2 diabetes



DMR is currently under investigation to treat T2DM

The duodenum plays a role in downstream glucose homeostasis and can contribute to hyperglycemia in T2DM:



Uncontrolled blood glucose

GLP-1 : Glucagon-like peptide 1
GIP : Glucose-dependent insulinotropic hormone
CCK : Cholecystokinin

Early studies indicate the potential of DMR to improve glycemia and metabolic parameters

WILEY

A LOOK AT DUODENAL MUCOSAL RESURFACING: RATIONALE FOR TARGETING THE DUODENUM IN TYPE 2 DIABETES
HOYT *et al.* (2024) | DOI: 10.1111/dom.15533

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