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Review Article

Endoscopic duodenal mucosal resurfacing for treating obesity and metabolic diseases: State-of-the-art review

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A B S T R A C T

Despite various advanced medical treatments for chronic metabolic diseases, such as type 2 diabetes and obesity, many fall short of their treatment goals. Bariatric surgery is one of the potential treatment options. However, with its invasiveness and association with some morbidity, minimally invasive endoscopic duodenal mucosal resurfacing has emerged in recent years. The procedure is performed based on an outpatient setting, and it enhances the duodenal capability to maintain metabolic homeostasis for treating insulin-resistance–related metabolic diseases, including type 2 diabetes mellitus. This article will provide a better insight into the novel therapeutic opportunity for treating metabolic disorders.

Keywords: Diabetes mellitus; Duodenum; Endoscopy; Obesity

Introduction

Type 2 diabetes mellitus (T2D) is a rapidly increasing metabolic disease worldwide, with an estimated 552 million cases by 2030.[1] T2D can frequently accompany obesity. Worldwide, 350 million people have obese-associated comorbid conditions such as T2D.[2] Although obesity and insulin resistance seem to be independent of each other, they share similar etiologies through neurohormonal and metabolic mechanisms. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) also share the same pathophysiology as obesity and T2D.

Despite lifestyle interventions and various advanced medical treatments for T2D, more than half of patients fall short of their treatment goal to achieve glycated hemoglobin (HbA1c) level ≤ 53 mmol/mol[3].[3] Thus, there is a desperate need for game-changing therapies to improve insulin resistance. Bariatric surgery is currently the most effective treatment for T2D patients with obesity. Patients undergoing Roux-en-Y gastric bypass surgery show impressive improvements in glycemic control and maintenance of ideal metabolic homeostasis. Notably, the improvement of these clinical indicators appears immediately after surgery or even before the appearance of weight loss.[4]

When sleeve gastrectomy and biliopancreatic diversion with duodenal switch as two types of bariatric surgery are compared, biliopancreatic diversion is superior in all indicators such as excess weight loss and reducing HbA1c.[5] This suggests that bypassing, excluding, or altering the presentation of nutrients to the duodenum can result in a weight-independent improvement in glycemia for people with T2D, implicating a key role of the duodenum in glucose regulation.

As most bariatric surgery procedures are invasive, irreversible, and associated with some morbidity, minimally invasive endoscopic procedures targeting the duodenum have emerged as options for bariatric surgical interventions. These procedures are known as endoscopic bariatric and metabolic therapies (EBMTs). Duodenal mucosal resurfacing (DMR) is the most innovative and notable treatment option of EBMT emerging in recent years. This review article will introduce the principles and methods of DMR procedure through the latest research results and discuss its possible application in future clinical treatment.

Duodenum in Modulating Insulin Sensitivity

The duodenum has become increasingly recognized as a metabolic signaling center that plays a role in regulating insulin action, thus modifying insulin resistance states.[6–9] This role of the duodenum appears in the duodenal mucosa. Dietary habits such as high fat and sugar-rich diets may lead to the development of

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hyperplasia of the duodenal mucosal lining, altering hormonal signaling and nutrient absorption pattern from the duodenum.[10] The duodenal mucosal hyperplasia can lead to insulin resistance, impaired glucose metabolism, and high blood pressure. Salinari et al[11] have conducted a study of the upper gastrointestinal tract in obese subjects with or without type 2 diabetes by infusing nutrients at three different starting points (duodenum, proximal jejunum, and mid-jejunum) in the small bowel through a balloon catheter. As a result, bypassing the duodenum resulted in an approximate 50% increase in insulin sensitivity.[11]

Therefore, efforts have been made to improve metabolic homeostasis and treat obesity by altering contact between the duodenal mucosa and dietary nutrition. Altering the presentation of nutrients to the duodenum has three ways, including duodenojejunal diversion, jejuno-ileal diversion, and DMR. Earlier researchers have tried to minimize nutrient-tissue interaction in the duodenum using a flexible tube called the duodenal-endoluminal sleeve as a barrier, which can result in body fat loss and improve glucose and lipid metabolism in diabetic fatty rats. They were the first to suggest that this bypass could result in an increase in mucosal villus length and lead to metabolic improvements.[12,13]

Partial jejunal diversion (PJD) has also been tested in obese patients with T2D. A self-assembling magnetic system was introduced to create an incisionless magnetic gastrojejunal anastomosis. This PJD brought food and digestive enzymes to enter the ileum early, leading to increased secretion of glucagon-like peptide-1 (GLP-1), peptide YY, and other gut hormones that could improve glucose homeostasis.[14] After a year, HbA1c level and body weight were significantly decreased in all human patients with a reduction in the use of diabetes medications.[14]

Duodenal Mucosal Resurfacing Procedure

Since the duodenum has an easy endoscopic accessibility, it is a potential target for disease-modifying intervention. DMR procedure can be performed using specially designed balloon catheters (Revita DMR system; Fractyl Health, Inc., Lexington, MA, USA) advanced over a guidewire into the channel of an endoscope (Fig. 1). It is a single endoscopic procedure with circumferential hydrothermal ablation of the duodenal mucosa that can result in subsequent mucosal regeneration. This ablation by thermal energy is similar to the treatment method for Barrett's esophagus-related neoplasia.[15]

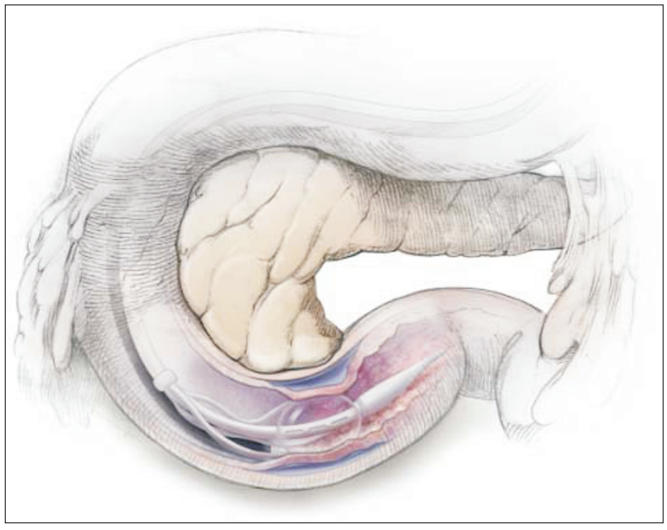

Fig. 1. Duodenal mucosal resurfacing uses a hydrothermal ablation device designed to remodel the duodenal lining (courtesy of Fractyl Health, Inc., Lexington, MA, USA).

Before ablation, the mucosa is lifted with saline to protect outer layers of the duodenum. Submucosal injection is then performed along with the duodenum from 1 cm distal to the ampulla of Vater to proximal to the ligament of Treitz. After the injection, a second balloon catheter performs thermal ablation on the lifted area. Under endoscopic visualization of ablated mucosa, up to five longitudinally separated sessions of circumferential thermal ablations (~90°C) of ~10 seconds each are applied along the length of the postpapillary duodenum. Some ablations may require pre-cooling and post-cooling. Patients can be discharged within 24 hours after the procedure. They are instructed to follow a progressive diet from liquid to soft diet within two weeks. A re-epithelialization of the treated duodenal mucosa seems to initiate quite instantly. Within days following procedure, a reset of duodenal mucosa in patients with T2D can be achieved.

Preclinical studies conducted in Goto-Kakizaki rat, a rodent model of human T2D, have shown that selective ablation of the duodenal mucosa can improve glucose tolerance compared with sham-treated diabetic controls.[16] Using a porcine model, subsequent studies have shown the safety of hydrothermal ablation, which is limited to the superficial intestinal mucosa without damaging deeper structures such as muscularis mucosa.[16] These results suggest that DMR can lead to insulin-sensitizing, resembling metabolic improvements observed after a bariatric surgery apart from its associated weight loss.

In 2016, the first 6-month interim analysis result of DMR testing in humans was published.[17] A total of 39 treated patients were analyzed, with a mean procedure time of 54 minutes. Fasting plasma glucose (FPG) reductions were noted within the first week of the procedure and HbA1c reductions were observed as early as one month. These reductions were observed without a change in fasting plasma insulin level. Improvements in plasma glucose and HbA1c were maintained throughout six months of observation. DMR appeared to exhibit a dose dependency (longer segmental ablation showing more potent glycemic effects). This result provides striking human-based evidence that a procedure targeting organs of the digestive tract could affect fasting blood glucose and HbA1c, not postprandial blood glucose.

Possible Indications and Efficacy

In 2018, Hadefi et al[18] reported a case of DMR in a 44-year-old male whose T2D was not adequately controlled with oral hypoglycemic agents (baseline HbA1c: 8.2%). As a result, three months after the procedure, HbA1c decreased by 1.2% to 7.0% and FPG dropped from a baseline of 14.5 to 10.4 mmol/L. There was no side effect such as elevation of alanine transferase (ALT) or accompanying pancreatitis.

An international multi-centered study[19] of patients (body mass index 24–40 kg/m^2) with T2D (HbA1c: 59–86 mmol/mol [7.5%–10.0%]) on stable oral glucose-lowering medication has analyzed efficacy and safety profiles such as HbA1c, FPG, weight, hepatic transaminases, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), and adverse events (AEs) at 24 weeks post DMR In that study, DMR was successful in the majority (80%) of patients, whereas 52% of patients experienced one or more AEs, of which 81% were classified as mild. At 24 weeks post DMR, HbA1c (–10 ± 2 mmol/mol [–0.9% ± 0.2%], $P < 0.001$), FPG (–1.7 ± 0.5 mmol/L, $P < 0.001$), and HOMA-IR (–2.9 ± 1.1, $P < 0.001$)

showed improvements with weight reduction (–2.5 ± 0.6 kg, $P < 0.001$). This reduction effect of 0.9% additional HbA1c after six months of treatment was similar or superior to the addition of a pharmacologic agent, showing the potential of DMR as an adjunctive treatment in the treatment of T2D. In addition, ALT was measured as a quantified level of NAFLD. It also dropped from 40 ± 4 U/L at baseline to 31 ± 2 U/L at 24 weeks after DMR ($P = 0.016$). ALT was maintained lower during the follow-up period of 12 months (30 ± 3 U/L, $P < 0.001$). Although it had a limitation in that patients with severe hyperglycemia who required insulin were not included in the study, it showed that DMR could improve HbA1c through an insulin-sensitizing effect in T2D patients and manage NAFLD through an additional ALT reduction effect. Unlike T2D, NAFLD has no proven pharmacological treatment available. Meanwhile, consequences of NAFLD are evident with increasing incidence of NASH, cirrhosis, liver transplantation, and hepatocellular carcinoma. In this regard, DMR is an innovative, novel treatment option for NAFLD.

On the other hand, one study has investigated whether insulin could be stopped when DMR and GLP-1 RA (liraglutide) are administered together to T2D patients who are using insulin.[20] In that study, 16 subjects received DMR treatment. Of them, 69% were able to take off insulin therapy after six months. It was difficult to measure the quantified effect because there was no control group. In addition, cases with uncontrolled HbA1c at 8.0% or more were enrolled.

In a recent randomized, double-blind, sham-controlled trial (REVITA-2)[21] conducted across 11 sites (nine in Europe and two in Brazil), patients with HbA1c levels of 59–86 mmol/mol (7.5%–10.0%) and body mass index ≤ 40 kg/m^2 who were treated with more than one oral antidiabetic medication without insulin or GLP-1 agonist were included. Investigators compared the safety, change from baseline in HbA1c at 24 weeks, and liver MRI proton-density fat fraction (MRI-PDFF) at 12 weeks as primary endpoints. They found that European and Brazilian result were slightly different. In European intention to treat (ITT) population, median HbA1c change was –6.6 mmol/mol in the DMR group and –3.3 mmol/mol in the sham group ($P = 0.033$). At 12 weeks, liver-fat change was –5.4% in the DMR group and –2.2% in the sham group ($P = 0.035$). In the European population, DMR demonstrated statistically significant beneficial effects on other markers of insulin resistance, including HOMA-IR and Matsuda index. On the other hand, Brazilian ITT results showed a trend toward a DMR benefit in HbA1c, but failed to show efficacy in liver fat reduction probably due to a relatively large sham cohort effect. In a recently published 2-year follow-up of the REVITA study, DMR has proven to have durable improvements in insulin sensitivity and multiple metabolic parameters regarding type 2 diabetes through 24 months of period. No long term procedure-related serious adverse events (SAE) was reported.[22]

The DOMINO trial (investigation of the metabolic effects of duodenal resurfacing on insulin resistant women with polycystic ovarian syndrome) was designed to investigate the mechanism of action of DMR in a cohort of insulin resistant women with polycystic ovarian syndrome (PCOS), obesity, and oligomenorrhea.[23] In this population, improvements in insulin sensitivity could appear as an increased number of menses. Thirty-two insulin-resistant, obese PCOS women were randomized into a DMR or a sham endoscopy group in a double-blinded manner. As a result, total body insulin sensitivity measured by euglycemic hyperinsulinemic clamp glucose infusion rates were not significantly different between DMR and sham groups at 12 weeks after treatment (mean: 5.4 vs. 5.6, $P = 0.37$). HOMA-IR at 24 weeks post DMR was also similar (mean: 5.5 vs. 5.0, $P = 0.30$). In a reproductive point of view, the DMR group showed a significant increase from one menstruation in six months pre-procedure to three in six months, whereas the sham group only showed a slight increase from 1.5 times of menstruation in six months pre-procedure to two times of menstruation in six months post-procedure. Although this difference did not reach statistical significance, PCOS symptoms were alleviated clinically. Results of this study did not show an increase in insulin sensitivity in PCOS patients, suggesting that

Table 1 Clinical Outcomes of Duodenal Mucosal Resurfacing for Type 2 Diabetes Mellitus

Author (year)	Study design	Intervention	Total (*n*)	Inclusion criteria	Outcome	Notes
Rajagopalan et al[17] (2016)	Single-arm Open-label	DMR	39	HbA1c 7.5%–12.0% with BMI ≥ 31 kg/m^2	HbA1c was reduced by 1.2% at 6 months	Three patients experienced duodenal stenosis
Hadefi et al[18] (2018)	Case report	DMR	1	44-year-old, overweight (BMI = 28 kg/m^2) with T2D treated with OHA	HbA1c decreased by 1.2% (8.2% to 7.0%) at 3 months	Presented with a video demonstration
van Baar et al[19] (2020)	Multi-center (seven sites, internationally) Single-arm Open-label	DMR	46	HbA1c 7.5%–10.0% with BMI 24–40 kg/m^2	HbA1c was reduced by 0.9% at 24 weeks, with preservation of the effect up to 12 months HOMA-IR was reduced by 2.9 at 24 weeks, by 3.3 at 12 months	DMR was completed successfully in 80% of the enrolled patients 81% of adverse events related to DMR was classified as 'mild'
van Baar et al[20] (2021)	Single-arm Open-label	DMR combined with GLP-1RA (liraglutide)	16	HbA1c < 8.0% with BMI 24–40 kg/m^2 with fasting C-peptide > 0.5 nmol/L using long-acting insulin	69% patients met adequate glycemic control at 6-month follow-up without insulin, 56% patients were still responders at the 12-month follow-up	No device-related AEs or treatment-related SAEs were reported
Mingrone et al[21] (2022)	Double-blind RCT	DMR Control	DMR, 56; sham, 52	HbA1c 7.5%–10.0%, BMI 24–40 kg/m^2, fasting insulin > 48.6 pmol/L with ≥ 1 OHA	HbA1c change was –6.6 mmol/mol in DMR group versus –3.3 mmol/mol post-sham 12-week post-DMR liver-fat change was –5.4% in DMR group versus –2.2% post-sham	South American cohort failed to prove relative efficacy of DMR in liver fat reduction

DMR, duodenal mucosal resurfacing; HbA1c, hemoglobin A1c; BMI, body mass index; T2D, type 2 diabetes mellitus; OHA, oral hypoglycemic agent; HOMA-IR, homeostatic model assessment for insulin resistance; RCT, randomized controlled trial.

DMR was not insulin-sensitizing in all patients. It might be more beneficial for certain groups. Results of this study indicate that future research directions should address the intestinal metabolic mechanism of DMR. Table 1[17–21] describes the clinical outcomes of DMR for T2D conducted so far. The beneficial metabolic effects of DMR is also validated by a recent systematic review and meta-analysis.[24]

Mechanism of Efficacy

It is still unclear how DMR improves T2D and reduces hepatic fat disposition based on relatively limited studies. It has been speculated that DMR can alter duodenal signaling and lead to insulin sensitization.[20] In fact, mechanisms of the efficacy of a bariatric surgery for treating obesity and T2D, particularly the role of the small intestine during the process, also remain poorly understood.

One study on intestinal stem cell-derived enteroids in lean, overweight, or morbidly obese patients has found that intestinal glucose absorption and gluconeogenesis are significantly elevated in enteroids from a cohort of obese patients.[25] Increased expression levels of SGLT1 and GLUT2 are associated with elevated glucose absorption and elevated gluconeogenesis linked to overexpression of GLUT5, PEPCK1, and G6Pase. This result shows that a dynamic regulation of intestinal mucosal proteins for glucose absorption and transport is important for glucose metabolism. It may explain the mechanism of action of DMR. However, there have been no studies on protein expression in the intestinal mucosa before and after DMR up to date.

Another idea proposed to improve T2D post-DMR is regeneration of GLP-1 producing L-cells located in the duodenal epithelium.[20] GLP-1 agonist can improve metabolic markers of T2D through actions such as weight loss, improved blood lipid and blood pressure by stimulating insulin, inhibiting glucagon secretion, increasing the intake of muscle, and inhibiting hepatic glucose production. GLP-1 producing L-cells are located on the duodenal mucosa, which normally releases GLP-1 into the bloodstream when excessive carbohydrates are presented to the proximal small intestine. It has been speculated that DMR might increase the GLP-1 producing capacity or adjust the threshold through this regeneration of L-cells.[26] Well-designed follow-up studies are needed to elucidate this hypothesis.

Change in the composition of bile acid is also noteworthy for explaining the mechanism of DMR. Bile acids participate in glucose metabolism in the gut via secondary signaling molecules such as fibroblast growth factor 19 (FGF19). When analyzing post-DMR bile acid compositions, increased postprandial unconjugated bile acid responses and an overall increased secondary bile acid response were observed. Postprandial FGF19 concentration was decreased after a DMR procedure.[27] These alterations in postprandial bile acid and FGF19 responses might have resulted from changes in intraluminal microbiome, ileal bile acid uptake, and improved insulin sensitivity. More controlled studies are needed to determine the causal relationship between these factors.

Safety

In a single-arm feasibility study, no reported hypoglycemia was found among 16 patients who underwent DMR.[19] Gastrointestinal symptoms that were related to the procedure was reported in 50% of patients, and most of them was mild abdominal pain that few required medications for symptom control. According to a randomized study (REVITA-2) that investigated safety profiles for 24 weeks immediately after DMR treatment in a total of 56 cases, most AEs were mild and transient.[21] AEs can be broadly divided into gastrointestinal disorders and metabolism or nutrition disorders. In a European DMR cohort, approximately 33% of patients in the DMR group experienced a device-related or procedure-related AEs of special interest compared with 27% of patients in the sham procedure group. The most common AEs within 30 days post procedure were abdominal pain (15.4%) and hypoglycemia (7.7%). However, even in the sham procedure group, hypoglycemia appeared at a similar rate. Relatively smaller number of patients suffered diarrhea (2.6%) and nausea (2.6%) in the sham procedure group. SAE related to the procedure occurred in two cases. One SAE was a mild hematochezia at eight days after the DMR procedure. However, visible external hemorrhoids were observed after hospitalization, which was highly unlikely to be due to DMR. A jejunal perforation which required surgical repair was also reported. Thus, caution is required when performing endoscopic manipulation of the small intestine during DMR. Since there is a possibility of such SAEs with the risk not negligible, individualized risk and benefit should be fully considered when selecting a subject for treatment.

Conclusions

DMR is expected to provide novel treatment opportunities to treat T2D, NAFLD, and NASH. In addition, it may serve as a non-surgical, non-invasive treatment option for other chronic, progressive diseases related to glucose and energy metabolism. However, due to insufficient evidence-based studies, mechanisms underlying effects of DMR remain unclear. Possible mechanisms include changes in glucose uptake in the duodenum, altered incretin secretions, and amelioration of the gut microbiome. Longer-term effects of DMR should be confirmed through future randomized controlled trials. Whether repeated DMR can improve outcome should also be evaluated. A potential change in dietary preference after the procedure as seen in gastric bypass surgery should also be investigated.

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Conflicts of Interest

Jun Kyu Lee has been an editor of the International Journal of Gastrointestinal Intervention (*IJGII*) since 2017; however, Jun Kyu Lee has not been involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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