Hydrothermal Duodenal Mucosal Resurfacing

Role in the Treatment of Metabolic Disease

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KEYWORDS

• Type 2 diabetes • Metabolic disease • Insulin resistance
• Nonalcoholic fatty liver disease • Duodenum • Duodenal mucosal resurfacing
• Endoscopic treatment • Hydrothermal ablation

KEY POINTS

- The dysmetabolic states of type 2 diabetes and fatty liver disease have a common pathophysiologic foundation in the form of insulin resistance, which drives end-organ disorder in beta cells and the liver respectively.
- Bariatric surgery has uncovered a potent metabolic role of the duodenum that can exert powerful effects on insulin resistance and dysmetabolic states.
- Hydrothermal duodenal mucosal resurfacing (Revita DMR) is an investigational, catheter-based, upper endoscopic procedure designed to modify signaling from the duodenal surface, thereby eliciting beneficial metabolic effects.

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- Early clinical experience with hydrothermal DMR suggests that the endoscopic procedure can be safely implemented in humans, with evidence that it elicits improvements in diabetic state with potential to also affect fatty liver disease.
- Further studies are necessary to examine its clinical utility as an important treatment of the metabolic diseases that burden the modern day health care system.

INTRODUCTION

The duodenum has become increasingly recognized as a metabolic signaling center that seems to play a role in regulating insulin action and, therefore, insulin resistance states.[1–5] Insulin resistance is at the core of many dysmetabolic states, and recent advances in pharmacologic development, as well as the recognition that bariatric surgery has a major impact on glucose levels, has heightened interest in the benefits of insulin sensitization as a treatment. Data from studies of bariatric surgery and other manipulations of the upper intestine, in particular the duodenum, show that limiting nutrient exposure or contact in this key region exerts powerful metabolic effects.[1,2,6–12] Duodenal mucosal resurfacing (DMR) targets this specific biology with the assumption that the duodenal surface is in some way mediating an abnormal signal that emanates to endogenous insulin-sensitive tissues. Resurfacing through hydrothermal ablation allows a restoration of a normal mucosal interface that corrects this abnormal signal. This article describes this endoscopic approach, including the rationale for DMR and its early human use, showing its safety, tolerability, and beneficial effects on metabolism.

INSULIN-RESISTANT STATES: BACKGROUND AND CURRENT MANAGEMENT

Background

Insulin resistance is the underlying cause of several metabolic disorders, including type 2 diabetes and fatty liver disease, which affect a large segment of the general population.[13] Collectively, this pathophysiologic defect drives a massive health economic burden, manifesting with end-stage diabetes complications and premature cardiovascular disease, as well as an increasing recognition that it will also become the primary driver of end-stage liver disease.[14] Through the introduction of the insulin clamp technique in the 1970s,[15] detailed examination of the metabolic state was possible and insulin resistance was made quantifiable. This technique led to a greater understanding of the role of insulin resistance in dysmetabolic states and how insulin-sensitizing interventions exert their effects.

Lifestyle/Behavior Modification

It is recognized that lifestyle modification through healthy exercise and good nutrition can improve the metabolic state. Both lifestyle modification resulting in weight loss and the independent effects of chronic exercise reduce insulin resistance in humans. The current standard of care for treatment of type 2 diabetes promotes lifestyle and behavior modification related to exercise, weight loss, and diet before pharmacologic intervention is considered. At present, lifestyle modification is the only recognized treatment available for fatty liver disease.[16] Two landmark trials, the Diabetes Prevention Program (DPP) trial[17] and, more recently, the Look Action for Health in Diabetes (AHEAD) trial,[18,19] have shown the metabolic benefit of applying lifestyle modification in prediabetic patients and patients with frank diabetes in a controlled trial setting.

However, it is also well recognized that patients struggle to adhere to a lifestyle modification program over time and the real-world impact is transient and/or suboptimal.

Pharmacologic Treatment

Targeted treatment of insulin resistance was made available through the introduction of the thiazolidinedione (TZD) insulin-sensitizing class of agents for the treatment of type 2 diabetes.[20,21] The long-used biguanide, metformin, was also shown to have insulin-sensitizing properties at that time.[21] More recently, the glucagon-like peptide 1 receptor (GLP-1R) agonist[22] and sodium/glucose cotransporter 2 (SGLT2) inhibitor[23] classes have also been shown to have weak insulin-sensitizing properties, which may or may not have a weight-independent component.

It was through the use of these pharmacologic agents in the clinic that a wider array of their effects was observed beyond improved glycemic control: reductions in blood pressure, lowering of hepatic transaminase levels, altered lipid metabolism, and restoration of ovulation in previously anovulatory women with features of the insulin-resistant condition polycystic ovarian syndrome (PCOS; also termed metabolic reproductive syndrome). These effects allowed a broader view of insulin action and insulin-sensitive end-organs (ie, liver, skeletal muscle, adipose tissue, ovary) and how they are each affected by insulin resistance. Metformin, the TZDs and GLP-1r agonists have each shown positive attributes in one or more insulin-sensitive end-organ systems beyond their ability to improve glycemia. More specifically, both TZDs and GLP-1r agonists have been explored in fatty liver disease,[24] and metformin, TZDs, and GLP-1r agonists have shown positive effects in patients with PCOS.[25]

However, although pharmacologic intervention has brought a broad array of benefits through insulin sensitization, a major drawback of these agents has been the ability of patients to adhere to regular daily dosing,[26] which is related in part to these agents' unattractive side effects, including gastrointestinal intolerance (metformin and GLP1r agonists), edema (TZDs) and heart failure (TZDs). In the case of GLP-1r agonists, route of administration (ie, injection) may also pose a barrier.

Bariatric Surgery

Over the last 20 years, bariatric surgery involving bypass of the upper intestine has become established as a highly impactful intervention that elicits beneficial metabolic effects. It has been shown to result in dramatic improvements in the glycemic state and so-called disease remission in some patients with type 2 diabetes.[27] It has also been shown to halt or reverse disease progression of nonalcoholic steatohepatitis (NASH),[10] and to correct anovulation in PCOS.[28] The groundswell of interest in surgery and its metabolic effects has resulted in the recent authoring of a consensus statement, embraced by multiple professional organizations, recommending that bariatric (now termed metabolic) surgeries be included in the treatment algorithm for patients with type 2 diabetes.[9] It is notable that much of the metabolic benefit is observed acutely, within days of the procedure, preceding by weeks and months the substantial weight loss that is also seen with bariatric surgery.[29–31] This effect is noted particularly after Roux en Y gastric bypass, suggesting that avoiding the contact of food with the duodenum and proximal jejunum may quickly elicit beneficial metabolic effects. More recently, detailed accounts of metabolic changes by various investigators have shown that there is a clear and measurable insulin-sensitizing effect within the first 2 weeks postsurgery that is sustained over time (a year or more).[29,31–33] The insulin-sensitizing response seems to be an important contributor to the observed metabolic effect, and it is hard to consider either short-term caloric restriction as a consequence of the surgery or a surgery-mediated

incretin effect to be a major confounder of this observation. As further evidence of the substantial regulatory role this gut-borne signal apparently plays in diabetic rats and humans with type 2 diabetes, reintroduction of nutrients to the bypassed section of duodenum rapidly elicits a return to hyperglycemia and restores insulin resistance.[34,35]

The duodenal-jejunal bypass sleeve (or EndoBarrier GI liner [GI Dynamics, Inc, Boston, MA]) gives further credence to the mechanism observed with bariatric surgery. The sleeve is anchored in the duodenal bulb and prevents contact of food with the mucosal surface of the duodenum and proximal jejunum. The implanted sleeve device is placed for up to 12 months in situ and it has been shown to induce some weight loss in obese patients and to improve glucose homeostasis in patients with type 2 diabetes.[36–38]

Bariatric surgery is likely to remain a key component of the type 2 diabetes treatment algorithm and, as more data accumulate, it may establish a therapeutic role in fatty liver disease and other dysmetabolic states, and even more so as technological and surgical techniques advance. However, bariatric surgery is unlikely to become a major solution at a population level, because it is not an easily scalable intervention and surgery remains a disincentive for many patients.

METABOLIC ROLE OF THE DUODENUM

An increasing body of evidence suggests that the duodenum is a key metabolic signaling center and the mucosal surface may manifest with some form of maladaptation when exposed to unhealthy nutrients through fat and sugar ingestion. These changes imply a role of the duodenum in the development of insulin resistance and the pathogenesis of related metabolic diseases.

Evidence from Animal Models

In animal studies, researchers have described both morphologic and functional changes in the duodenum following unhealthy nutrient exposure. Adachi and colleagues[39] reported morphologic changes in the small intestines of 3 types of diabetic rats and observed intestinal hyperplasia in all of the models. These researchers also showed that markers of proliferation were increased in diabetic strains compared with controls. In the Wistar rat, Gniuli and colleagues[40] found that a high-fat diet stimulates duodenal proliferation of endocrine cells differentiating toward K cells and oversecreting gastric inhibitory polypeptide (GIP). Bailey and colleagues[41] showed in obese hyperglycemic (ob/ob) mice that a high-fat diet stimulates the production and secretion of intestinal immunoreactive GIP, a mediator of insulin secretion, and increases the density of GIP-secreting intestinal K cells compared with a stock diet. Ponter and colleagues[42] have similarly shown alterations in plasma and small intestinal GIP in response to a high-fat diet in pigs.

Lee and colleagues[43] observed impaired glucose sensing in the enteroendocrine and enterochromaffin cells in a diabetic rodent model, with evidence of impaired downstream neural signaling in the gut.

Salinari and colleagues[44] tested the effects of proteins extracted from the duodenum-jejunum conditioned-medium of db/db (diabetic) or Swiss (nondiabetic) mice, or from the jejunum of insulin-resistant human subjects captured during abdominal surgery. The mouse proteins were tested in several experimental settings, including in vivo in Swiss mice during an intraperitoneal caloric challenge, and in Swiss mice soleus muscle in vitro, whereas human-extracted proteins were

studied on human myotubes ex vivo. Overall, these proteins were found to cause insulin resistance in cultured muscle cells, whether of murine or human origin, providing strong evidence that a factor isolated from the duodenal or jejunal tissue may affect insulin sensitivity.

Evidence from Humans

In concert with animal findings, studies in humans also reveal abnormal mucosal hypertrophy, hyperplasia of enteroendocrine cells, and increases in enteroendocrine cell and enterocyte numbers in the upper GI tracts of diabetic patients compared with nondiabetic controls.[3,5]

Theodorakis and colleagues[3] specifically noted an increase in L and L/K cells in the duodenal mucosa of type 2 diabetic patients compared with nondiabetic controls, whereas Verdam and colleagues[5] showed increases in small intestinal enterocyte mass and increases in enterocyte loss related to chronic hyperglycemia in severely obese subjects. Salinari and colleagues[12] conducted an intricate study of the upper GI tract in obese subjects with and without type 2 diabetes by infusing nutrients at 3 different starting points in the small bowel (duodenum, proximal jejunum, and mid-jejunum) through a balloon catheter. They showed that bypass of the duodenum, with delivery of nutrients to the jejunum instead, resulted in an approximate 50% increase in insulin sensitivity in both groups. This finding offers direct evidence of the apparent insulin-resisting signal that seems to emanate from the region of the duodenum and how it is attenuated when nutrient delivery to the region is prevented.

DUODENAL MUCOSAL RESURFACING: METHOD FOR CORRECTING DUODENAL METABOLIC SIGNALING

Rationale for Targeting Duodenal Mucosa

Collectively, the observations described earlier support an approach that targets the duodenum mucosal surface for the treatment of metabolic disease without the need for placing a permanent implant. To this end, a novel endoscopic catheter system (Revita DMR system [Fractyl Laboratories, Inc, Lexington, MA]) was designed to deliver a hydrothermal exchange at the mucosal surface, resulting in superficial tissue ablation. Currently under investigation in the United States, the Revita DMR system holds a CE (Conformité Européene) mark in Europe.

As background, ablation is a common treatment modality for a wide variety of medical conditions (**Table 1**). Intervention involves the physical removal of superficial abnormal tissue and the regrowth and restoration of normal tissue through a stem cell–mediated healing response. The most anatomically analogous approach to DMR is endoscopic ablative therapy through either radiofrequency (Barrx, Covidien, Sunnyvale, CA) or argon plasma coagulation for Barrett's esophagus, a precancerous condition and complication of gastroesophageal reflux disease, in which the normal squamous epithelium of the distal esophagus transforms to a columnar-lined intestinal metaplasia.[45,46] This treatment modality has become well established and its efficacy and safety are well described.[47] Ablation is followed by restoration of the squamous epithelium.[48]

Targeting Duodenal Mucosa in Animal Models: Proof of Concept

As described by Rajagopalan and colleagues,[60] Revita DMR was first explored in preclinical rodent and porcine models. In diabetic rats (Goto-Kakizaki), selective denudation of the duodenal mucosa conducted by an abrasion device improved

Table 1
Examples of ablation methods and their clinical applications

Ablation Method	Examples of Clinical Use
Radiofrequency	Barrett's esophagus[46] Atrial fibrillation[49] Liver tumors[50]
Laser	Benign prostatic hyperplasia[51] Dermatologic conditions[52]
Cryoablation	Atrial fibrillation[49] Actinic keratosis[53] Warts[54]
Chemical	Cardiac arrhythmias[55] Telangiectasias[56] Facial rejuvenation[57]
Mechanical	Dermatologic conditions[58]
Hydrothermal	Heavy uterine bleeding[59] Type 2 diabetes (investigational [United States], approved [European Union])[60] NAFLD/NASH (investigational)[61]

Abbreviation: NAFLD, nonalcoholic fatty liver disease.

glucose tolerance compared with preprocedure tolerance and also compared with sham-treated diabetic controls (Fig. 1). Of note, in nondiabetic (Sprague-Dawley) rodents that received the same treatment, there was no improvement in glucose tolerance. These findings suggest that this duodenum-directed intervention was effective in treating abnormal hyperglycemia, but without an effect in normal animals. Subsequent safety studies conducted in a porcine model showed that hydrothermal ablation was feasible and, when applied as described, was limited to the superficial intestinal mucosa and did not damage the underlying muscularis mucosa or deeper structures (Rajagopalan H et al, unpublished data, Fractyl Laboratories, Inc, Lexington, MA).

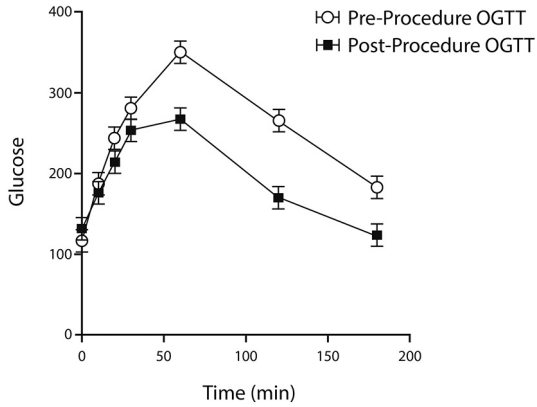

Fig. 1. Oral glucose tolerance test (OGTT) results in the Goto-Kakizaki rat (n = 9) before and after duodenal abrasion. Duodenal abrasion was associated with a 25% improvement in area under the curve for OGTT.

Duodenal Mucosal Resurfacing Catheter (Revita) and Procedure

DMR is an upper endoscopic, catheter-based procedure that uses a combination of circumferential mucosal lift (via a homogeneous submucosal injection, separating superficial mucosa from underlying muscularis) of the target segment of duodenum and hydrothermal ablation via a novel, wire-guided balloon catheter system (Fig. 2). This ablation is followed by a re-epithelialization of the treated duodenal lumen that seems to initiate fairly immediately, within days following procedure, achieving a reset of duodenal mucosa in patients with type 2 diabetes.

The procedure is performed on patients under general anesthesia with a duration of just less than 60 minutes. The catheter is used to first size the duodenum and then circumferentially lift the mucosa from the underlying muscularis with saline submucosal injection to provide a uniform ablative surface and a thermally protective layer of saline between the mucosa and deeper tissue layers. Under direct endoscopic visualization, discrete circumferential hydrothermal ablations lasting approximately 10 seconds each are applied at temperatures of approximately 90°C, with the goal of obtaining up to 5 longitudinally separated ablations along a length of approximately 9 to 10 cm of post-papillary duodenum (Fig. 3). The procedure is performed starting at the post-papilla and ending proximal to the ligament of Treitz. It is monitored and controlled by the physician from a stand-alone console. In the 24 hours postprocedure, patients are able to resume an oral diet but are counseled to adhere to a puree/semisolid diet for the next 10 to 14 days without an intended caloric restriction.

First-in-Human Study of Revita Duodenal Mucosal Resurfacing in Type 2 Diabetes

Six-month safety and efficacy data from a single-arm, open-label, nonrandomized, first-in-human (FIH) study of Revita DMR has recently been published.[60] At the time of the report the study, performed at a single site in South America, had enrolled 44 patients with type 2 diabetes who were poorly controlled and were on at least 1 oral antidiabetic medication. At screening, patients had hemoglobin A1c (HbA1c) levels that ranged from 7.5% to 12% (average of 9.5%). Enrolled patients ranged in age from 38 to 65 years, had type 2 diabetes for a duration of less than 10 years, and were overweight or obese as defined by body mass index (average, 30.8 kg/m^2). Patients on injectable medications, including insulin, were excluded from participation.

Safety Profile of Duodenal Mucosal Resurfacing in Early Human Use

Of the original patient cohort, the DMR procedure was completed without periprocedural complication in all 40 treated patients and was well tolerated. There was no

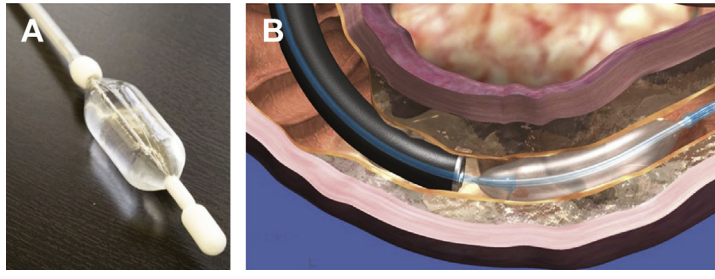

Fig. 2. Revita DMR catheter. (*A*) First-generation, single-use balloon catheter used to perform hydrothermal ablation of the duodenal mucosa. (*B*) The balloon inflated in the duodenum during hydrothermal ablation. (*Courtesy of* Fractyl Laboratories, Inc, Lexington, MA; with permission.)

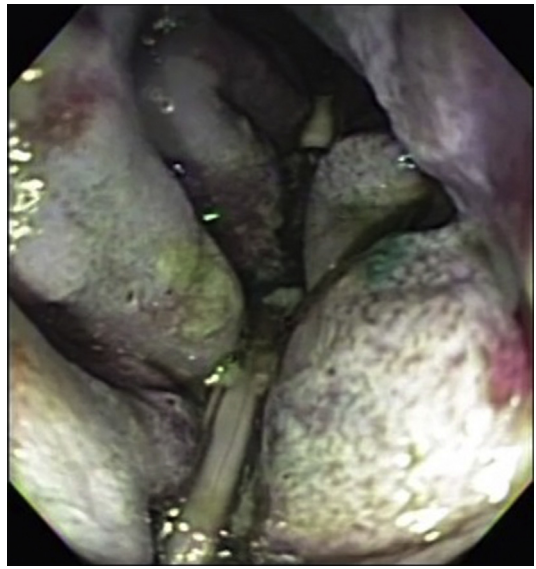

Fig. 3. The duodenal mucosa immediately after hydrothermal ablation. (*Courtesy of* Fractyl Laboratories, Inc, Lexington, MA; with permission.)

observed bleeding, perforation, infection, or pancreatitis. In addition, there were no obvious features of malabsorption (as indicated by hematological and chemistry measures) and DMR did not seem to cause hypoglycemia. The most common study-related adverse event was mild, transient, postprocedural abdominal pain in 20% of patients (8 out of 40) that resolved without treatment within 48 hours. Follow-up endoscopies and duodenal biopsies in a subset of patients from the FIH study showed mucosal healing in all evaluated patients. Three patients had procedure-related duodenal stenosis, which was successfully treated by single nonemergent endoscopic balloon dilation in each case without further complications. In total, 90 DMR procedures have been conducted thus far with no further stenosis cases since those reported in the original cohort.

Glycemic Improvement in Subjects with Type 2 Diabetes in the First-in-Human Study

In the FIH 6-month interim report, DMR elicited a decrease of glycemia that was prompt (in the first 1–2 weeks) and resulted in significant lowering of HbA1c levels (**Fig. 4**A). It was also observed that subjects who had longer segment ablation (average length, ~9 cm) showed a greater glycemic improvement than those subjects who had a shorter segment ablation (~3 cm), thus indicating an ablation dose dependency. Closer assessment showed that most of the plasma glucose level lowering was a reflection of fasting glucose reduction (~40–50 mg/dL), suggesting a predominant impact on overnight basal hepatic production. There was nonetheless a small additional reduction of the postprandial glycemic excursion contributing to the overall effect. There was some rebound or loss of glycemic effect observed in certain patients at 6 months, but this observation was confounded by a reduction in background medication in many. For patients who remained on stable medication postprocedure, there seemed to be a greater reduction in HbA1c level at 6 months (−1.8%) and better durability of the glycemic effect than in patients whose medications were changed during the course of the study. This improvement in glycemic state was accompanied by a

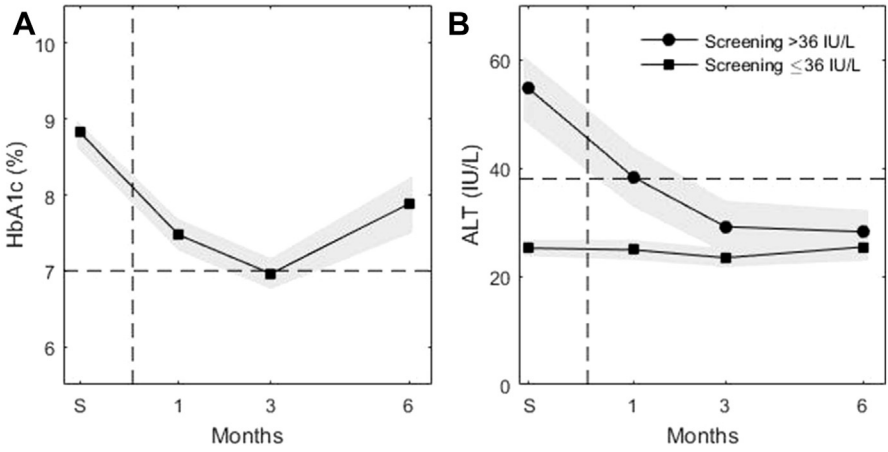

Fig. 4. Effect of DMR on HbA1c level and liver enzymes in the FIH cohort (most recent data capture of n = 48). Shaded area is ±1 standard error of the mean. (*A*) HbA1c levels at screening, 1, 3, and 6 months in subjects with preprocedure HbA1c levels of 7.5% to 10% and 3 or more ablations (n = 19). (*B*) Impact of DMR on alanine transaminase (ALT) by screening ALT level in subjects with 3 or more ablations (highest screening ALT, n = 15; lowest screening ALT, n = 15).

significant lowering of HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) as an indicator of improved insulin sensitivity (Rajagopalan H et al, unpublished data, Fractyl Laboratories, Inc, Lexington, MA). Of note, there was a modest effect on body weight during the 6 months, with a ~3-kg weight loss noted at 3 months and a return toward preprocedure weight by 6 months, suggesting that the effect was unlikely to be explained by alterations in body weight.

Wider Metabolic Effects of Duodenal Mucosal Resurfacing Observed in Human Subjects

As described with insulin-sensitizing pharmacologic approaches (eg, TZD) and bariatric surgery, a wider array of metabolic effects could be anticipated with DMR. In the FIH study, a lowering of hepatic transaminase levels from preprocedure values was observed, and the reductions were more striking in subjects with higher preprocedure levels (Fig. 4B). In the patients receiving long-segment ablation (n = 28), both alanine transaminase (ALT) and aspartate transaminase (AST) levels were reduced by approximately 30% at 6 months.[61] Moreover, reductions in ALT and AST were also seen in a subset of patients from the FIH study who had incidental findings of fatty liver on ultrasonography examination in the months before procedure. Although these findings are preliminary, further study of liver indices (including circulating, radiological, elastographic, and tissue indices) in patients post-DMR are warranted to determine whether DMR has an important impact on fatty liver disease pathophysiology. In addition, in anticipation of other apparent insulin-sensitizing effects, assessment of DMR effects on cardiovascular (ie, blood pressure, microalbumin) indices and ovulatory function in women are necessary.

SUMMARY

Early human clinical trial data suggest that endoscopic hydrothermal DMR ablation is well tolerated in humans with an acceptable safety profile thus far. This novel,

single-point procedure elicits an improvement in the metabolic state through substantial reductions in glycemia in patients with poorly controlled type 2 diabetes. Preliminary data also suggest an improvement of hepatic transaminase levels when increased before treatment. These findings underscore the notion of the duodenum as an important metabolic signaling center that plays a role in regulating insulin sensitivity. As westernized countries face an increasing economic health burden from diseases driven by insulin resistance (eg, diabetes, fatty liver disease, cardiovascular disease) and the shortcomings of lifestyle, pharmacologic, and surgical approaches limit their applicability and efficacy, this novel endoscopic treatment approach may offer an important alternative for patients. Further studies are necessary to understand the core mechanism, how the procedure performs in a randomized clinical trial setting, and the duration of the beneficial effect, while also embracing the potential for wider metabolic benefits.

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