COMMENTARY

Ablation of the Duodenal Mucosa as a Strategy for Glycemic Control in Type 2 Diabetes: Role of Nutrient Signaling or Simple Weight Loss

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As our understanding of the pathophysiology of type 2 diabetes (T2D) has advanced, new oral and injectable medications have been developed that target a growing number of the pathophysiological processes that cause hyperglycemia. In addition, weight-loss therapy, involving lifestyle interventions, antiobesity medications, or bariatric surgery, has been demonstrated to be highly effective in T2D management. The expanded number of treatment options has provided an increased capacity for glycemic control. Even so, T2D remains a progressive disease, requiring the intensification of therapy over time, and many patients still do not achieve HbA_{1c} targets. Therefore, new therapeutic strategies for effective and safe glycemic control are critically needed.

DUODENAL MUCOSAL RESURFACING

In this issue of *Diabetes Care*, Rajagopalan et al. (1) present a new therapeutic strategy for treatment of T2D. The strong point of the study is that the authors have developed and studied a novel therapeutic approach in T2D that could elucidate new disease mechanisms involving the role of the duodenum in metabolic regulation. The authors present a 6-month interim analysis of a phase I, single-arm, nonrandomized cohort study assessing safety and efficacy of endoscopic duodenal mucosal resurfacing (DMR) for treatment of T2D. This is a first-in-human experience with this intervention, which ablates the duodenal mucosa between the ampulla of Vater and the ligament of Treitz in a two-step endoscopic procedure. First, a catheter with a terminal balloon is passed into the duodenum that has three needles spaced at 120° around the balloon's circumference. The needles are used to inject saline into the submucosal space in order to circumferentially separate and lift the mucosa from underlying tissues in the duodenal wall. A second catheter then introduces another balloon that thermally ablates (i.e., burns) the lifted mucosa at a temperature of ~90°C (194°F).

The conceptual basis of the procedure is derived from observations that bariatric bypass procedures eliminating the duodenal mucosa as an absorptive surface for food, such as the Roux-en-Y gastric bypass, produce weight loss and improvements in glycemia that cannot be explained by a malabsorptive process (2,3). Further rationale is that placement of an endoluminal sleeve preventing physical contact between the duodenal mucosa and ingested food has been observed to improve glucose tolerance and promote weight loss (4). These observations have given rise to the hypothesis that nutrient absorption at the level of the duodenum triggers processes that regulate metabolism via effects on insulin sensitivity, insulin secretion, and/or hypothalamic control of satiety and caloric intake. Various authors have suggested that duodenal bypass *1*) alters enteroendocrine cell secretion of factors such as glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide, and peptide YY; *2*) mediates changes in the gastrointestinal microbiome; or *3*) produces changes in bile acids that signal through intestinal membrane-bound G-protein–coupled receptors (e.g., TGR5) or hepatocellular farnesoid X receptors with downstream effects on GLP-1 production and secretion of fibroblast growth factors, respectively (5). In the study by Rajagopalan et al. (1), DMR was used to prevent nutrient signaling from the duodenum in patients with T2D, and HbA_{1c} lowering constituted the primary outcome measure.

DOES DMR WORK?

The weakness of the study by Rajagopalan et al. (1) relates to effectiveness for HbA_{1c} lowering relative to less invasive approaches using lifestyle therapy and/or medications, as well as the unknown risks of repeated procedures that appear to be necessary to chronically sustain a glucose-lowering effect. A total of 39 patients with T2D were included in the study, with 11 receiving short-segment ablation (~3.4 cm) and 28 long-segment ablation (~9.3 cm) of duodenal mucosa (1). The overall mean HbA_{1c} fell from 9.6% at baseline to 8.4% at 6 months. Effects of long-segment ablation were more

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pronounced than that of short-segment ablation, with HbA_{1c} reductions of 1.4% and 0.7%, respectively, at 6 months. However, the glucose-lowering effect of DMR at 6 months was waning, as observed HbA_{1c} values were lower at 3 months compared with 6 months of follow-up. Management of these patients necessitated reductions of oral diabetes medications in approximately one-half of the patients. Given the high value of HbA_{1c} at baseline, this degree of lowering (1.4% units) could easily be achieved with any number of diabetes drugs. Further, given the waning effects on glycemia, DMR would presumably need to be repeated at intervals that could be as short as 6 months for longer-term glycemic control. A total of 10% of patients could not be treated on the basis of findings at the initial endoscopy, and 10 of the 39 treated patients were primary failures in that they did not experience HbA_{1c} lowering at 6 months. The authors stated that DMR had "an acceptable safety and tolerability profile" (1). Indeed, the most common study-related adverse event was abdominal pain in eight patients, which resolved within 48 h of the procedure. However, three patients developed symptomatic duodenal stenosis requiring endoscopic balloon dilation therapy. If serial DMRs were required for chronic glycemic control, it is possible this complication could become more problematic with repeated injury to the duodenum.

HOW DOES DMR LOWER HbA_{1c}?

Further questions can be raised regarding the mechanisms by which DMR improves glycemia and whether it is necessary to postulate an effect on duodenal nutrient signaling. The authors speculate that DMR, by eliminating the duodenum for nutrient absorption, ameliorates metabolism through a correction in gastrointestinal hormone signaling, corresponding to the improvement in insulin release and glucose tolerance, and an assumed increase in postprandial GLP-1 levels as is observed following gastric bypass (5–11). Both foregut and hindgut hypotheses have been proposed to explain the rise in GLP-1 levels: the foregut hypothesis supposes that the critical event occurs at the level of the duodenum with blockage of exposure to nutrients, whereas the hindgut hypothesis suggests that this is due to more rapid delivery of nutrients to the distal small bowel or distal ileum, the location of the GLP-1–secreting L cells. In fact, these are not mutually exclusive, and both mechanisms may act to increase GLP-1 levels. Rajagopalan et al. (1) propose a foregut mechanism to explain the improvement of glycemia with DMR and suggest that DMR corrects an overgrowth of enteroendocrine cells and dysregulated secretion of gastrointestinal hormones. However, the foregut hypothesis has been challenged by data suggesting that the sleeve gastrectomy, which does not exclude the duodenum, also increases incretin levels and is similarly effective in improving diabetes status (12,13). Suffice it to say that the putative mechanisms linking the elimination of duodenal nutrient absorption with metabolic benefits remain controversial and each hypothesis fails to consistently explain improvements in glycemia across model systems (5). For example, equivalent weight loss through gastric banding does not increase GLP-1 but can also be associated with substantial diabetes improvement or remission (14).

EFFECTS OF WEIGHT LOSS ASSOCIATED WITH DMR

To this latter point, Rajagopalan et al. (1) have not excluded a substantial effect of hypocaloric feeding and weight loss associated with the procedure that could explain effects of DMR on glycemia. Following the endoscopic procedure, patients were fed a progressive diet, advancing from liquids to soft foods to pureed foods over 2 weeks (1). The authors did not describe caloric intake, time to resumption of normal food, or effects on body weight over this time period. The authors report that mean weight loss was 4.6% at 3 months and 3.0% at 6 months. This degree of weight loss per se can effectively reduce glycemia in T2D. A very low-calorie diet over short periods of time (5–7 days) can markedly reduce both intramyocellular (15) and intrahepatocellular (16) lipids with corresponding increases in insulin action in muscle and liver, respectively, together with preferential mobilization of intra-abdominal fat. In patients with T2D, the mobilization of fat from these depots results in an increase in systemic insulin sensitivity and reduced rates of hepatic glucose output with concomitant reductions in glycemia. These same mechanisms are likely operative in patients with T2D undergoing bariatric surgery, which necessitates a need for reductions in diabetes medications over several days following surgery, even before substantial changes in body weight have occurred (17). With weight loss over a more extended period of several weeks,

Table 1—Relationship between weight loss at 6 months and HbA_{1c} lowering in patients with T2D following various interventions

Intervention trials in patients with T2D	Ref. no.	HbA_{1c} (%), baseline	HbA_{1c} (%), 6 months+	Weight (kg), baseline	Weight loss (%), 6 months
DMR	1	9.6	8.4	84.4	3.0; 4.6 at 3 months
Lifestyle intervention					
Motivational interviewing	23	7.5	6.74	97.0	4.8
Attention control	23	7.6	7.1	97.0	3.2
Weight loss medications					
Orlistat	24	9.0	8.1	102.0	4.0
Lorcaserin	25	8.1	7.1	103.7	4.6
Naltrexone ER/bupropion ER	26	8.0	7.2	106.3	5.0
Liraglutide 3 mg	27	7.9	6.6#	105.7	5.8
Phentermine/topiramate ER	28	8.8	7.5	94.9	10

ER, extended release. +All studies required reductions in diabetes medications as clinically necessary. #HbA_{1c} is the data point at 56 weeks; however, fasting plasma glucose was identical at 6 months and 56 weeks.

the ongoing reduction in glycemia is associated with a reduction in "glucose toxicity" with reversal of key pathophysiological processes that establish and maintain the diabetic state (18–22). Therefore, in T2D, weight loss over weeks to months enhances glucose homeostasis and lowers HbA_{1c} not only via reductions in intramyocellular, intrahepatocellular, and intra-abdominal adipose tissue but also by reversal of glucose toxicity resulting in enhanced insulin action and secretion. Therefore, hypocaloric feeding in the early weeks following DMR, as well as sustained weight loss over the 6-month duration of the study, would explain at least a portion of the improvement in HbA_{1c} despite the fact that this possibility is minimalized or dismissed by the authors. Table 1 illustrates that lifestyle interventions and weight-loss medicines can achieve reductions in HbA_{1c} with weight loss in the range of what was reported with DMR.

It is commendable that Rajagopalan et al. (1) are pursuing a novel therapeutic approach in T2D that has the potential to define new disease mechanisms. However, it appears from these early data that patients may need repeated DMR procedures to sustain improvements in HbA_{1c} over a longer term and that the efficacy may not be greater than that achievable with glucose-lowering diabetes medications or weight-loss therapy. Although one application of DMR was tolerated fairly well, the potential for duodenal stenosis may prove to be problematic with repeat procedures. Finally, the authors will need to conduct controlled randomized trials to demonstrate that the procedure adds value to the benefits of hypocaloric feeding necessitated by the procedure over the first 2 weeks and the 3–5% weight loss that is observed over the ensuing 3–6 months.

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