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

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 HbA1c 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 HbA1c lowering constituted the primary outcome measure.

DOES DMR WORK?

The weakness of the study by Rajagopalan et al. (1) relates to effectiveness for HbA1c 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 HbA1c fell from 9.6% at baseline to 8.4% at 6 months. Effects of long-segment ablation were more...
pronounced than that of short-segment ablation, with HbA1c 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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c?**

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 hormonal 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 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 HbA1c lowering in patients with T2D following various interventions

| Intervention trials in patients with T2D | Ref. no. | HbA1c (%) baseline | HbA1c (%) 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. #HbA1c 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 HbA1c, 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 HbA1c despite the fact that this possibility is minimized or dismissed by the authors. Table 1 illustrates that lifestyle interventions and weight-loss medicines can achieve reductions in HbA1c 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 HbA1c 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.

References
1. Rajagopalan H, Cherrington AD, Thompson CC, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes: 6-month interim analysis from the first-in-human proof-of-concept study. Diabetes Care 2016;39:2254–2261
2. Schauer PR, Bhatt DL, Kirwan JP, et al.; STAMPEDE Investigators. Bariatric surgery versus intensive medical therapy for diabetes—3-year outcomes. N Engl J Med 2014;370:2002–2013
3. Batterham RL, Cummings DE. Mechanisms of diabetes improvement following bariatric/metabolic surgery. Diabetes Care 2016;39:893–901
4. Koehestanie P, de Jonge C, Berends FJ, Janssen IM, Bouvy ND, Greve JW. The effect of the endoscopic duodenal-jejunal bypass liner on obesity and type 2 diabetes mellitus, a multicenter randomized controlled trial. Ann Surg 2014;260:984–992
5. Grams J, Garvey WT. Weight loss and the prevention and treatment of type 2 diabetes using lifestyle therapy, pharmacotherapy, and bariatric surgery: mechanisms of action. Curr Obes Rep 2015;4:287–302
6. le Roux CW, Ayliwin SJ, Batterham RL, et al. Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann Surg 2006;243:108–114
7. Morinigo R, Moizé V, Musi M, et al. Glucagon-like peptide-1, peptide YY, hunger, and satiety after gastric bypass surgery in morbidly obese subjects. J Clin Endocrinol Metab 2006;91:1735–1740
8. Lafferrère B, Heshka S, Wang K, et al. Incretin levels and glucose kinetics markedly enhance 1 month after Roux-en-Y gastric bypass surgery in obese patients with type 2 diabetes. Diabetes Care 2007;30:1709–1716
9. Lafferrère B. Diabetes remission after bariatric surgery: is it just the incretins? Int J Obes 2011;35(Suppl. 3):S22–S25
10. Jørgensen NB, Dirksen C, Bojsen-Møller KN, et al. Restoration of insulin responsiveness in type II diabetes mellitus. Diabetes 1986;35:990–997
11. Salehi M, Prigeon RL, D’Alessio DA. Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. Diabetes 2011;60:2308–2314
12. Nannipieri M, Baldi S, Mari A, et al. Roux-en-Y gastric bypass and sleeve gastrectomy: mechanisms of diabetes remission and role of gut hormones. J Clin Endocrinol Metab 2013;98:4391–4399
13. Gill RS, Birch DW, Shi X, Sharma AM, Karmali S. Sleeve gastrectomy and type 2 diabetes mellitus: a systematic review. Surg Obes Relat Dis 2010;6:707–713
14. Korner J, Bessler M, Inabnet W, et al. Exaggerated GLP-1 and blunted GIP secretion are associated with Roux-en-Y gastric bypass but not adjustable gastric banding. Surg Obes Relat Dis 2007;3:597–601
15. Lara-Castro C, Newcomer BR, Rowell J, et al. Effects of short-term very low-calorie diet on intramyocellular lipid and insulin sensitivity in nondiabetic and type 2 diabetic subjects. Metabolism 2008;57:1–8
16. Kirk E, Reeds DN, Finck BN, Mayurranjan SM, Patterson BW, Klein S. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. Gastroenterology 2009;136:1552–1560
17. Isbell JM, Tamboli RA, Hansen EN, et al. The importance of caloric restriction in the early improvements in insulin sensitivity after Roux-en-Y gastric bypass surgery. Diabetes Care 2010;33:1438–1442
18. Henry RR, Wallace P, Olefsky JM. Effects of weight loss on mechanisms of hyperglycemia in obese non-insulin-dependent diabetes mellitus. Diabetes 1986;35:990–997
19. Friedman JE, Dohm GL, Leggett-Frazier N, et al. Restoration of insulin responsiveness in skeletal muscle of morbidly obese patients after weight loss. Effect on muscle glucose transport and glucose transporter GLUT4. J Clin Invest 1992;89:701–705
20. Garvey WT, Olefsky JM, Matthei S, Marshall S. Glucose and insulin co-regulate the glucose transport system in primary cultured adipocytes. J Biol Chem 1987;262:189–197
21. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Koltermann OG. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. Diabetes 1985;34:222–234
22. Rossetti L, Giacca A, DeFronzo RA. Glucose toxicity. Diabetes Care 1990;13:610–630
23. West DS, DiLillo V, Bursac Z, Gore SA, Greene PG. Motivational interviewing improves weight loss in women with type 2 diabetes. Diabetes Care 2007;30:1081–1087
24. Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes: A 1-year randomized controlled trial. Diabetes Care 2002;25:1033–1041
25. O’Neil PM, Smith SR, Weissman NJ, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. Obesity (Silver Spring) 2012;20:1426–1436
26. Hollander P, Gupta AK, Plodkowski R, et al.; COR-Diabetes Study Group. Effects of naltrexone sustained-release/bupropion sustained-release combination therapy on body weight and glycemic parameters in overweight and obese patients with type 2 diabetes. Diabetes Care 2013;36:4022–4029
27. Davies MJ, Bergenstal R, Bode B, et al.; NNN89022-1922 Study Group. Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial. JAMA 2015;314:687–699
28. Garvey WT, Ryan DH, Bohannan NJ, et al. Weight-loss therapy in type 2 diabetes: effects of phentermine and topiramate extended release. Diabetes Care 2014;37:3309–3316