Minireview: Current status of endoscopic duodenal mucosal resurfacing

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Review

Minireview: Current status of endoscopic duodenal mucosal resurfacing

Giancarlo Condello [a], Chih-Yen Chen [b,cdefg,*]

[a] Graduate Institute of Sports Training, Institute of Sports Sciences, University of Taipei, Taipei, Taiwan
[b] Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Faculty of Medicine and Institute of Emergency and Critical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan
[d] Institutional Review Board, Taipei Veterans General Hospital, Taipei, Taiwan
[e] Association for the Study of Small Intestinal Diseases, Guishan, Taoyuan, Taiwan
[f] Chinese Taipei Society for the Study of Obesity, Taipei, Taiwan
[g] World Health Organization-Strategic Initiative for Developing Capacity in Ethical [illegible] Forum for Ethical Review Committees in the Asian and Western Pacific Region

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ABSTRACT

Several strategies are being pursued to overcome the alarming pandemics of obesity and type 2 diabetes (T2D). In recent years, duodenal mucosal resurfacing (DMR) has shown its potential to improve glycemic indices. Following animal studies, which demonstrated feasibility and safety, the procedure has been applied in two human studies. The DMR procedure has been considered feasible and safe in humans with a limited occurrence of complications and adverse events. Reductions in glycated haemoglobin, weight, fasting plasma glucose, and alanine transaminase have been proven at different follow-up time-points. The length of the ablation may induce different outcomes, having the patients with long duodenal segment ablated showed greater beneficial effects. The current evidence does not still prove the apparent insulin-sensitizing mechanism explaining the impact of the DMR procedure on hepatic glucose production. However, the initial findings have demonstrated a positive risk-benefit ratio and an effect on the treatment of metabolic diseases, such as T2D. Future studies should clarify the mechanisms underlying the positive effects and durability of the treatment using controlled trial conditions on larger number of patients.

Introduction

The most alarming pandemics in current society are obesity and type 2 diabetes (T2D), with an estimated global prevalence of 552 million by 2030 for T2D [1]. The prevalence of T2D is particularly influenced by demographic changes, such as ageing, as well as other risk factors, such as increasing sedentary lifestyles and decreasing levels of physical activity. Therefore, a multidisciplinary approach for the examination of health-related issues should always consider a combination of the determinants of diet, physical activity, and sedentary behaviors [2].

Several approaches for managing obesity and T2D can be pursued, such as behavioral therapy, pharmacotherapies, and dietary modification [3]. However, the rate of weight loss is moderate (5%), whilst long-term recidivism is high (>99%) [4]. Conversely, bariatric surgery is considered more effective than medical therapy to guarantee durable remission of T2D and other cardiovascular risk factors [5–11]. However, bariatric surgery is also expensive, invasive, and irreversible, has low acceptance rate, and is associated with some morbidity, limiting their applicability to a majority of the population with obesity and T2D.

The rationale behind the use of surgery is to bypass the small intestine, in particular the duodenum, in order to affect the physiology and pathophysiology of glucose homeostasis [12–14]. In fact, the duodenum represents the first site of fuel recognition at the time of nutrient intake, thus preventing contact between duodenal mucosa, bile, and nutrients could improve insulin sensitivity and β-cell function [15]. On the basis of these pathophysiological considerations, duodenal mucosal resurfacing (DMR) has been proposed as an endoscopic procedure to treat patients with T2D and nonalcoholic fatty liver disease/nonalcoholic steatohepatitis [16]. DMR procedure in-

* Corresponding author at: Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 11217, Taiwan.
E-mail address: chency@vghtpe.gov.tw (C-Y Chen)

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volves the circumferential hydrothermal ablation of the duodenal mucosa in order to allow the regeneration of the mucosa. The most recent procedure firstly includes to mark the location of the papilla of Vater and to insert a guidewire past the ligament of Treitz. Therefore, the DMR catheters is advanced over the guidewire. Subsequently, the procedure consists of a submucosal expansion in order to provide a protective layer of saline between the mucosa/submucosa and duodenal proper muscle layer, and a stepwise circumferential hydrothermal ablation at 90 °C for 10 s over 9–10 cm of the postpapillary duodenum. The ablation is performed at a position just distal to the papilla of Vater and progressively distal duodenal areas are then ablated [17]. As a consequence, a reset of the duodenal enteroendocrine cells may restore signaling and amplify the incretin effect [18].

DMR was first applied in small animals to prove the efficacy of the procedure, and subsequently tested in large animals to demonstrate its safety and feasibility [16]. The proof-of-concept study was conducted on Goto-Kakizaki (GK) rat model of insulin-resistant diabetes and wild-type (Sprague Dawley rat) nondiabetic controls. They were divided into abrasion and sham procedure groups. For the first group a balloon-inflated abrasion device was inserted into the duodenum and inflated with air, and mucosal abrasion was performed via anterograde swipes at successively increasing balloon pressures. For the second group, an atraumatic probe was inserted into the duodenum for the same total procedure time without disrupting the mucosa. Therefore, post procedure glucose tolerance testing or histologic specimens, for nonsurvival rats, were conducted [16]. The safety and feasibility of the procedure was tested in Yorkshire swine, due to the similarity with humans in luminal diameter, mucosal thickness, and endoscopic access. DMR was performed from the distal duodenum to 8 cm from the pylorus. The evidence of harm or adverse events were evaluated with endoscopy at 7 days after the procedure and then animals were killed at different time point for the histologic analysis of the duodenum. The results from small animals showed a reduction in hyperglycemia in the treated GK rat. The investigation in large animals revealed the absence of adverse events, systemic infections or blood loss from gut, obstruction or restriction, thermal necrosis or damage to the muscularis propria, whilst it was revealed normal blood chemistry and post procedure blood counts and progressive regenerative mucosal healing process completed by week 6 [16].

At present, only two in-human studies [15,17] and a case report [19] are available. The first-in-human clinical study was conducted in a single center in Santiago, Chile (CCO Clinical Center for Diabetes Obesity and Reflux), using a single-procedure DMR in 44 patients (females = 16; males = 28) with T2D for a 6-month interim analysis [15]. The baseline clinical characteristics were the following: age = 53.4 ± 7.5 yrs[illegible]eight = 84.4 ± 11.9 kg; height 165.3 ± 8.4 cm; BMI [illegible] 30.8 ± 3.5 kg/m^2; duration T2D = 5.7 ± 2.2 yrs.; HbA1c 9.[illegible]4% (81 ± 16 mmol/mol); fasting plasma glucose = 187 ± 58[illegible]L. A second investigation was conducted using an international, open-label, prospective, multicentre study in which 46 patients (females = 17; males = 29) with T2D had been followed for a year [17]. The baseline clinical characteristics were the following: age = 55 yrs.; weight = 90.3 ± 13.1 kg; BMI 31.6 ± 4.3 kg/m^2; duration T2D = 6 yrs.; HbA1c 8.6 ± 0.8% (70 ± 9 mmolmol); fasting plasma glucose = 193 ± 49 mg/dL.

The feasibility, safety, efficacy, and the comparison of DMR with duodenal-jejunal bypass liner are separately discussed in the following sections.

Duodenal mucosal resurfacing: feasibility and safety

The two human studies showed a feasibility of 90% [15] and 80% [17], respectively. In the first study, 4 patients did not receive the complete DMR procedure due to failing the screening endoscopy (n = 2), tortuous anatomy (n = 1), or to avoid prolonged anesthesia (n = 1) [15], whilst in the second study the causes for 9 patients not receiving the complete DMR procedure were attributed to catheter failure (n = 4), difficult catheter tracking and positioning (n = 3), duodenal tortuosity (n = 1), or inadequate lifting (n = 1) [17].

The safety of the application of DMR was carefully considered in light of adverse events, complications, and discomfort. The 40 treated patients in the first-in-human study [15] did not report any complications, as there were no cases of perforation, pancreatitis, or bleeding, and no apparent evidence of malabsorption. Post procedure gastrointestinal symptoms were, however, transient and of mild or moderate severity. The 3 cases of duodenal stenosis, causing epigastric pain and vomiting within 6 weeks after the procedure, were treated with endoscopic balloon dilation without further consequences. Therefore, for the first time optimistic findings were provided with a safe and well tolerated Revita DMR procedure [15]. The second-in-human study presented some adverse events [17]. During follow-up, only 1 out of the 6 severe adverse events was related to the procedure, reporting general malaise, mild fever, and increased c-reactive protein, which were normalized within 3 days. Conversely, during the first year 54 adverse events were reported in 24 patients, of which 41% were treated with medications. Although some issues have been speculated, as the novelty of the procedures for the endoscopists and the underdeveloped status of DMR technology, the safety and tolerability of the DMR procedure have been considered encouraging [17].

Duodenal mucosal resurfacing: efficacy

The efficacy of DMR has been investigated at the light of the improvements in glycemic indices after the procedure. The level of glycated haemoglobin (HbA1c) was evaluated at different time-points in the two studies. Overall, a reduction in HbA1c after the DMR procedure was observed as early as 1 month in both studies and was still present at the 3 and 6 months follow-ups in the first-in-human study [15] and during the entire year of analysis for the second-in-human study (i.e., at 3, 6, 9, and 12 months) [17]. The magnitude of reduction at 6 months was 1.2% ± 0.3% [14] and 0.9% ± 0.2% [17], respectively. However, considering the length of the treated duodenal mucosa, patients with a long duodenal segment ablated (average of 9.3 cm of ablation) showed a higher reduction at 3 months (2.5% ± 0.2% vs. 1.2% ± 0.5%, respectively) and 6 months (1.4% ± 0.3% vs. 0.7% ± 0.5%, respectively) compared with patients with a short duodenal segment ablated (average of 3.4 cm of ablation) [15]. The reduction of HbA1c at 6 months did not occur with a concomitant change in fasting plasma insulin [15]. Conversely, fasting plasma glucose reduced within 1 week and it was more evident for patients with a long duodenal segment ablated [15]. A reduction in fasting plasma glucose was also observed at 6 (by 1.7 ± 0.5 mmol/L) and 12 (by 1.8 ± 0.d mmol/L) months follow-ups [17]. The second-in-human study provided results on further indicators [17]. For homeostatic model assessment for insulin resistance

(HOMA-IR), a reduction by 2.9 ± 1.1 at 24 weeks and by 3.3 ± 0.9 at 12 months post DMR were significantly observe ($p < 0.001$) compared with baseline (8 ± 5.7). Moreover, C-peptide levels did not differ between stable medication (1.1 ± 0.1 nmol/L) ad increased medication groups (0.8 ± 0.1 nmol/L) compared with baseline (0.97 ± 0.40 nmol/L, known in 28 patients). Similarly, baseline fasting plasma insulin levels (91 ± 57 pmol/L) did not significantly change between stable medication (94 ± 11 pmol/L) and increased medication (102 ± 26 pmol/L).

A significant weight reduction was revealed in both first-in-human study [15] (3 months: −3.9 ± 0.5 kg and 6 months: −2.5 ± 0.1 kg) and second-in-human study (6 months: −2.5 ± 0.6 kg and 12 months: −2.4 ± 0.7 kg) [17].

Finally, the DMR treatment reached also a high degree of satisfaction, increasing from 6 to 12 months (from +11.8 ± 1.2 pt to +12.7 ± 0.8 pt, respectively) [17].

At moment, further results were found in a case report on a 44-year-old man (BMI = 28 kg/m^2) with T2D showing a reduction in HbA1c of 1.2% at 3 months with a concomitant drop in fasting plasma glucose of 28.3%, whilst no change in alanine transaminase was observed [19].

Duodenal mucosal resurfacing versus duodenal-jejunal bypass liner

The duodenal-jejunal bypass liner (DJBL) is a common form of treatment for obesity, T2D, and nonalcoholic fatty liver disease. The procedure consists of an implant anchored in the proximal duodenum and a sleeve extended into the jejunum, forming a bypass/biliopancreatic diversion, hence the mix of pancreatic/bile juices and food will occur only after the sleeve [20]. DJBL mimics Roux-en-Y (RYGB)-related proximal small intestinal exclusion, and the linear is impermeable with 60 cm long [21].

The DJBL procedure is widely s[illegible] with a recent r[illegible]alysis showing an improved glycemic control after DJBL in patients with obesity and T2D [22]. A pilot study, attempting to investigate the mechanisms for the improvement in glycemic control, examined the hormones involved in glucose homeostasis [21]. A possible explanation for the decline of fasting and postprandial glucose levels has been attributed to the increased insulin sensitivity and/or decreased hepatic glucose production. Moreover, the improvement of glycemic control also depended on the changes in glucagon, glucagon-like peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP). These findings emphasized the rational for the exclusion of the proximal small intestine with the DJBL procedure in order to affect insulin sensitivity and hepatic glucose production [21]. A significant reduction in HbA1c in patients treated with the DJBL procedure was also observed in the last cohort study [23]. Although the DJBL procedure showed positive effects, the safety of this treatment still must be cautiously considered. In fact, serious adverse events have been registered, such as dislocation, gastrointestinal bleeding, sleeve obstructions, duodenal ulcers, biliary colic, oesophageal lesions, and, of major concern, hepatic abscesses, which require mandatory strategies to reduce the rate of their occurrence [24].

Therefore, an attempt to compare the DMR and DJBL procedures may reveal that both treatments induce improvements in glycemic indices and weight control, and both have a putative effect on gastrointestinal hormones. However, DMR is a relatively new procedure which still requires further investigations to confirm its efficacy, whilst DJBL has been mostly investigated, including randomized controlled trials. Nonetheless, given that safety is of major concern, DMR has already demonstrated a high level of safety, whilst a high occurrence of severe adverse events has been registered after DJBL.

Conclusion

The current sparse knowledge on DMR does not allow drawing definitive conclusions on the efficacy of the procedure. However, the available evidence might reveal an encouraging degree of feasibility, safety, and efficacy for the DMR procedure for the treatment of patients with obesity and T2D. Although, the number of adverse events is not negligible, an initial positive risk-benefit ratio has been obtained considering the positive effects on glycemia with minimal perturbation and assuring safety.

From the current findings, it can be speculated an apparent insulin-sensitizing mechanism behind the durable effect on hepatic glucose production [15,17]. The improvement of glycemia with DMR could be attributed to a correction of the overgrowth of enteroendocrine cells and dysregulated secretion of gastrointestinal hormones, hypothesizing a foregut mechanism [15]. However, this hypothesis is not exhaustive, and it remains unclear whether the mechanism underlying the effects of the DMR procedure is antidiabetic, hepatic or both. Possible speculative mechanisms were attributed to changes in gut microbiome, bile acid composition or gut permeability [17].

Moreover, it remains questionable whether the reduction in HbA1c is concurrently achieved by hypocaloric feeding immediately after the DMR procedure and weight loss over a 6-month period [15,17]. In fact, similar reductions in HbA1c have been observed with lifestyle interventions and weight-loss medicines [25]. However, a reduction in HbA1c without a consistent decrease in body weight has been demonstrated [17]. In fact, body weight markedly decreased only during the 4 weeks post procedure, but this reduction did not correlate with change in HbA1c at 24 weeks or 12 months [17]. Therefore, weight loss cannot fully explain the reduction in HbA1c, highlighting the possible benefit of DMR procedure for T2D remission.

More research is necessary to further exploit DMR procedure. In particular, future research should be conducted taking in to account [26]: (a) the homogeneity of sample in terms of age, gender, race, duration of T2D; (b) the clinical characteristics in the per-protocol population; (c) the long-term effects; (d) the repeated DMR procedures to sustain improvement in HbA1c over a longer period of time; (e) the control of confounders, such as a potential change in dietary preferences after procedure. The latter suggestion might be supported by a previous evidence of a reduction in the desire of carbohydrates and fats consumption in patients after a gastric bypass surgery [27].

In conclusion, future research is necessary to understand the mechanism by which this procedure may impact metabolic diseases, such as T2D and non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, and to evaluate the durability of the treatment using controlled trial conditions in larger numbers of patients.

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Ethical statement

The authors declare that this manuscript is written down according to high standard of ethical regulation.

Conflict of interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Giancarlo Condello: Methodology, Writing - original draft, Writing - review & editing. **Chih-Yen Chen:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.orcp.2020.09.001.

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