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REVIEW

Metabolic Effects of Endoscopic Duodenal Mucosal Resurfacing: a Systematic Review and Meta-analysis

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Abstract

Duodenal mucosal resurfacing (DMR) is an innovative endoscopic bariatric and metabolic therapy (EBMT) emerging in recent years. It uses the duodenum to achieve better glycemic and weight control. This study aimed to evaluate in a critical and systematic way the metabolic effects of this procedure. Electronic searches were performed evaluating the DMR procedure based on predefined inclusion and exclusion criteria. Changes in measured outcomes were evaluated using random-effects models by computing weighted mean differences (MD) and corresponding 95% CIs between pre-and post-procedure metabolic characteristics. Four studies were selected for qualitative and quantitative analysis. DMR demonstrated beneficial glycemic and hepatic metabolic effects among patients with non-insulin dependent type 2 diabetes (T2D) at 3 and 6 months post-procedure.

Keywords Duodenal mucosal resurfacing · DMR · Diabetes · Hydrothermal ablation · Hepatic steatosis · Systematic review

Introduction

The prevalence of obesity and concomitant metabolic dysfunction has rapidly increased within the last several decades. Worldwide, there are over 650 million adults with obesity, with approximately 350 million individuals living with obesity-associated comorbid conditions like type 2 diabetes mellitus (T2D) [1–4]. Importantly, both obesity and the development of insulin resistant, while these may occur independently, share a similar pathogenesis including underlying mechanisms such as complex neurohomonal and metabolic responses [5]. While these two entities, obesity and T2D, may occur indepedently, more than half of individuals with T2D have a body mass index (BMI) > 30 kg/m^2 with previous literature demonstrating that the relative risk of T2D increases by approximately 7.5% for every kilogram of weight gained

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[6, 7]. Alongside this increase in obesity and T2D, so too as the frequency of other diagnoses such as non-alcoholic steatohepatitis (NASH) and metabolic dysfunction associated with fatty liver disease (MFALD), mainly due to the excessive consumption of diets rich in carbohydrates and fat [8, 9].

Given the shared pathophysiology and development of insulin resistance, strategies such as bariatric surgery which are designed to primary achieve weight loss, also demonstrated stark benefits in metabolic disease and insulin resistance [10–12]. These improvements and alterations in metabolic health have been extensively documented with previous and current surgical procedures, relying on the gut-brain axis as well as foregut and hindgut theories [13, 14]. Based upon these mechanisms, surgery acts to manipulate the small bowel, which plays a central role in metabolic homeostasis, especially concerning the modulation of glycemic levels [15–18].

Despite effectiveness of Roux-en-Y gastric bypass and other bariatric surgical interventions, the invasive nature and the low acceptance of surgical procedures among patients with metabolic diseases limit its applicability as a universal treatment option. Like the cardiovascular field, which has established less-invasive alternatives for open-heart surgery, such as transcatheter aortic valve replacement and stent implantation in the coronary artery, recently, minimally invasive endoscopic procedures have emerged as options for bariatric surgical interventions. These procedures are known as bariatric and metabolic endoscopic therapies (EBMTs).

Duodenal mucosal resurfacing (DMR) is a novel EBMT that utilizes a minimally invasive single-use balloon catheter and involves hydrothermal ablation of the post-papillary duodenal mucosa and mucosal healing. This therapeutic strategy aims to decrease anti-incretins' role in the proximal small bowel and serve a possible therapy for patients with poorly controlled T2D. The rationale is to provide the formation of new enterocytes and re-establish a healthy neuroendocrine axis. Based on this mechanism and action, we aimed to perform a structured systematic review and meta-analysis to evaluate this procedure's effectiveness and investigate the metabolic impact of DMR.

Material and Methods

Protocol and Registration

The study protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO) (CDR42020191800), an international database of prospectively registered systematic reviews in health and social care. Additional, this systematic review and meta-analysis was approved by the ethics committee.

Eligibility Criteria

Only studies evaluating the Revita duodenal mucosal resurfacing procedure (Fractyl Laboratories, Lexington, MA, USA) device were included. Given current limited data with an additional mucosa ablation device and to reduce heterogeneity of reporting results, studies evaluating the Diagone (Digma Medical, Peta Tikva, Israel) device were excluded. Additionally, included studies were required to be performed for patients ≥ 18 years of age, with evidence of or risk for inappropriate glycemic indexes (i.e., elevated glycated hemoglobin (HbA1C), non-insulin-dependent and insulin-dependent patients with T2D. All relevant English language articles irrespective of year of publication, type of publication, or publication status were included. Full-text manuscripts as well as abstracts were considered for inclusion in this meta-analysis. Studies with concern for duplication in the population of patients, studies with patients on concomitant pharmacological interventions in conjunction with the procedure, and those in which additional procedures were performed (i.e., ablative technique other than hydrothermal) were excluded. A study was also excluded if deemed to have insufficient data, as were review articles, editorials, and correspondence letters that did not report independent data.

Duodenal Mucosal Resurfacing Procedure

All patients included underwent DMR with the Revita procedure, a catheter-based, upper endoscopic treatment that applies superficial ablation to approximately 10 cm of the duodenal mucosa distal to the ampulla. A flexible endoscope is inserted into the proximal duodenum, followed by positioning of a deflated balloon catheter in the duodenum between the papilla and ligament of Treitz. Upon inflation of this balloon, a complete mucosal lift with saline injection is performed, then sequential ablation applied using a pump that circulates hot and cold water. This lifting and ablation process can be repeated within a single-treatment session until the desired area of duodenum resurfacing has been completed.

Measured Outcomes

The primary outcome measurement in this systematic review and meta-analysis was effectiveness of the DMR procedure, defined as improvement in metabolic health. This was further defined by change in metabolic parameters or outcomes at 3 and 6 months post-procedure, including change in HbA1C levels, fasting plasma glucose (FPG), fasting plasma insulin, homeostatic model assessment of insulin resistance (HOMA-IR), liver enzymes, weight loss in kg, or reduction on hepatic steatosis as measured by magnetic resonance imaging derived proton-density-fat-fraction (MRI-PDFF).

Research Strategy and Sources

The research strategy was designed according to the Cochrane Manual of Systematic Reviews of Interventions and the Preferred Items for Systematic Review and Meta-Analysis Reports (PRISMA) [19]. Electronic searches were performed using the Medline (PubMed), LILACS, Cochrane Library, and EMBASE databases, from inception to August 31, 2020. In attempt to reduce publication bias, a gray literature search, defined as literature that is not formally published in sources such as books or journal articles, as also performed to complete the PRISMA search criteria. The terms used for the protocolized literature search were "Endoscopic Mucosal Resection" OR "Resurfacing" OR "DMR" OR "Hydrothermal" AND "Diabetes." The search was initiated by two researchers independently, reviewing the title and summary of each article. Any disagreements were resolved through consultation with a third researcher. Items or studies considered relevant were selected for full-text review.

Quality Evaluation

The risk of bias in non-randomized studies was assessed using the risk of bias tool to evaluate non-randomized intervention studies (ROBINS-I) [20]. For randomized controlled trials, the JADAD score was used to evaluate study quality [21]. The quality of the evidence was assessed using the objective criteria of GRADE (Evaluation, Development, and Evaluation of Classification Recommendations) for each outcome using the GRADEpro—Guideline Development Tool software [22].

Data Analyses

This systematic review was performed by means of proportion meta-analysis. Measured outcomes comparing pre- and post-procedure characteristics were also obtained. From this, weighted mean difference was calculated and transformed to the natural logarithm before pooling, and the variance was calculated. Random-effects models were applied to pre- and post-procedure data to determine effect size and corresponding 95% confidence intervals (CIs). For continuous outcomes, inverse variance test was used, and for dichotomous outcomes, the Mantel-Haenszel test was used. Heterogeneity was assessed for the individual meta-analyses using the chi squared test and the I^2 statistic [23]. Significant heterogeneity was defined as $P < 0.05$ using the Cochran Q test or $I^2 > 50\%$, with values > 50% indicating substantial heterogeneity. Further quantification of heterogeneity was categorized based upon I^2 with values of 25%, 50%, and 75% indicating low, moderate, and high amounts of heterogeneity, respectively. We used tabular and graphical displays in Review Manager 5 (RevMan 5.4). Statistical significance for the differences between groups included the 95% CIs of the two pooled proportions considered, and the differences of proportions and 95% CIs were calculated. All calculated p values were 2-sided, and p values < 0.05 were considered statistically significant.

Results

Literature Search Results

The initial literature search identified 619 records in all databases with 12 studies selected for full-text evaluation. Eight articles were excluded, due to duplication of patient data (i.e., overlapping patient populations) [24–28], application of some pharmacological intervention in conjunction with the procedure [29], and application of a technique other than hydrothermal ablation [30]. Therefore, 4 studies [31–34] were selected for qualitative and quantitative analysis. The selection process is summarized in the PRISMA flow diagram (Fig. 1).

Study Characteristics

Four studies [31–34] were included for the meta-analysis: an open; non-randomized single-center study [31]; 2 international multi-center; prospective studies [32, 33]; and lastly, a randomized, prospective, double-blind, multi-center, international study [34]. Based upon inclusion of these 4 studies, a total of 127 patients were analyzed.

Risk of Bias in Studies

The ROBINS-I and JADAD scoring system were used to evaluate risk of bias for observational and randomized studies, respectively. We identified a low risk of bias in the three non-randomized studies (supplementary table 1), and a strong methodological quality in the randomized study (supplementary table 2). The objective criteria of GRADE analysis to evaluate the quality of evidence identified high certainty for most of the outcomes (supplementary table 3).

Change in HbA1C

HbA1C After 3 Months

Two studies [31, 32] reported data regarding changes in HbA1C after 3 months of performing DMR. Based upon these 2 studies, a total of 52 patients were evaluated, demonstrating a significant drop in HbA1C (1.72%) values. [MD, 1.72 (95% CI, 0.25 to 3.19); $I^2 = 95\%$; $P = 0.020$] (Fig. 2). GRADE analysis revealed a low certainty evidence with concern for publication bias.

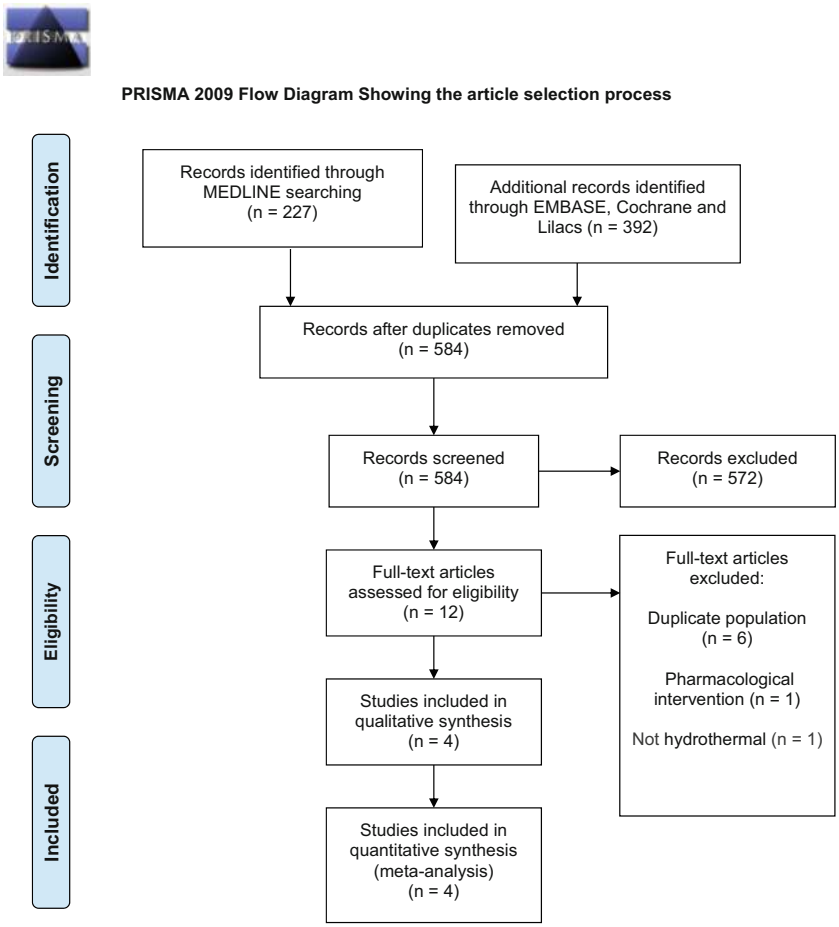

Fig. 1 Flow diagram of the study selection

HbA1C After 6 Months

Three studies [31, 33, 34] reported changes in HbA1C 6 months after hydrothermal ablation with DMR. Of the 103 patients analyzed, there was a drop in this parameter value (0.94%) after the intervention. [MD, 0.94 (95% CI, 0.68 to 1.21); $I^2 = 0\%$; $P < 0.001$] (Fig. 2). GRADE analysis revealed high certainty of evidence with low concern for publication bias.

Fasting Plasma Glucose

Two studies [33, 34] have data regarding FPG after 6 months of the procedure, including a total of 75 patients. There was a significant reduction in FPG during the analyzed period [MD, 15.84 (95% CI, 2.91 to 28.77); $I^2 = 0\%$; $P = 0.020$] (Fig. 3). GRADE analysis revealed high certainty of evidence.

Weight Loss

Weight After 3 Months

Two of the four studies [31, 32] reported information on the impact on weight, in kg, after 3 months of the intervention. With 52 patients analyzed, there was a mean 3.1 kg weight reduction during this period. [MD, 3.10 (95% CI, 2.01 to 4.18); $I^2 = 0\%$; $P < 0.001$] (Fig. 4). GRADE analysis revealed high certainty of evidence.

Weight After 6 Months

Three studies [31, 33, 34] reported changes in weight 6 months post-procedure for total of 103 patients. However, at 6 months after the DMR procedure, there was no significant change in weight [MD, 1.84 (95% CI, −2.09 to 5.78); $I^2 = 0\%$; $P = 0.360$] (Fig. 4). GRADE analysis revealed moderate certainty of evidence.

Alanine Aminotransferase

ALT After 3 Months

Two studies [31, 32] documented data regarding changes in ALT (U/L) levels after 3 months, finding there was a significant reduction in this parameter. [MD, 10.48 (95% CI, 8.75 to 12.22); $I^2 = 0\%$; $P < 0.001$] (Fig. 5). GRADE analysis revealed high certainty of evidence.

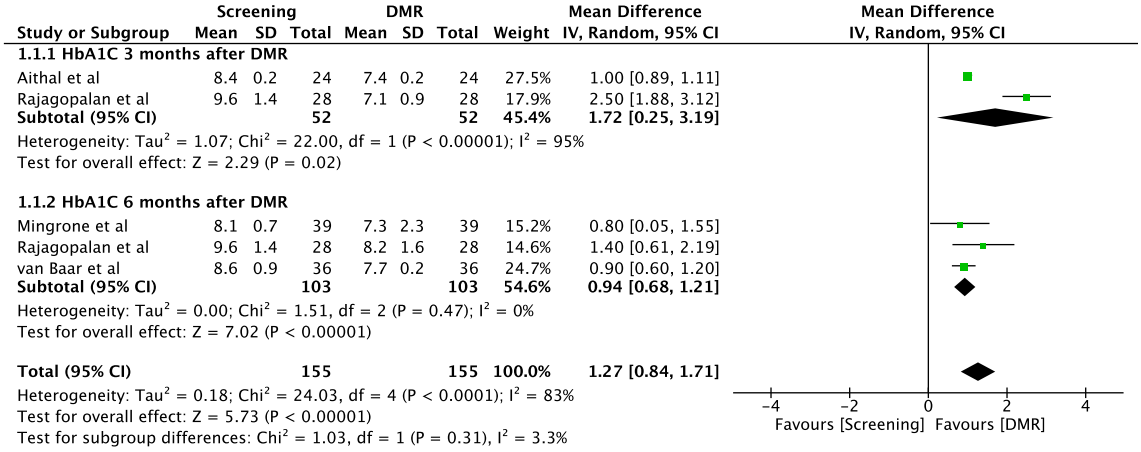

Fig. 2 Glycated hemoglobin (HbA1C) 3 and 6 months after duodenal mucosal resurfacing (DMR)

ALT After 6 Months

Two of the four studies [31, 33], with 64 patients, reported data on ALT changes after 6 months. The improvement at 6 months post-procedure wa also significant [MD, 10.82 (95% CI, 4.80 to 16.84); $I^2 = 50\%$; $P < 0.001$] (Fig. 5). GRADE analysis revealed moderate certainty of evidence.

Hepatic Steatosis

Two authors [32, 34] evaluated the effects on the liver fat, using MRI-PDFF, after performing DMR 3 months prior. Based on the 50 patients analyzed, there was a significant decrease in the hepatic steatosis post-DMR [MD, 6.59 (95% CI, 5.05 to 8.12); $I^2 = 18\%$; $P < 0.001$] (Fig. 6). GRADE analysis revealed high certainty of evidence.

Discussion

This systematic review and meta-analysis is the first in the literature to analyze and compare the effectiveness of DMR. Based upon this study including 127 patients from 4 studies [31–34], DMR appears to be an effective procedure to improve glycemic control and decrease hepatic steatosis. Despite a small number of peer-reviewed studies, and relatively short follow-up period of reporting results and assessing change, we found that this innovative therapeutic strategy has advantageous effects in liver and glycemic parameters.

In this meta-analysis, there were significant changes in glycemic control at 3 and 6 months, post-DMR (HbA1C decrease of 1.72% and 0.94%, respectively). Fasting plasma glucose was, not surprisingly, also improved. Despite patients undergoing a single, one-time hydrothermal ablation session, these results suggest the response is durable, with lasting effects up to at least 6 months. Additionally, one study by van Baar et al. [33] in 2020, reported similar results up to a follow-up period of 12 months. Importantly, these results become even more powerful considering most oral anti-diabetic medications achieve a decrease in HbA1C of 0.5% to 1.25% [35]. Simply put, this one-time ablation session may be equivalent to many current pharmacologic treatments over a 6-month periods, without the need to ensure medication adherence. Furthermore, it is possible, an additive or synergistic effect may be achieved for patients combining DMR with anti-diabetic drugs.

With regard to EBMTs, small bowel-specific therapies are designed, unlike their gastric-specific counterparts, to have a primary effect on metabolic health.

Two main theories (foregut and hindgut) involving the incretin and anti-incretin effect help to explain this metabolic and neuro-hormonal response related to obesity and its associated comorbidities. The foregut theory presumes that the duodenum has a central role in the genesis of obesity and underlying metabolic disorders, and that T2D results from an overproduction of an anti-incretin inhibitory product. Cells in the duodenal mucosa are fundamental in the balance of incretins production. The small bowel plays a primary role in energy homeostasis, where bile and pancreatic enzymes mix with

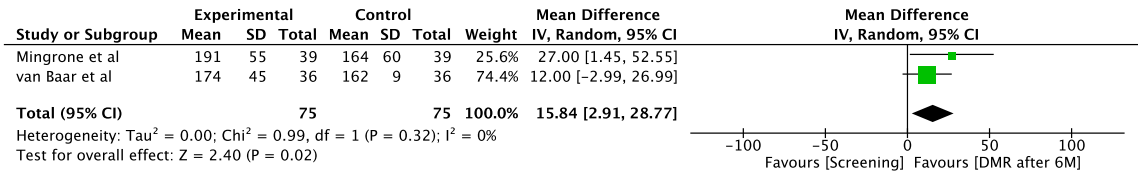

Fig. 3 Fasting plasma glucose (FPG) after 6 months of duodenal mucosal resurfacing (DMR)

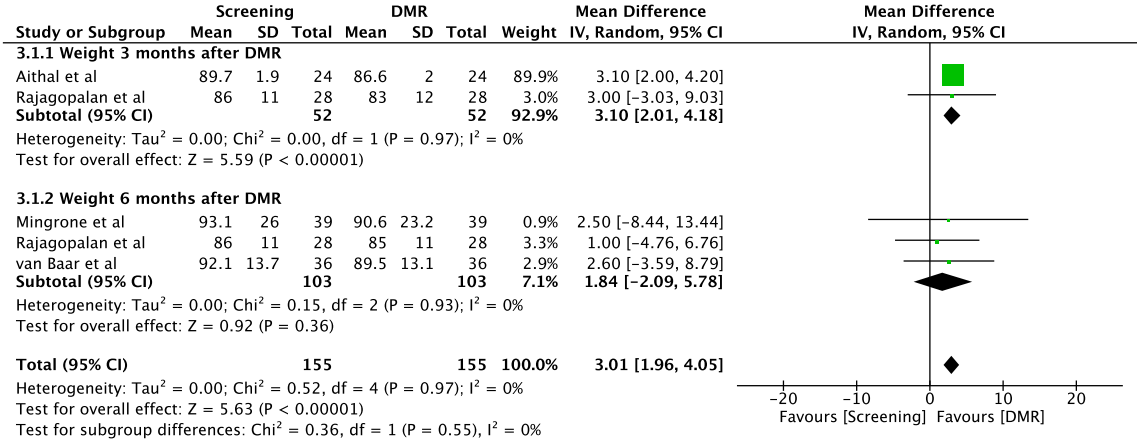

Fig. 4 Weight after 3 and 6 months of duodenal mucosal resurfacing (DMR)

macronutrients and begin the process of digestion—involving intestinal satiety peptides such as cholecystokinin (CCK), anorexigenic peptides like peptide YY (PYY) and oxyntomodulin (OXM), intestinal incretin peptides (glucagon-like peptide-1 [GLP-1] and gastric inhibitory peptide [GIP]), adipocytokine leptin, bile salts, and intestinal lipid metabolites (long-chain fatty acids) to regulate energy homeostasis [36].

GLP-1 is produced in the enteroendocrine L-cells in the intestinal mucosa, mainly in the ileum and colon while GIP is produced by enteroendocrine K cells in the duodenal mucosa and upper part of the jejunum. Both incretins are secreted in response to increased intestinal glucose concentration and stimulate beta cells in the pancreas to secrete insulin (incretin effect). GIP has a stronger effect compared to GLP-1 in the stimulation of beta cells. Due to the incretin effect, healthy people are able to maintain their glucose plasma concentration quite constant [37]**.** GLP-1 and GIP have other effects as well, involving the central nervous system, adipose cells, and bones. GLP-1 reduces appetite and food intake, increases satiety, and retards gastric emptying. GIP is thought to have a role in triglyceride storage in adipose tissue, primarily based on the results of animal studies. GIP receptor signaling in mice seems to limit bone resorption and to promote bone formation [16, 38].

This is critical to understand as the foregut effect theorizes that exclusion or ablation of the duodenum from absorption of nutrients and chyme may prevent the secretion of negative signals (i.e., anti-incretin) and improve insulin resistance and glucose regulation [13, 14]. Additionally, direct delivery of nutrients to the distal small bowel act upon the hindgut theory to stimulate the secretion of incretin substances, increase insulin production, and improve glucose homeostasis. Ultimately, these results reinforce the fundamental role that the small bowel, and duodenum specifically, plays in glycemic regulation.

In terms of weight loss, DMR did not produce any significant change in weight at 6 months post-procedure. Despite a small, albeit significant, decrease in weight at 3 months, the difference in weight at 6 months, was not statistically significant. While an individual's dietary changes before and after the procedure may explain such results, this is likely based upon the mechanism of action, suggesting that focused ablation on the proximal intestine may not sufficient for long-term weight control. However, given the significant improvement in HbA1C, demonstrated in this pooled analysis, future studies should evaluate this therapy as an adjunctive metabolic treatment to other endoscopic weight loss modalities,

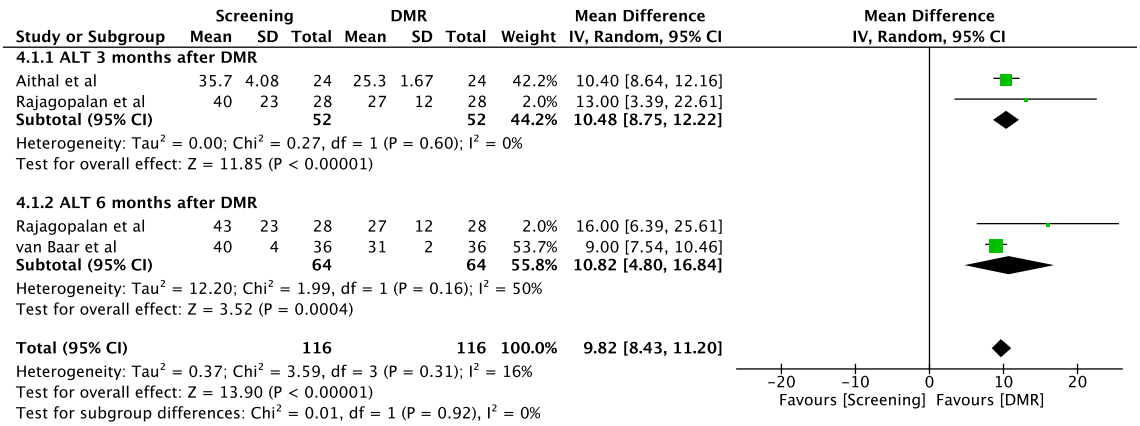

Fig. 5 Alanine aminotransferase (ALT) 3 and 6 months after duodenal mucosal resurfacing (DMR)

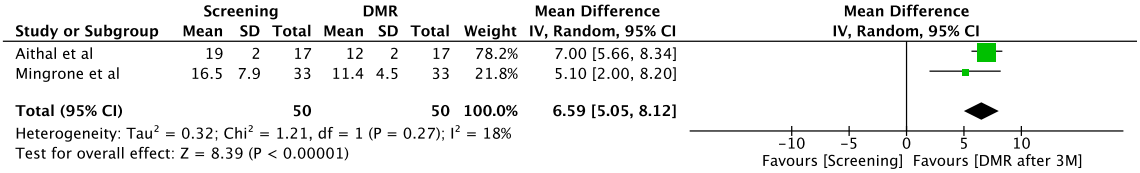

Fig. 6 Liver fat 3 months after duodenal mucosal resurfacing (DMR)

especially for poorly controlled patients T2D who may benefit from a reduction in weight and better glycemic control.

Weight-independent effects in liver chemistries and hepatic steatosis were evidence with a single ablation. ALT levels were noted to significantly improve at both 3 and 6 months post-procedure. Given the shared pathophysiology of insulin resistance, elevated levels of this enzyme may reflect the existence of some hepatocellular aggression and can be considered, together with other laboratory parameters, an indirect marker of NALFD and NASH [39]. There was a reduction of 10.48 U/L after 3 months which persisted at 6 months.

Additionally, evaluation of hepatic steatosis via MRI-PDFF revealed a 6.59% reduction in liver fat. Among the methods to quantifying liver fat, MRI-PDFF is increasingly recognized as the preferred modality. MRI-PDFF allows for accurate and reproducible quantitative assessment. Due to time effectiveness, precision and, easy post-processing, this imaging modality has become the imaging method of choice for primary diagnosis, disease monitoring, and clinical trial reporting [40]. However, while a 10% total body weight loss has been shown to reduce hepatic fibrosis, there is still no qualified consensus on the percentage of liver fat reduction needed to be considered clinically significant [41].

This systematic review and meta-analysis is not without limitations. Most importantly, there remain a limited number of studies included in this meta-analysis. However, given the novelty of the duodenal mucosal resurfacing procedure, early pooled results and data are paramount to ensure further investment and study among individuals. At this time, there are 3 registered trials enrolling patients [42–44]. These studies will likely provide more information to corroborate the therapeutic indication for DMR and evaluate for alterations in glycemic control, metabolic health, as well as underlying liver disease. Nevertheless, despite these forthcoming trials, longer term follow-up studies are needed. Furthermore, it is important to note that every study included in this analysis was financed by Fractyl Laboratories, the developer of the Revita device. While we have no conflicts of interests to report, it is possible these finding may be prone to selection or publication bias as result. Lastly, an additional limitation to consider is the lack of safety evaluated in this meta-analysis.While this is critically important for new or novel devices and techniques, a previous study by our group has confirmed that DMR promotes superficial mucosal ablation of the villus tips to the crypt base and protection against deeper tissue injury [45].

Yet, despite these limitations, this study possesses several strengths. In addition to this being the first systematic review and meta-analysis to summarize DMR data, the study was associated with very little heterogeneity, suggesting similar findings despite there being few included studies. Additionally, we included several measures of effectiveness to simulate real-world clinical practice including changes in FPG, HbA1C, ALT, as well as hepatic steatosis—all relevant measures aimed to treat the underlying mechanisms of insulin resistance.

Currently, upcoming protocols and studies should evaluate the impact of this technique has on gut permeability [46], intestinal microbiome [17], and the composition of bile acids [47] . Endotoxemia occurs in several metabolic disorders and may be associated with low-grade systemic inflammation. Endotoxin is a major component of the cell wall of gram-negative bacteria and is derived from the gut and reflects enhanced intestinal permeability or major changes in gut bacterial species [46]. A previous systematic review reported a significant increase in microbial diversity and gene richness of the gut microbiota among patients after sleeve gastrectomy and Roux-en-Y gastric bypass [48]. These changes are thought to result in the improvement of metabolic health via alterations of the biosynthesis of fatty acids and carbohydrate metabolism. An increase in bile acid concentrations after metabolic surgery has been positively correlated with the improvement of glycemic control in patients with T2D [47]. To date, no data are available regarding alterations in none of these variables following endoscopic bariatric procedures. Additionally, assessment of other metabolic outcomes, such as changes in the lipid profile, thyroid studies, gut hormone levels, and/or hypo-pituitary-gonadal axis, may aid clinicians to better understanding mechanisms of EBMTs. Assessing changes in blood pressure, body fat percentage, abdominal circumference, and inflammatory markers would be of clinical interest as well.

In summary, the present study is the only one in the literature that evaluated this topic in a broad, critical, and systematic way. Based on this systematic review and meta-analysis, DMR has beneficial glycemic and hepatic metabolic effects on patients with T2D after 3 and 6 months post-procedure. Minimal weight loss was observed only in the initial 3 months after the procedure; however, this reduction did not maintain in the 6 months analyses. Therefore, the currently available data suggest that DMR may be used as an alternative

treatment for short-term glycemic control and to reduce hepatic steatosis in non-insulin-dependent patients with suboptimal control T2D.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11695-020-05170-3.

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Compliance with Ethical Standards

Conflict of Interest Dr. Moura reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work.

Ethical Statement The study was approved by the Research Ethics Committee of the University of São Paulo School of Medicine *Hospital das Clínicas*.

Informed Consent Statement For this type of study, formal consent is not required.

References

1. World Health Organization. Obesity and Overweigh. 2020 [cited 2020 Sep 12]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
2. World Health Organization. Diabetes. 2020 [cited 2020 Dec 9]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes.
3. Kotinda APST, de Moura DTH, Ribeiro IB, et al. Efficacy of intragastric balloons for weight loss in overweight and obese adults: a systematic review and meta-analysis of randomized controlled trials. Obes Surg. 2020;30:2743–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32300945
4. de Miranda Neto AA, de Moura DTH, Ribeiro IB, et al. Efficacy and safety of endoscopic sleeve gastroplasty at mid term in the management of overweight and obese patients: a systematic review and meta-analysis. Obes Surg. 2020;30:1971–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32107706
5. Eckel RH, Kahn SE, Ferrannini E, et al. Obesity and type 2 diabetes: what can be unified and what needs to be individualized? J Clin Endocrinol Metab. 2011;96:1654–63. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21602457
6. Hartemink N, Boshuizen HC, Nagelkerke NJD, et al. Combining risk estimates from observational studies with different exposure cutpoints: a meta-analysis on body mass index and diabetes type 2. Am J Epidemiol. 2006;163:1042–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16611666
7. Schienkiewitz A, Schulze MB, Hoffmann K, et al. Body mass index history and risk of type 2 diabetes: results from the European Prospective Investigation into Cancer and Nutrition (EPIC)–Potsdam Study1–3. Am J Clin Nutr. 2006;84:427–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16895894
8. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73:202–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32278004
9. Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27:1047–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15111519
10. Schauer PR, Burguera B, Ikramuddin S, et al. Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Trans Meet Am Surg Assoc. 2003;121:160–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14530719
11. Aldoheyan T, Hassanain M, Al-Mulhim A, et al. The effects of bariatric surgeries on nonalcoholic fatty liver disease. Surg Endosc. 2017;31:1142–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27405478
12. de Moura EGH, Ribeiro IB, Frazão MSV, et al. EUS-guided Intragastric injection of botulinum toxin a in the preoperative treatment of super-obese patients: a randomized clinical trial. Obes Surg. 2019;29:32–9. Available from: http://link.springer.com/10.1007/s11695-018-3470-y
13. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann Surg. 2006;244:741–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17060767
14. McCarty TR, Thompson CC. Bariatric and metabolic therapies targeting the small intestine. Tech Innov Gastrointest Endosc. 2020;22:145–53. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32905221
15. van Baar ACG, Nieuwdorp M, Holleman F, et al. The duodenum harbors a broad untapped therapeutic potential. Gastroenterology. 2018;154:773–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29428335
16. Mudaliar S, Henry RR. The incretin hormones: from scientific discovery to practical therapeutics. Diabetologia. 2012;55:1865–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22555471
17. Verdam FJ, Greve JWM, Roosta S, et al. Small intestinal alterations in severely obese hyperglycemic subjects. J Clin Endocrinol Metab. 2011;96:E379–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21084402
18. Cherrington AD, Rajagopalan H, Maggs D, et al. Hydrothermal duodenal mucosal resurfacing. Gastrointest Endosc Clin N Am. 2017;27:299–311. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28292408
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
20. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;
21. Jadad AR, Moore RAA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12. Available from: http://www.ncbi.nlm.nih.gov/pubmed/721797
22. GRADE Working Group. GRADEpro guideline development tool [software]. McMaster Univ. 2015.
23. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ [Internet]. 2003;327:557–60.

Available from: http://www.bmj.com/cgi/doi/10.1136/bmj.327.7414.557
24. Magee C, Everson M, Mok J, et al. PTH-040 Endoscopic duodenal mucosal resurfacing in type 2 diabetes – a single centre experience. Endoscopy. BMJ Publishing Group Ltd and British Society of Gastroenterology; 2018. p. A32.2-A32. Available from: http://gut.bmj.com/lookup/doi/10.1136/gutjnl-2018-BSGAbstracts.61
25. van Baar ACG, Beuers U, Wong K, et al. Endoscopic duodenal mucosal resurfacing improves glycaemic and hepatic indices in type 2 diabetes: 6-month multicentre results. JHEP Reports. 2019;1:429–37. Available from:http://www.ncbi.nlm.nih.gov/pubmed/32039394
26. van Baar ACG, Nieuwdorp M, Holleman F, et al. Single duodenal mucosal resurfacing elicits improvements in glycaemic and hepatic parameters in type 2 diabetes mellitus: Complete 1 year results from the first prospective multicenter study. United Eur Gastroenterol J. 2018;A135–747. Available from: http://journals.sagepub.com/doi/10.1177/2050640618792819
27. Neto MG, Rajagopalan H, Becerra P, et al. 829 Endoscopic duodenal mucosal resurfacing improves glycemic and hepatic parameters in patients with type 2 diabetes: data from a first-in-human study. Gastroenterology. 2016;150:S174. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0016508516306722
28. van Baar AC, Nieuwdorp M, Batterham R, et al. Improvement in hepatic transaminases over 12 months after single procedure duodenal mucosal resurfacing in type 2 diabetes patients. United Eur Gastroenterol J. 2017;A161–836. Available from: http://journals.sagepub.com/doi/10.1177/2050640617725676
29. van Baar A, Smeele P, Vriend TM, et al. Sa1962 duodenal mucosal resurfacing (DMR) combined with GLP-1 receptor agonism may eliminate insulin treatment while maintaining glycaemic control and improving overall metabolic health in type 2 diabetes. Gastrointest Endosc. 2019;89:AB260. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0016510719304845
30. Mraz M, Marcovitch I, Lankova I, et al. 1131-P: endoscopic duodenal submucosal laser ablation for the treatment of type 2 diabetes mellitus: results of first-in-human pilot study. Diabetes. 2019;68:1131-P. Available from: http://diabetes.diabetesjournals.org/lookup/doi/10.2337/db19-1131-P
31. 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;39:2254–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27519448
32. Aithal G, Sakai N, Chouhan M, et al. PS-112-endoscopic duodenal mucosal resurfacing improves hepatic fat fraction, glycemic and lipid profiles in type 2 diabetes. J Hepatol. 2019;70:e70–1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0618827819301240
33. van Baar ACG, Holleman F, Crenier L, et al. Endoscopic duodenal mucosal resurfacing for the treatment of type 2 diabetes mellitus: one year results from the first international, open-label, prospective, multicentre study. Gut. 2020;69:295–303. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31331994
34. Mingrone G, Hopkins D, Aithal G, et al. 121-LB: durable glycemic improvements after duodenal mucosal resurfacing (DMR) in patients with type 2 diabetes (T2D): 48-week results from the REVITA-2 European cohort. Diabetes. 2020;121–LB. Available from: http://diabetes.diabetesjournals.org/lookup/doi/10.2337/db20-121-LB
35. Sherifali D, Nerenberg K, Pullenayegum E, et al. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. Diabetes Care. 2010;33:1859–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20484130
36. Buhmann H, le Roux CW, Bueter M. The gut–brain axis in obesity. Best Pract Res Clin Gastroenterol. 2014;28:559–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25194175
37. van Olst N, Meiring S, de Brauw M, et al. Small intestinal physiology relevant to bariatric and metabolic endoscopic therapies: Incretins, bile acid signaling, and gut microbiome. Tech Innov Gastrointest Endosc [Internet]. 2020;22:109–19. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2590030720300878
38. Nauck MA, Meier JJ. Incretin hormones: their role in health and disease. Diabetes, Obes Metab. 2018;20:5–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29364588
39. Vilar-Gomez E, Chalasani N. Non-invasive assessment of non-alcoholic fatty liver disease: clinical prediction rules and blood-based biomarkers. J Hepatol. 2018;68:305–15. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29154965
40. Starekova J, Reeder SB. Liver fat quantification: where do we stand? Abdom Radiol. 2020;45:3386–99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/33025153
41. Caussy C, Reeder SB, Sirlin CB, et al. Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology. 2018;68:763–72. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29356032
42. Safety & effectiveness of duodenal mucosal resurfacing (DMR) using the Revita™ system in treatment of type 2 Diabetes. [cited 2020 Dec 9]. Available from: https://clinicaltrials.gov/ct2/show/NCT03653091
43. Evaluation of the Efficacy and Safety of Duodenal Mucosal Resurfacing Using the Revita™ System in Subjects With Type 2 Diabetes on Insulin Therapy (REVITA-T2Di). [cited 2020 Dec 9]. Available from: https://clinicaltrials.gov/ct2/show/NCT04419779
44. Effect of DMR in the Treatment of NASH (DMR_NASH_001). [cited 2020 Dec 9]. Available from: https://clinicaltrials.gov/ct2/show/NCT03536650
45. de Moura EGH, Ponte-Neto AM, Tsakmaki A, et al. Histologic assessment of the intestinal wall following duodenal mucosal resurfacing (DMR): a new procedure for the treatment of insulin-resistant metabolic disease. Endosc Int Open. 2019;7:E685–90. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31098390
46. Pendyala S, Walker JM, Holt PR. A high-fat diet is associated with endotoxemia that originates from the gut. Gastroenterology. 2012;142:1100-1101.e2. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22326433
47. Gerhard GS, Styer AM, Wood GC, et al. A role for fibroblast growth factor 19 and bile acids in diabetes remission after Roux-en-Y gastric bypass. Diabetes Care. 2013;36:1859–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23801799
48. Davies NK, O'Sullivan JM, Plank LD, et al. Altered gut microbiome after bariatric surgery and its association with metabolic benefits: a systematic review. Surg Obes Relat Dis. 2019;15:656–65. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30824335