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1 **Endoscopic duodenal mucosa ablation: the future of diabetes**
2 **treatment?**

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9
10 **KEY WORDS:** duodenal mucosal resurfacing, recellularization via electroporation therapy,
11 ReCET

12
13 **Abstract**
14

15 Duodenal mucosa ablation (DMA) is a novel approach to treat diabetes, consisting of endoscopic
16 ablation of dysfunctional diabetic duodenal mucosa, which, following the healing response, is
17 replaced by normally functioning mucosa. Two techniques, duodenal mucosal resurfacing (DMR)
18 and recellularization via electroporation therapy (ReCET), recently showed promise in type 2
19 diabetes(T2DM) patients.

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26 **The unmet needs of type 2 diabetes**

27 Type 2 diabetes mellitus (T2DM) is a significant health concern throughout the world, with 463
28 million adults affected in 2020s and 700 million cases projected by 2045 ([IDF Diabetes Atlas:
29 Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045
30 <https://diabetesatlas.org/scientific-papers-and-posters/>). Hyperglycemia is the hallmark of diabetes,
31 and glycemic control is essential to prevent injury to the heart and blood vessels, eyes, kidneys and
32 nerves [1].

33 Currently only 50% of T2DM patients achieve and/or maintain adequate glycemic control due to
34 poor adherence to pharmacological regimens, drug-to-drug interactions, side effects, and patient
35 dissatisfaction [1]. For most of these patients, insulin therapy remains the final treatment option.
36 However, this approach does not address the key pathogenic factor of T2DM, that is insulin
37 resistance, but rather the resulting hyperinsulinemia promotes weight gain and further deteriorates
38 patient's metabolic health.

39 The newer antidiabetic drugs, including Glucagon-like peptide-1 receptor agonists (GLP-1RA) and
40 Sodium Glucose cotransporter 2 inhibitors (SGLT2i), showed robust glycemic and nonglycemic
41 benefits without inducing weight gain or hypoglycemia in clinical trials and are now recommended
42 as second-line therapies by international guidelines [1,2]. Yet, in real world 40% T2DM patients
43 quit newly prescribed second-line non-insulin medications within 1 year, with GLP-1RA
44 (discontinued in 50% patients) and SGLT2i (discontinue in 39.5% patients) being at greatest risk of
45 discontinuation [3].

46 Metabolic surgery, including techniques like Roux-en-Y gastric bypass procedure, which creates a
47 small pouch from the stomach and connects it directly to the small intestine, bypassing the
48 duodenum, showed superior efficacy in weight reduction and glycemic control compared to
49 antidiabetic drugs, including GLP-1RA [4], but is not feasible for most T2D patients due to its
50 invasiveness and side-effects.

51 Moving from efficacy data of metabolic surgery and from the easy endoscopic accessibility of the
52 duodenum, minimally invasive approaches have been recently proposed to mimic surgical duodenal
53 exclusion: these are based on endoscopic ablation of dysfunctional diabetic duodenal mucosa,
54 which subsequently undergoes a stem cell-mediated healing response and is thereby reset to
55 normally functioning mucosa (Galvao Neto MP. Duodenal Mucosal resurfacing: where do we
56 stand? SAGES 2019 annual meeting, Baltimore 3-6 April 2019. https://youtu.be/UdvXTs2_yio).
57 Two endoscopic techniques have recently advanced to clinical stage of development and showed
58 potentially disease-modifying properties in T2DM: duodenal mucosal resurfacing (DMR) and
59 duodenal recellularization via electroporation therapy (ReCET).

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61 **DMR and ReCET: technical aspects and mechanisms for metabolic** 62 **improvement**

63

64 Both DMR and ReCET procedures aim at resetting dysfunctional duodenal mucosa, which is
65 subsequently replaced by normally functioning mucosa through a healing process. The two
66 procedures require general anesthesia and last approximately 60 minutes. Patients can resume an
67 oral diet in the 24 hours after the procedures and are counseled to adhere to a puree/semisolid diet
68 for the following 10-14 days without any intended caloric restriction.

69 The improvement in glycemic parameters is appreciable several weeks after the procedures [5] and
70 involves mechanisms demonstrated in rigorous, sham-controlled studies on streptozocin-induced
71 T2D rodents [5](**Table 1**).

72 The main difference between DMR and ReCET regards the type of energy used to ablate duodenal
73 mucosa: DMR uses a single-use hydrothermal balloon catheter to perform (1) a circumferential
74 mucosal lift (via saline submucosal injection, which dissects superficial mucosa from underlying
75 muscularis and provides a barrier protecting deeper tissue layers against thermal injury) of the target
76 segment of duodenum and (2) hydrothermal mucosal ablation via a wire-guided polyethylene
77 terephthalate balloon catheter system [6].

78 The ablation length of the duodenum approximates 10 cm, and the length of the ablation segment
79 correlates with the efficacy of DMR [6]. Follow-up duodenal endoscopic and histologic
80 assessments for up to 3 months after the procedure showed that DMR effectively promotes
81 superficial mucosa ablation of the villus tips to the crypt base, followed by a re-epithelialization of
82 the treated duodenal tract that initiates within days after procedure and is complete within 6 weeks,
83 and confirmed that the submucosal lift creates a submucosal barrier protection against deeper tissue
84 injury, allowing no inflammatory reaction and negligible fibrosis in <10% of treated patients
85 **[Errore. Il segnalibro non è definito.]**

86 ReCET uses the new Generation 2 catheter ReCET system (Endogenex, Plymouth, MN, USA) to
87 elicit duodenal mucosa cell apoptosis by irreversible electroporation (IRE)[7]. IRE is a form of non-
88 thermal ablation which applies pulsed electric fields (PEF, i.e., short high-voltage electrical
89 impulses: 10–90 impulses 1000–2500 V/cm, 50–100 μ s) to cells to provoke nanoscale pores
90 formation through the cell membrane. Irreversible permeabilization of cell lipid membranes results
91 in transmembrane electrolyte transfer, osmotic swelling, cytoskeleton destabilization, and adenosine
92 triphosphate (ATP) depletion, irreparably disrupting cell homeostasis and eventually leading to cell
93 death within 24 hours of the procedure, without affecting extracellular matrix, blood vessels, and
94 nerves. The ablation length of the duodenum in Endoscopic ReCET procedure is approximately 11
95 cm (range 9-13 cm), and the dose of energy applied (either single energy or double energy)
96 positively correlated with the efficacy [8].

97 Theoretical advantages of ReCET over DMR include the avoidance of thermal energy to disrupt
98 duodenal mucosa and the precisely controlled, limited depth of ablative energy penetration, which
99 may prevent heat-generated damage to the surrounding normal tissue and incomplete ablation due
100 to adjacent blood flow.

101
102 **Efficacy and safety of DMR and ReCET in T2DM**
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104 **DMR:** After the first-in human study [6], the feasibility, safety, efficacy and durability of a single
105 procedure DMR in T2DM patients were evaluated for up to 24 months in the multicenter
106 uncontrolled REVITA-1 trial[9,10, 11] and in the randomized sham-controlled REVITA-2 study
107 [12](**Table 2**).

108 Overall, the procedure was feasible and well tolerated: the most common adverse event was
109 transient, postprocedural abdominal pain in 20% patients) due to air insufflation and/or
110 endotracheal intubation, Duodenal stenosis, the most serious complication, occurred after DMR
111 in 3 patients in the first-in human study[6], resolved after endoscopic balloon dilation, and did not
112 recur following device and procedural improvements. Notably, the high incidence (52%) of
113 periprocedural hypoglycemic events in the Brazilian cohort of the REVITA-2 study highlights the
114 need to adjust or discontinue glucose-lowering medications periprocedurally, as it was done in the
115 REVITA-1 study.

116 In all studies, substantial and durable improvement in mean HbA1c and fasting plasma glucose
117 (FPG) levels were observed despite net medication reduction, occurring in about 50% of patients[6,
118 9,-12] and a modest body weight reduction (averaging 3%), suggesting that the glycemic benefits
119 were not attributable to weight loss.

120 The REVITA-2 study indicated also that glycemic benefits of DMR were more robust in patients
121 with more pronounced hepatic insulin resistance, as signified by a FPG \geq 180 mg/dL at baseline [12],
122 suggesting this threshold might be useful to select T2DM patients who may benefits most from the
123 procedure.

124 **ReCET:** the feasibility, safety, efficacy and durability of a single ReCET procedure in T2DM
125 patients were evaluated for up to 6 months in the REGENT-1 trial [8]: 30 T2DM patients
126 underwent ReCET via either single energy or double energy application. with a technical success of
127 100% and no device/procedure-related severe adverse events. One-month follow-up endoscopy
128 showed completely healed, almost unidentifiable treated areas, with no signs of stricture, ulceration,

129 or other significant findings. The improvement in metabolic parameters was similar to that obtained
130 with DMR, with an energy dose-response relationship between the single and double dose levels.

131

132 **Efficacy and safety of DMR and ReCET added to newer antidiabetic drugs to** 133 **discontinue insulin therapy**

134 Insulin is the final therapeutic tool in poorly controlled T2DM, but promotes weight gain and
135 hypoglycemia, thereby further deteriorating a patient's metabolic health. Hence, the potential
136 synergy of duodenal mucosa ablation procedures (DMR and ReCET) plus newer antidiabetic drugs
137 to allow insulin discontinuation while achieving glycemic targets is being explored.

138 DMR was investigated in the uncontrolled "Effect of INtervention with DMR, GLP-1 and lifestyle
139 intensification -in Subjects with insulin dePendent type 2 diabetes- on Insulin Requirement and
140 mEtabolic parameters (INSPIRE) [13] and in the ongoing multicenter randomized sham-controlled
141 REVITALIZE-1 trials [14].

142 In the INSPIRE, DMR plus the GLP-1RA liraglutide allowed insulin discontinuation *and* glycemic
143 control in 69%, 56% and 53% patients at 6, 12 and 18 months, respectively, a percentage
144 significantly higher than that obtained with liraglutide alone, and with a durable ~8% weight loss
145 goals significantly better than those obtained with liraglutide alone [2].

146 The ongoing REVITALIZE-1 expanded the target population to inadequately controlled (HbA1c at
147 entry: 7.5-9.5%) T2DM patients and used DMR plus empagliflozin. Preliminary 12-month follow-
148 up data confirm clinically meaningful metabolic benefits, with all patients achieving a HbA1c \leq
149 7.0% with a 9.3% weight loss while discontinuing or reducing insulin therapy (**Table 1**).

150 The effect of ReCET plus the GLP-1RA semaglutide 1 mg/week was investigated in the
151 uncontrolled EMINENT trial [15]: at 6 months, 86% of them were off insulin, and they achieved a
152 mean 0.6% HbA1c reduction, a 19% increase in time-in-range and a 14.4% weight loss.

153 The findings of the EMINENT trial will be verified in the randomized, sham-controlled EMINENT-
154 2 trial (NCT05984238¹) which plans to enroll 32 patients with $HbA1c \leq 8.0\%$.

155 **Concluding remarks**

156 In summary, preliminary data indicate DMR and ReCET procedures are feasible and effective in
157 T2DM. However, while efficacy and safety of DMR was evaluated in randomized controlled trials
158 and for up to 24 months, ReCET was only assessed in uncontrolled trials with a maximum follow-
159 up length of 6 months, which mandates further confirmation.

160 More intriguingly, preliminary uncontrolled data would suggest the combination of endoscopic
161 duodenal mucosa ablation with SGLT2i/GLP-1RAs enables insulin discontinuation and weight
162 reduction to a greater extent than that obtained with medications alone in poorly controlled T2DM
163 patients [2]: such potential, clinically relevant synergy of a combined (endoscopy plus medication)
164 approach in difficult-to-treat T2DM patients will require further confirmation in head-to-head
165 randomized trials .

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169 **Table 1.** Mechanisms of dysfunctional duodenal mucosa in type 2 diabetes that are corrected by
 170 endoscopic duodenal mucosal ablation procedures (from ref 5).

Increased duodenal mucosal absorptive ability	
Mechanism	Biological consequence
<ul style="list-style-type: none"> ● villous cell hyperplasia → 40% increased surface area ● enhanced expression of glucose transporters GLUT2, GLUT5 and SGLT1 	<p>enhanced glucose and nutrient absorption</p>
Dysregulated enteroendocrine and incretin axis	
<ul style="list-style-type: none"> ● Glucagon-like peptide-1 (GLP-1) secretion by L cell ● ↓ gastric inhibitory peptide (GIP) secretion by K cells ● ↓ Cholecystinin (CCK) secretion by I cells 	<ul style="list-style-type: none"> ● ↑ glucagon secretion by pancreatic α-cells ● ↓ insulin secretion by pancreatic β-cells ● ↓ glucose and fat oxidation ● ↑ gastrointestinal motility, appetite, and food intake
Altered bile acid composition and Farnesoid X receptor (FXR) activity	
<ul style="list-style-type: none"> ● ↓ unconjugated bile acids (BA) ● ↓ secondary BA ● ↓ 12a-hydroxylated BA 	<ul style="list-style-type: none"> ● ↓ FXR activation → ↑ insulin resistance and inflammation ● ↑ FGF19 response
Unhealthy gut microbiota composition and function*	
<ul style="list-style-type: none"> ● ↑ Turicibacter/Blautia/ Clostridium <i>spp</i> ● ↓ Proteobacteria/ Phascolarctobacteria/ Actinomyces/ ● ↓ Micrococcus/Rothia <i>spp</i> 	<ul style="list-style-type: none"> ● ↑ endotoxin production ● ↑ energy harvest ● ↓ short-chain fatty acid (SCFA)

	production ●Altered bile acid metabolism
Altered intestinal barrier function and increased endotoxemia	
●Impaired function of tight-junction (TJ) proteins (occludin, claudin and zonulin)# ●↑ endotoxemia	●Chronic low-grade inflammation ●Insulin resistance

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172 **Abbreviations:** FGF19: Fibroblast Growth Factor 19; FXR: Farnesoid X Receptor; GLUT: glucose
173 transporters; SGLT: sodium-glucose cotransporters

174 **Footnotes** **The duodenum, jejunum, and ileum harbor trillions of bacteria, which steadily increase in*
175 *numbers from the duodenum to the colon and regulate energy harvesting, body energy homeostasis,*
176 *inflammatory and metabolic state through a variety of mechanisms*

177 *Proof-of-concept human studies showed prominent changes in T2DM gut microbiota, coupled with altered*
178 *insulin sensitivity, energy expenditure, intestinal transit time, faecal short-chain fatty acids (SCFA) and bile*
179 *acids, and inflammatory markers*

180 *Endoscopic duodenal mucosa ablation procedure reversed gut microbiota changes observed in T2DM*
181 *towards a healthy phenotype, and gut microbiota changes correlated with T2DM indicators: more*
182 *specifically, a reduction in Turicibacter strains, which alter host bile acid and lipid metabolism through*
183 *substrate-specific bile salt hydrolases and short chain and long chain fatty acid dicarboxylases and an*
184 *enrichment in Blautia, which was inversely associated with visceral fat accumulation, and*
185 *Phascolarctobacterium faecium, both major producers of short-chain fatty acids, key regulators of*
186 *intestinal barrier integrity, motility and systemic inflammation*

187 *#Tight junction (TJ) is an important junction complex between intestinal epithelial cells, mainly composed*
188 *of the transmembrane protein family (occludin and claudin) and perimembrane protein family (ZO protein),*
189 *which play a role in paracellular permeability barrier and maintaining cell polarity. An increased intestinal*
190 *permeability, chronic low-grade endotoxemia, and systemic inflammation characterizes obese and T2DM*
191 *patients.*

192 *Endoscopic Duodenal Mucosa Ablation increased duodenal barrier function and reduced systemic*
193 *endotoxemia.*

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217 **Table 2.** Human trials with duodenal mucosal ablation by duodenal mucosal resurfacing (DMR) or

218 Re-Cellularization via Electroporation Therapy(ReCET) in type 2 diabetes (T2DM) patients.

Duodenal Mucosal Resurfacing (DMR)

Study	Design Treatme	Baseline	Efficacy				Safety
			6 mo	12 mo	18 mo	24 mo	
Rajagopalan ¹²	Single centre Uncontrolled	44 T2DM Age 53 yr DM duration: 5.7 yr BMI 30.8 HbA1c 9,6% FPG 187	HbA1c: -1.2% (LS cohort, 72%: -1.4% SS cohort, 28%: -0.7%) FPG: -27 mg/dL BW:-3%				Duodenal stenosis (7%) Abdominal pain(20%)
REVITA 1	Multicenter Prospective	50 T2DM Age 56 yr DM duration: 6.1 yr BMI 41.6 HbA1c 8.6% FPG 193	HbA1c: -0.9% FPG: -37 mg/dL BW:-3%	HbA1c: -0.8% FPG: -44 mg/dL BW:-2.6%	-	HbA1c: -0.8% FPG: -35 mg/dL BW:+0.5%	
REVITA 2	Randomized multicenter Double-blind	108 T2DM age 58 DM duration 9.5 yr BMI 31 HbA1c 8.2% HbA1c 9.6% FPG 188	European cohort HbA1c:-0.6 HbA1c≤7%(%): 26%* FPG(mg/dL):-27 BW(%):-2.8*				Abdominal pain (15%) Hypoglycemia(11% in EU and 52% in Br)
			Brazilian cohort HbA1c(%):-1.85% HbA1c≤7%(%): 36% FPG(mg/dL):-65 BW(%):-4.5				

Re-Cellularization via Electroporation Therapy (ReCET)

Study	Design treatme	Baseline	Efficacy				Safety
			6 mo	12 mo	18 mo	24 mo	
		20 T2DM	HbA1c:				Feasibility

Duodenal Mucosal Resurfacing (DMR) plus GLP-1RA

INSPIRE	Single center Uncontrolled	16 T2DM age 61 DM duration 11 yr BMI 28.8 HbA1c 7.5% FPG 182 Daily insulin; 31 IU/d	69% pts off insulin with HbA1c≤7.5% FPG:-38 mg/dL BW:-8.8%	56% pts off insulin with HbA1c≤7. 5% FPG:-54 mg/dL BW:-7.9%	53% pts off insulin with HbA1c≤7. 5% FPG:-50 mg/dL BW:-8.1%		
REVITALIZE-1	Randomized multicenter Double-blind Sham-controlled	9 T2DM (420 estimated) age 60 DM duration 13 yr BMI 33 HbA1c 8.5% FPG 182 Long-acting insulin; 33 IU/d	29% pts off insulin with HbA1c≤7% 71% pts reduced insulin with HbA1c≤7% HbA1c: -1.5% FPG:-82 mg/dL BW:-9.3%	22% pts off insulin with HbA1c≤7 % 44% pts reduced insulin with HbA1c≤7 % HbA1c: - 1.6% FPG:-77 mg/dL BW:-9.3%			

Re-Cellularization via Electroporation Therapy (ReCET) plus empagliflozin

EMINENT	Single arm single center	14 T2DM age 62 DM duration 13 yr BMI 28.8 HbA1c 7.2% FPG:158 Daily insulin; 26 IU/d	86% patients off insulin with HbA1c≤7.5% HbA1c: -0.6% Time-in- range:+19% FPG:-36 mg/dL BW: -14.4%	86% patients off insulin with HbA1c≤7. 5% HbA1c: - 0.6% Time-in- range:+19 % FPG:-39 mg/dL BW: 14.4%			
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220 **Abbreviations:** BW: body weight, LS: long segment(>9 cm) ablation; SS: short segment(<6 cm)

221 ablation; AUC: during a mixed meal tolerance test; FPG: fasting plasma glucose; GLA: glucose-

222 lowering agents: mr-pdff. Magnetic Resonance Proton Density Fat Fraction; OAD: oral

223 antihyperglycemic drugs; ; TIR: Time-in-Range during Continuous Glucose Monitoring(CGM);

224 SU: sulfonylureas; GLP-1RA: GLP-1 Receptor agonists;

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231 **Declaration of interests:** The authors declare no competing interests.

232

233 **Author contribution**

234

235 **Giovanni Musso:** conceived the study, acquired and analyzed data, drafted the work,
236 approved the final version, agreed to be accountable for all aspects of the work

237 **Maurizio Cassader:** gave substantial contributions to the study design and data
238 acquisition, revised the work critically for important intellectual content; approved the
239 final version to be published; agreed to be accountable for all aspects of the work.

240 **Roberto Gambino:** gave substantial contributions to the study design and data
241 acquisition, revised the work critically for important intellectual content; approved the
242 final version to be published; agreed to be accountable for all aspects of the work

243

244 **Resources**

245 ¹ <https://classic.clinicaltrials.gov/ct2/show/NCT05984238>

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