



Endovascular Celiac Denervation for Glycemic Control in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Purpose: To investigate the safety and efficacy of catheter-based endovascular denervation (EDN) at the celiac artery and abdominal aorta around the celiac artery on glycemic control in patients with type 2 diabetes mellitus (T2DM).

Materials and Methods: With a novel catheter system, EDN was conducted at the celiac artery along with the abdominal aorta around the celiac artery in patients with T2DM whose glycosylated hemoglobin (HbA1c) level was $>7.5\%$. The primary outcome was HbA1c level at 6 months. Other outcomes included safety, oral glucose tolerance test, homeostasis model assessment of insulin resistance (HOMA-IR), fasting plasma glucose (FPG) level, 2-hour postprandial plasma glucose (2hPG) level, and C-peptide test.

Results: A total of 11 subjects were included for analysis. The technical success was 100%, and no severe treatment-related adverse events or major complications were observed. Both HbA1c level and HOMA-IR were significantly reduced at 6 months (9.9% vs 8.0% , $P = .005$; 13.3 vs 6.0 , $P = .016$). Decreases in FPG and 2hPG levels were observed (227.2 vs 181.8 mg/dL, $P < .001$; 322.2 vs 205.2 mg/dL, $P = .001$). The C-peptide test indicated improved β -cell function (area under the curve, 0.23 vs 0.28 pmol/mL, $P = .046$). A reduction of daily insulin injection ($P = .02$) and improvement of liver function (alanine aminotransferase, $P = .014$; γ -glutamyl transpeptidase, $P = .021$) were also observed.

Conclusions: EDN in the celiac artery and abdominal aorta around the celiac artery elicited a clinically significant improvement in glycemic control and insulin resistance in patients with T2DM, with good tolerability as demonstrated by 6-month follow-up.

ABBREVIATIONS

EDN = endovascular denervation, FPG = fasting plasma glucose, HbA1c = glycosylated hemoglobin, HOMA-IR = homeostasis model assessment of insulin resistance, IQR = interquartile range, NAFLD = nonalcoholic fatty liver disease, OGTT = oral glucose tolerance test, RDN = renal denervation, T2DM = type 2 diabetes mellitus, 2hPG = 2-hour postprandial plasma glucose

Type 2 diabetes mellitus (T2DM) has caused a huge health burden worldwide, with the global prevalence of chronic hyperglycemia or diabetes being approximately 1 in 11 among adults (1). Even in patients who are compliant, glycemic control may still be inadequate (2). Chronic elevation of activity of the

sympathetic nervous system has been identified as a factor contributing to T2DM (3). The role of catheter-based renal denervation (RDN), which had been introduced as a minimally-invasive method to treat autonomic nervous system-driven hypertension, is still the subject of considerable controversy. Renal denervation has also

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Figures E1, E2 and Appendix A can be found by accessing the online version of this article on www.jvir.org and selecting on the Supplemental Material tab.

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RESEARCH HIGHLIGHTS

- Intra-celiac and peri-celiac intra-aortic endovascular denervation (EDN) was safe and significantly improved glycosylated hemoglobin and homeostasis model assessment of insulin resistance in patients with type 2 diabetes mellitus at 6 months (9.9% vs 8.0%, $P = .005$; 13.3 vs. 6.0, $P = .016$).
- EDN contributed to a reduction of daily insulin requirement ($P = .02$) and improvement of liver function (alanine aminotransferase, $P = .014$; γ -glutamyl transpeptidase, $P = .021$).
- Peri-celiac EDN using a novel catheter system was safe in treating patients with type 2 diabetes mellitus and elicited a clinically significant improvement in glycemic control.

been proposed as a possible tool to address the sympathetic neural contribution to metabolic syndrome and T2DM, but was found to be ineffective in a small trial (4).

Anatomically, the sympathetic nerves supply the islets and liver via the splanchnic nerves, which originate from the prevertebral celiac and superior mesenteric ganglia, and directly innervate them to control hormone secretion, glucose production, and metabolism (5–7). An early study (8) showed that celiac ganglionectomy improved the glucose tolerance of rats. However, celiac ganglion blockade and neurolysis performed surgically or percutaneously in a clinical setting are less precise and controllable than in an animal model (9). Experimental evidence demonstrates that surgical or chemical sympathetic denervation of the common hepatic artery improves glucose tolerance and enhances postprandial glucose clearance in dogs and improves hepatic steatosis in mice (10,11). Catheter-based hepatic denervation was previously introduced in a porcine model for the prospective treatment of T2DM (12). Clinical research, however, has not approached catheter-based denervation of other metabolism-related organs other than the kidneys.

Therefore, a minimally invasive, catheter-based endovascular denervation (EDN) procedure, aimed at the region surrounding the celiac artery, was developed to treat T2DM using a novel 6-electrode catheter system. Rather than the renal afferent and efferent nerves, this procedure targets the postganglionic nerves that originate from the celiac and superior mesenteric ganglia. This technique has been proven to be feasible and safe in relieving cancer pain in a previous study (13), in which 2 of the 7 patients also showed serendipitous improvement in glycemic control. Herein, a first-in-human pilot clinical study of EDN in patients with T2DM was conducted, hypothesizing that this technique would improve the glycemic control of patients with T2DM. The safety, tolerability, and effectiveness of EDN from the first interim 6-month analysis on the first 11 patients is presented.

STUDY DETAILS

Study type: Prospective, non-randomized trial

Study phase: Pilot

Level of evidence: 4 (SIR-D)

MATERIALS AND METHODS

Study Design

This was an interim 6-month analysis of a first-in-human, open-label, proof-of-concept, single-arm, single center, nonrandomized study, assessing the safety and effectiveness of EDN for glycemic control in patients with T2DM. The study protocol was approved by the Ethics Committee/Institutional Review Board for Clinical Research at Zhongda Hospital Southeast University in compliance with the recommendations of the Declaration of Helsinki. All subjects gave written informed consent before the procedures for their inclusion in this study. The study is registered on [ClinicalTrials.gov](https://www.clinicaltrials.gov) (study ID NCT04086043, named “MILESTONE”). The study flowchart is shown in [Figure 1](#).

Subjects

Between September 2019 and July 2020, eligible subjects aged 18–75 years who were diagnosed with T2DM at least 5 years prior to enrollment were included in this study. Inclusion criteria included: (a) serum glycosylated hemoglobin (HbA1c) level of $>7.5\%$, (b) treatment regimen with at least 1 oral antidiabetic agent (with or without insulin injections), and (c) no changes in antidiabetic medications in the last 30 days. The exclusion criteria were: (a) type 1 diabetes mellitus, (b) aortic pathologies such as aneurysm or dissection confirmed by immediately preprocedural angiography that would preclude the EDN procedure, (c) pregnancy or planned pregnancy within 1 year, (d) orthostatic hypotension, (e) estimated glomerular filtration rate of <30 mL/min (modification of diet in renal disease formula), (f) acute or severe systemic infection, (g) cerebral apoplexy or transient ischemic attack in the past 3 months, and (h) acute coronary syndrome in the past 3 months. Eleven subjects were included in the analysis. The baseline characteristics are listed in [Table 1](#). The mean age of all subjects was 53.4 years \pm standard deviation (SD) 15.2, and 10 of them were men. At baseline, only 1 patient was not receiving insulin injections, whereas the maximum daily insulin dose among the others was 60 IU. All the 11 subjects completed the 6-month follow-up (the sample size calculation and rationale for reporting interim study outcomes after 11 patients are described in [Appendix A](#) [available online on the article’s [Supplemental Material](#) page at www.jvir.org]).

EDN Procedure

All procedures were performed by the same interventional radiologist (G.-J.T.) with more than 30 years of experience.

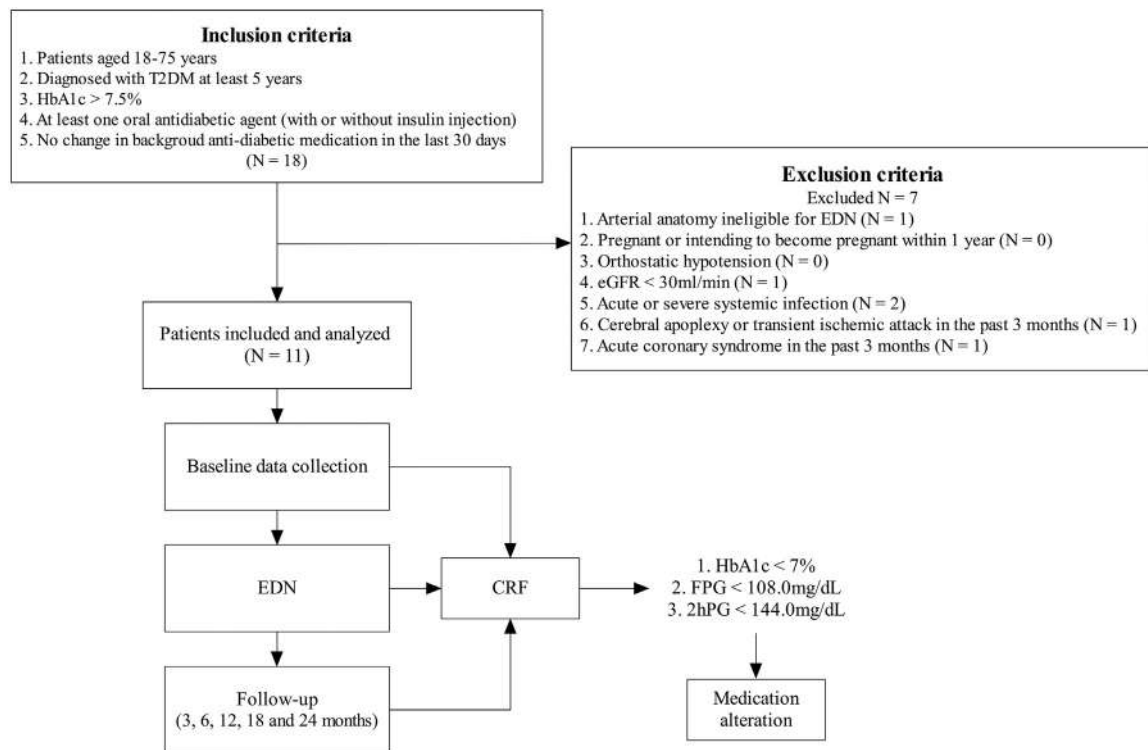


Figure 1. Clinical trial workflow. CRF = case report form; EDN = endovascular denervation; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; T2DM = type 2 diabetes mellitus; 2hPG = 2-hour postprandial plasma glucose.

Table 1. Baseline Demographics and Clinical Characteristics of the Intention-to-Treat Population

Patient characteristics	Value (n = 11)
Age, y (range)	53.4 ± 15.2 (28–72)
Sex, n (%)	
Female	1 (9.1)
Male	10 (90.9)
Weight (kg)	73.2 ± 15.3 (51–104)
BMI (kg/m ²)	25.8 ± 6.0 (19.7–40.6)
Waist circumference (cm)	91.3 ± 11.5 (78–114)
Systolic blood pressure (mm Hg)	142.8 ± 17.7 (122–176)
Diastolic blood pressure (mm Hg)	86.0 ± 12.4 (70–110)
Duration of type 2 diabetes, y (range)	15.1 ± 7.3 (5–28)
HbA1c (%)	9.9 ± 1.6 (7.5–11.4)
FPG (mg/dL)	277.2 ± 97.2 (138.6–486.0)
Oral antidiabetic agents (classes)	2.0 ± 0.6 (1–3)
Daily insulin injection requirement (IU)	27.4 ± 18.3 (0–60)

Note—Data are presented as mean ± SD or n (%), unless otherwise indicated.

BMI = body mass index; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin.

A surface grounding electrode was placed on the back of the patient and was connected to the console. Abdominal aortography was performed to identify the levels of the celiac artery and the superior mesenteric artery by means of

transfemoral access using an 8-F sheath (Cordis, Waterloo, Belgium) and a 5-F pigtail catheter (Cordis, Miami Lakes, Florida). An 8-F guiding catheter was navigated to the target artery over a 0.035-inch guide wire (ie, the celiac artery and then the abdominal aorta between the celiac artery and the superior mesenteric artery). The EDN 6-electrode radio-frequency catheter (Golden Leaf, Shanghai, China; **Fig 2**; the device description is provided in **Appendix A** and **Figs E1, E2** [available online at www.jvir.org]) was introduced through the 8-F guiding catheter (Boston Scientific, Marlborough, Massachusetts) and then fully exposed by triggering a deploy button after gently pulling back the guiding catheter (**Fig 3a–d**). Once deployed, the EDN catheter was connected to the console, and a test was performed to assess the apposition of the electrodes to the blood vessel wall, which was determined by temperature (approximately 37 °C) and impedance (<400 Ω). The subjects were under moderate analgesia with combinations of intravenous flurbiprofen and/or dezocine once EDN started. Denervation was carried out with an ablation duration of 120 seconds and temperature of 60 °C. Impedance was also monitored and limited up to 400 Ω. A total of 3 cycles of ablation were performed, including 1 cycle in the celiac artery and 2 in the peri-celiac abdominal aorta. After completion, angiography was performed to confirm any arterial changes or injury. The puncture site was closed with a vascular closure device (ProGlide; Abbott Vascular, Chicago, Illinois). By definition, technical success was achieved if 4 of 6

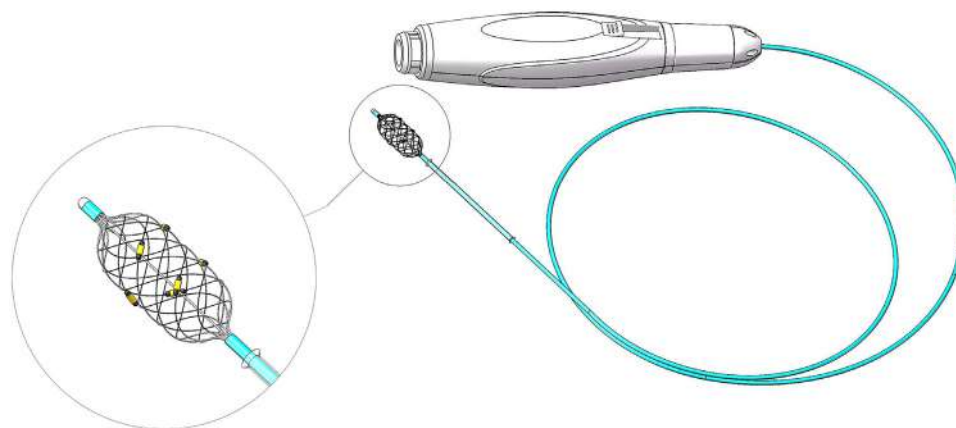


Figure 2. Illustration of radiofrequency endovascular denervation catheter (printed with permission from Golden Leaf, Shanghai, China).

electrodes reached 60 °C for 120 seconds during each ablation cycle.

Outcome Measures and Assessments

At baseline and outpatient follow-up visits, physical examination (including anthropometric measurements and systolic and diastolic blood pressures), glycemic indices (HbA1c, fasting plasma glucose [FPG], 2-hour postprandial plasma glucose [2hPG], fasting plasma insulin), and laboratory assessments (plasma norepinephrine, angiotensin II, liver biochemistry, and plasma lipids) were performed alongside recording of medication use and any adverse events. At each visit, the subjects were queried about the occurrence of self-measured hypoglycemia (glucose level < 55.8 mg/dL) and the occurrence of any other symptoms or adverse events (14). Adverse events were graded according to the Society of Interventional Radiology classification of adverse events (15). If any abnormality was found after the procedure, a follow-up computed tomography (CT) or CT angiography was performed. According to the subject's evolving glycemic profile, medication changes were made by endocrinologists dynamically if the HbA1c level reduced to <7%, if the FPG level was <108.0 mg/dL, if the 2hPG level was <144.0 mg/dL, or if the clinical risk of hypoglycemia appeared to be increased (16).

Physical examination data collected included anthropometrics, including waist circumference, body weight, height, and body mass index (measured as weight in kilograms divided by the square of height in meters). Measurements of blood pressure were performed according to the European Society of Cardiology and the European Society of Hypertension guidelines (17) using an automatic blood pressure monitor (Omron Healthcare, Bannockburn, Illinois). A food frequency questionnaire and international physical activity questionnaire were used to monitor diet and physical activity (18,19).

Comparisons were made between baseline and post-procedural metabolic parameters, lifestyle, and medication use. At baseline and during follow-ups, the C-peptide and

insulin release tests were performed by a 75-gram oral glucose tolerance test (OGTT) with plasma samples obtained at 0, 30, 60, 120, and 180 minutes after the glucose load. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: $(\text{FPG [in mIU/mL]} \times (\text{fasting insulin [in mmol/L]}) / 22.5)$ (20). Follow-up after EDN was planned for 2 years with visits scheduled at 3, 6, 12, 18, and 24 months. The primary outcome was HbA1c at 6 months, and interim data on the 11 subjects from the first 6 months of follow-up are reported. The secondary endpoints include safety, HOMA-IR, OGTT, plasma insulin, circulating catecholamines, blood pressure, liver biochemistry, and plasma lipids.

Statistical Analysis

All statistical analyses were performed using SPSS (v18.0; IBM Corp., Armonk, New York). Depending on the data distribution, continuous data were expressed as mean \pm standard deviation or median with interquartile range (IQR). The paired *t* test or Wilcoxon signed-rank test was used to analyze the difference of parameters between baseline and the 6-month follow-up. Changes in FPG, 2hPG, and systolic and diastolic blood pressures at baseline and at the 1-, 3-, and 6-month follow-ups were analyzed using 1-way repeated measures analysis of variance along with Bonferroni correction according to the normal distribution. All statistical tests were 2-sided at the α level of 0.05 unless stated otherwise.

RESULTS

Safety

Technical success was achieved in 100% of the treated subjects. No severe treatment-related adverse events such as aneurysm or dissection were observed. Immediately after EDN, 4 subjects (36.4%) showed arterial vasospasm on digital subtraction angiography, which resolved spontaneously within 20 minutes. One (9.1%) patient experienced nausea and vomiting, and 2 (18.2%) had minor abdominal distension and constipation, all of which resolved within 3

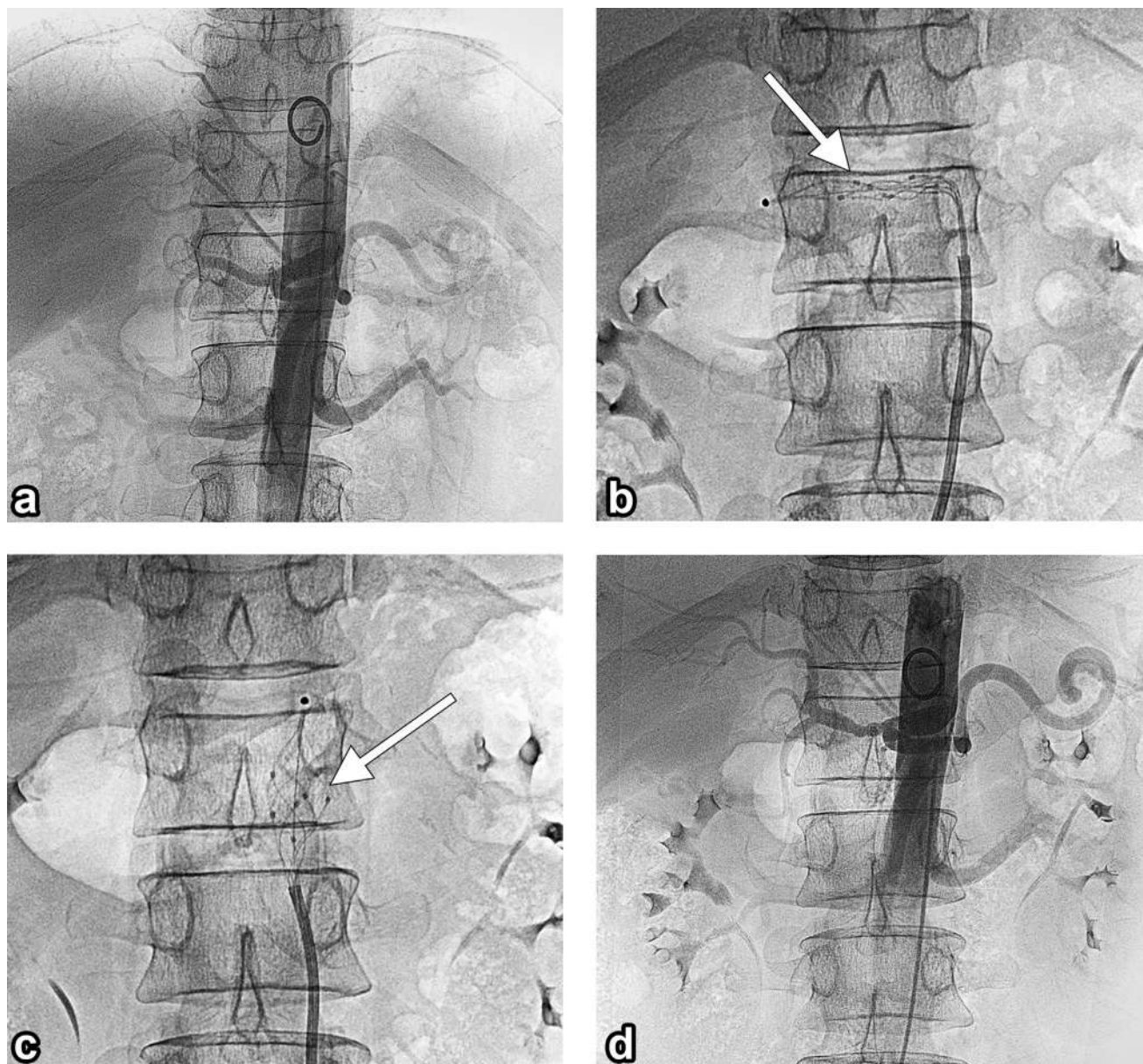


Figure 3. Fluoroscopic images during endovascular denervation. (a) Angiography of the abdominal aorta before endovascular denervation defined the location of the origins of the celiac and superior mesenteric arteries. (b) The 6-electrode catheter (arrow) was positioned in the celiac artery. (c) The 6-electrode catheter (arrow) was positioned in the abdominal aorta between the celiac artery and superior mesenteric artery. (d) Angiography of the abdominal aorta immediately after endovascular denervation showed vasospasm of the proximal common hepatic artery, which resolved within 20 minutes.

days (Table 2). All the observed adverse events were categorized as mild.

Changes in Glycemic Indices, Medications, and Lifestyle

As shown in Table 3, the mean HbA1c level decreased by 1.9% ($8.0\% \pm 2.4$ vs $9.9\% \pm 1.6$ at baseline, $P = .005$) at the 6-month follow-up. The median HOMA-IR decreased from 13.3 (IQR, 5.9–46.1) to 6.0 (IQR, 3.1–11.9) ($P = .016$) (Fig 4a, b). At 1-, 3-, and 6-month follow-up, the mean FPG levels were $183.6 \text{ mg/dL} \pm 14.4$, $181.8 \text{ mg/dL} \pm 21.6$, and $172.8 \text{ mg/dL} \pm 30.6$, respectively, compared with 277.2

Table 2. Treatment-Related Adverse Events

Adverse events	No. (%) of subjects (n = 11)
Arterial vasospasm	4 (36.4)
Nausea and vomiting	1 (9.1%)
Abdominal distension and constipation	2 (18.2%)

$\text{mg/dL} \pm 28.8$ at baseline ($P = .001$, $P < .001$, and $P < .001$, respectively), and the mean 2hPG levels were $212.4 \text{ mg/dL} \pm 54.0$, $205.2 \text{ mg/dL} \pm 72.0$, and $198.0 \text{ mg/dL} \pm 106.2$,

Table 3. Changes in Anthropometric, Medication, and Metabolic Measurements

Measurements	Baseline	6-month follow-up	P value
Glycemic indices			
HbA1c (%)	9.9 ± 1.6	8.0 ± 2.4	.005*
HOMA-IR	13.3 (5.9–46.1)	6.0 (3.1–11.9)	.016*
FPG (mg/dL)	277.2 ± 97.2	181.8 ± 32.0	<.001 [†]
2hPG (mg/dL)	322.2 ± 48.0	205.2 ± 32.0	.001 [†]
Fasting plasma insulin (nmol/L)	185 (76.4–299.2)	116.5 (79.1–217.7)	.075
AUC _{C-peptide} (pmol/mL)	0.23 (0.18–0.32)	0.28 (0.21–0.38)	.046*
AUC _{insulin} (pmol/mL)	0.47 (0.23–1.26)	0.51(0.28–1.03)	.345
Antidiabetic medication			
Oral antidiabetic agents (classes)	2.0 (2.0–2.0)	2.0 (1.0–2.0)	.059
Daily insulin injection requirement (IU) (n = 10)	24 (15.5–47)	19 (9–27.5)	.018*
Physical characteristics			
Weight (kg)	73.2 ± 15.3	70.5 ± 9.1	.263
BMI (kg/m ²)	25.8 ± 6.0	24.8 ± 3.3	.280
Waist circumference (cm)	91.3 ± 11.5	89.5 ± 9.2	.195
BP (mm Hg)			
Systolic	142.8 ± 17.7	136.9 ± 8.9	.298 [†]
Diastolic	86.0 ± 12.4	82.5 ± 7.5	.300 [†]
Sympathetic nervous system-related hormones (pg/mL)			
NE	226.0 (186.0–258.4)	205.8 (157.3–286.4)	.091
Angiotensin II	74.3 (68.5–83.7)	73.0 (68.2–77.7)	.091
Liver biochemistry (U/L)			
ALT	31.0 (25.0–46.0)	24.0 (14.0–38.0)	.014*
AST	24.0 (19.0–40.0)	21.0 (16.0–33.0)	.154
ALP	84.0 (64.0–104.0)	68.0 (65.0–91.0)	.181
GGT	47.0 (25.0–85.0)	27.0 (25.0–49.0)	.021*
Plasma lipids (mg/dL)			
TG	389.4 ± 477.9	318.6 ± 354.0	.244
TC	197.2 ± 69.6	177.9 ± 42.5	.157
HDL	54.1 ± 19.3	54.1 ± 7.7	.795
LDL	108.3 ± 23.2	92.8 ± 23.2	.080

Note—Data are presented as mean ± SD or median with interquartile range.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; AUC = area under the curve; BMI = body mass index; BP = blood pressure; FPG = fasting plasma glucose; GGT = γ -glutamyl transpeptidase; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; LDL = low-density lipoprotein; NE = norepinephrine; TC = total cholesterol; TG = triglyceride; 2hPG = 2-hour postprandial plasma glucose.

* $P < .05$.

[†] $P < .05/6 = .008$ according to Bonferroni correction.

respectively, compared with 322.2 mg/dL ± 108.0 at baseline ($P = .001$, $P = .001$, and $P = .002$, respectively) (Fig 4c, d). There was no statistically significant change in the fasting plasma insulin level. In addition, the OGTT results showed improvements in the 3-hour C-peptide release test (area under the curve_{C-peptide}, 0.23 pmol/mL [IQR, 0.18–0.32 pmol/mL] vs 0.28 pmol/mL [IQR, 0.21–0.38 pmol/mL], $P = .046$) but not in the insulin release test (Fig 5a, b).

Antidiabetic medication regimens remained stable immediately after EDN, but improved glycemic control achieved milestones that warranted changes in medications. Four of 11 (36.4%) subjects discontinued at least 1 class of oral antidiabetic agent (one patient reduced from 2 classes to

1, one from 2 to none, and two from 3 to 2). Since 1 subject was not on insulin injection at baseline, the change in insulin dose was measured in 10 subjects. The median daily total dose of insulin decreased from 24 IU (IQR, 15.5–47 IU) to 19 IU (IQR, 9–27.5 IU) at 6 months ($P = .018$), with the median dose reduction of 10 IU (IQR, 0–20.25 IU). Two subjects stopped insulin injections after EDN, with 1 of them discontinuing both insulin and oral antidiabetic agents.

One patient who developed lumbar disc herniation 1 month after EDN requiring bedrest for 3 months experienced rebound of glycemic indices (Fig 4). For the remaining 10 subjects, diet and physical activity did not show a significant change during follow-up based on the

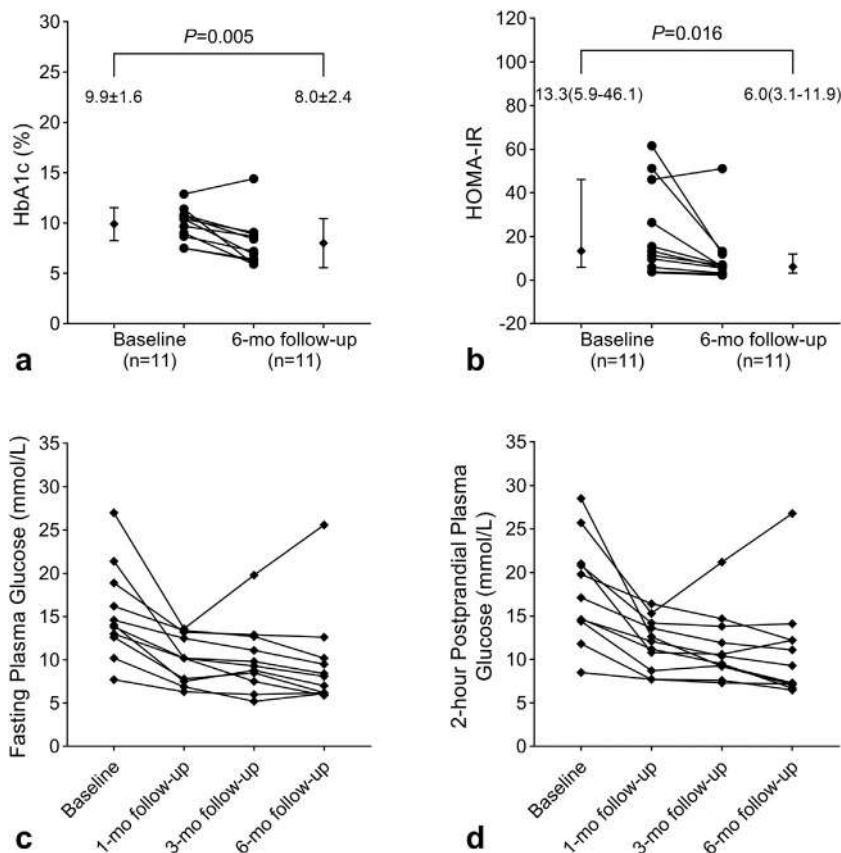


Figure 4. Changes in the glycemic indices between baseline and the 6-month follow-up. **(a)** Glycosylated hemoglobin (HbA1c). **(b)** Homeostasis model assessment of insulin resistance (HOMA-IR). **(c)** Fasting plasma glucose (FPG). **(d)** Two-hour postprandial plasma glucose (2hPG). For HbA1c data are expressed as mean \pm standard deviation; for HOMA-IR, data are expressed as median with interquartile range.

food frequency questionnaire and international physical activity questionnaire assessments.

Changes in Physical Conditions and Other Metabolic Measurements

At the 6-month follow-up, none of the patient's weight, body mass index, or waist circumference showed significant changes compared with those at baseline ($P = .263$, $P = .280$, $P = .195$, respectively), as shown in [Table 3](#). Systolic and diastolic blood pressures showed no significant differences between baseline and the 1-, 3-, and 6-month follow-up.

The plasma norepinephrine and angiotensin II levels did not significantly decrease at the 6-month follow-up. No significant differences were found in the triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein levels during the follow-up. However, improvements in liver biochemistry were observed. The median alanine aminotransferase level decreased from 31.0 U/L (IQR, 25.0–46.0 U/L) at baseline to 24.0 U/L (IQR, 14.0–38.0 U/L) at the 6-month follow-up ($P = .014$), and the median γ -glutamyl transpeptidase level decreased from 47.0 U/L (IQR, 25.0–85.0 U/L) at baseline to 27.0 U/L (IQR, 25.0–49.0 U/L) at the 6-month follow-up ($P = .021$). No

significant differences in aspartate aminotransferase or alkaline phosphatase levels were observed ([Fig 6a–d](#)).

DISCUSSION

In this interim analysis of a first-in-human study, a single-procedure EDN in the celiac artery and peri-celiac aorta elicited a statistically significant improvement in glycemic control and insulin resistance in suboptimally controlled patients with T2DM followed up at 6 months, with an acceptable safety and tolerability profile observed to date.

The safety profile from this early clinical experience of EDN is encouraging. Subjects who underwent the procedure experienced minimal adverse events. During the initial development of this technique, isolated cases of arterial vasospasm were observed immediately after the procedure and resolved spontaneously within 20 minutes without further sequelae. Consistent with a previous study ([13](#)), no additional symptoms were reported during the follow-up period of 6 months, suggesting that EDN is a safe technique. Previous human subject studies on RDN over the past decade ([21](#)) have also shown safety.

In the current study, reductions in the HbA1c, FPG, and 2hPG levels were observed at 6 months after EDN. The HOMA-IR also improved. These results of improved

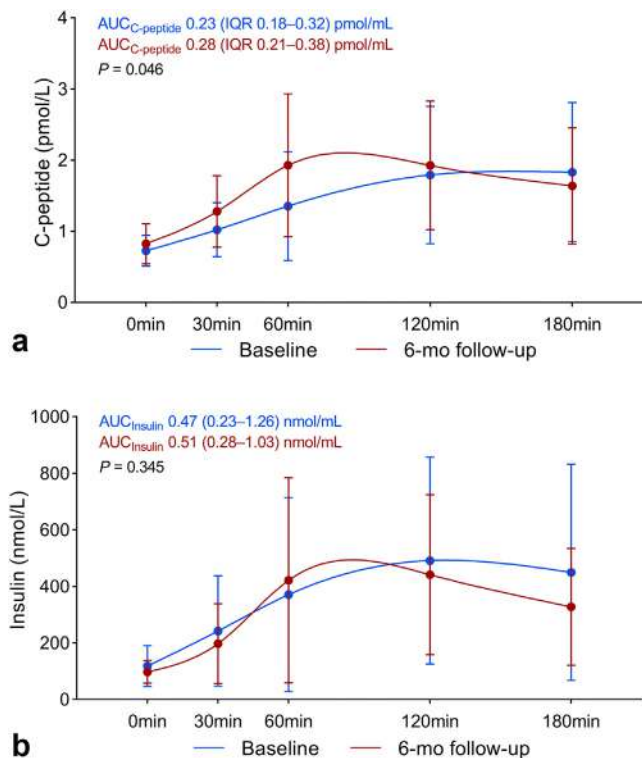


Figure 5. Changes in the C-peptide and insulin release tests between baseline and the 6-month follow-up. **(a)** C-peptide release tests. **(b)** Insulin release tests. AUC = area under the curve.

glycemic control were possibly driven by the partial resolution of insulin resistance, which was not observed in RDN-treated patients (22). Unlike the potential indirect effect of RDN on hepatic glucose metabolism, EDN may have had a direct influence on metabolism through direct interruption of the sympathetic signalling to the liver (23). In consideration of the C-peptide and insulin release tests (which need greater numbers of subjects for statistical power to confirm), EDN could lead to improvement in β -cell function, which was previously observed in RDN-treated patients (24). The sympathetic innervation of islets via the celiac ganglion suppresses insulin secretion. The effectiveness of EDN may be related in part to directly or indirectly reduced sympathetic signalling of the islets (5).

The reduction of serum alanine aminotransferase and γ -glutamyl transpeptidase observed with EDN suggests an additional modulating effect of EDN on nonalcoholic fatty liver disease (NAFLD), which is a strong co-factor for insulin resistance in T2DM (25,26). This is consistent with a recently published animal study (11) showing that manipulation of hepatic sympathetic innervation may present a novel therapeutic strategy for NAFLD.

Nerve regeneration could be an issue that may limit the efficacy and durability of EDN, as is observed in clinical celiac ganglion neurolysis to treat pain. In an animal model, focal terminal nerve regeneration was observed at the sites of ablation as early as 60 days after treatment and continued

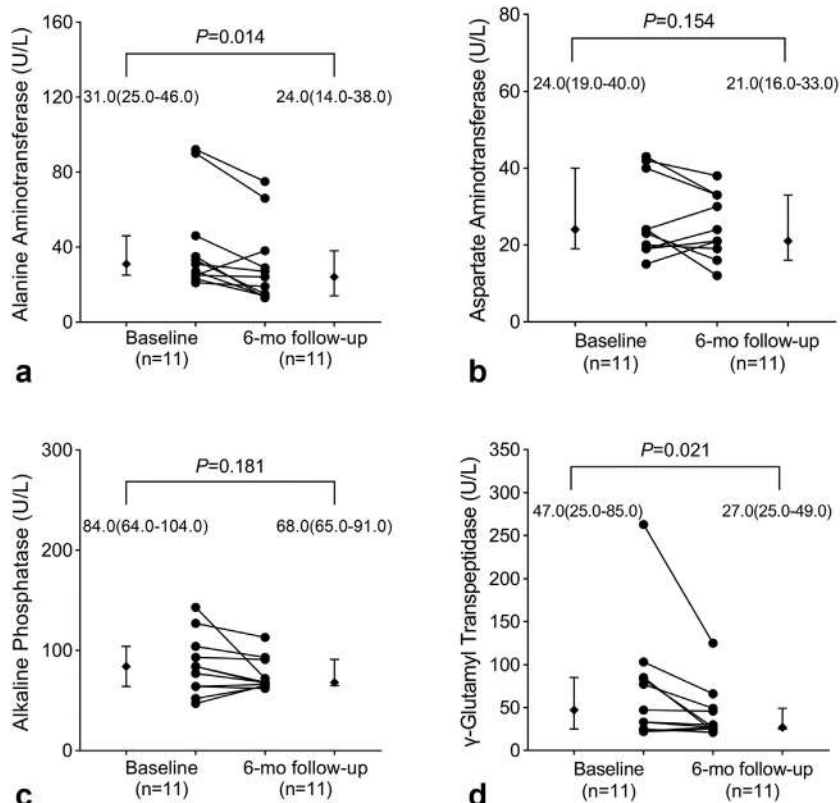


Figure 6. Changes in the serum hepatic enzyme levels between baseline and the 6-month follow-up. **(a)** Alanine aminotransferase. **(b)** Aspartate aminotransferase. **(c)** Alkaline phosphatase. **(d)** γ -Glutamyl transpeptidase. All data are expressed as median with interquartile range.

to 180 days (27). However, the disrupted architecture of the neuromatous tangles at the radiofrequency ablation sites resulted in poorly organized, non-functional regeneration (28).

The precise mechanisms underlying the effects of EDN are not well understood; changes in sympathetic activity, lipid metabolism, or hepatic glycogen metabolism are possible mechanisms of action (10,22,29). Further studies to unravel the mechanisms underlying the effect of EDN on hepatocyte function, β -cell function, adipose tissue metabolism, inflammation, and sympathetic activity are eagerly awaited (30). In addition, 1 patient developed nausea and vomiting and 2 developed minor abdominal distension and constipation, but none developed the diarrhea associated with clinical celiac ganglion blockade or neurolysis. Whether and how EDN affects gastrointestinal motility, absorption, and digestion remains unknown.

Any pilot study has implicit limitations. Small sample size and the lack of a control arm limit the measurement of the effect of EDN and its pattern of change over time. As a result, the potential for the placebo effect could not be excluded. Although no serious treatment-related adverse events were observed during the 6 month follow-up, there are currently no long-term imaging or clinical data. Moreover, despite the hyperinsulinemic-euglycemic step clamp being the criterion standard, the HOMA-IR was used instead to assess insulin sensitivity due to the unavailability of necessary equipment for this study. Additional limitations include the lack of hepatic imaging, histological data, and direct measurement of sympathetic activity, which will be addressed in future studies.

In conclusion, interim 6-month analysis of this study showed that EDN at the celiac artery and peri-celiac aorta using a novel 6-electrode catheter system elicited a clinically significant improvement in glycemic control and moderate improvement of insulin resistance in patients with T2DM. The EDN procedure appears to be safe and well tolerated. Achieving metabolic modulation through a minimally invasive interventional treatment potentially offers a new therapeutic option for patients with T2DM. Further work including a randomized controlled trial is needed to define the clinical utility of this technique, with key questions focusing on efficacy, durability, and underlying mechanisms.

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APPENDIX A

Sample Size Calculation

The mean glycosylated hemoglobin in Chinese patients with type 2 diabetes mellitus is $7.3\% \pm 1.6$, and this study estimated that glycosylated hemoglobin would decrease to 6.5% at 6 months after endovascular denervation (EDN). The between-group comparison would be powered at 95% to establish the superiority of EDN for the primary endpoint at a single-sided significance level of 0.025, and given an estimated dropout rate of approximately 20%, the sample size was approximately 30.

Rationale for Reporting Interim Study Outcomes after 11 Patients rather than 30-Patient Target Recruitment

Since this study was open-label and given that prominent improvements in the glycemic indices and the reduction of medications in the first several patients were observed, this interim analysis was designed based on the protocol (full version in Chinese) to check if this study could be discontinued early or if the sample size should be adjusted. Therefore, the protocol was modified by adding this interim analysis.

Authorization from Golden Leaf

All 6-electrode radiofrequency (RF) catheter systems were from Golden Leaf, Shanghai, China. [Figure 2](#) shows the illustration of this device, which is permitted from Golden Leaf.

Device Description

This description is also permitted from Golden Leaf.

The multielectrode artery RF ablation system comprised the multielectrode artery RF ablation catheter and the multielectrode artery RF generator.

1. The Multipole Artery RF Ablation Catheter (EDN Catheter)

The EDN catheter is a sterile, single-use device. The catheter is used in conjunction with the EDN RF generator.

The artery RF ablation catheter is composed of a central wire with a radio-opaque tip, a mesh tube connector, pre-mounted electrodes, a mesh stent, a mesh basket protective sheath, a 7-lumen tube, and a handle ([Fig E1](#)). The electrodes deliver the RF current emitted by the generator and ablate the artery at the target point. Each electrode is equipped with a thermocouple to monitor the temperature during ablation.

The electrodes in the RF segment are made of gold-gilt stainless steel with a built-in T thermocouple, the connection segment is made of Pebax (thermoplastic elastomers consist of polyamide and polyether backbone blocks), the control handle is made of acrylonitrile butadiene styrene materials, and the end of socket is connected to the RF generator with the connecting cable.

2. The Multielectrode Artery RF Generator (EDN RF Generator)

The artery RF generator consists of a main unit and related accessories. The main unit consists of a power supply circuit, a digital control circuit, power amplification, impedance detection, power detection, temperature signal linearization, and alternating current convert direct current acquisition; the related accessories include neutral electrodes, foot pedal, power cable, and data cable ([Fig E2](#)).

Each ablation catheter electrode forms a closed loop between the inner wall of the blood vessel and the circuit electrode, which releases the RF energy and increases the tissue temperature to the sympathetic nerve fibers in the artery wall, to achieve the purpose of ablation and damage of the sympathetic nerves. This ablation would result in the blocking or partially blocking of the sympathetic nerve signal transmission and reducing the excitability of the sympathetic nerve.

The RF ablation catheter has an adjustable net section, with 4 of 6 electrodes helically distributed on the surface. The diameter of the working section varies from $\Phi 2$ to $\Phi 12$ mm, the temperature measurement range is $0\text{ }^{\circ}\text{C}$ to $99\text{ }^{\circ}\text{C}$, and the temperature control range is $40\text{ }^{\circ}\text{C}$ and $99\text{ }^{\circ}\text{C}$.

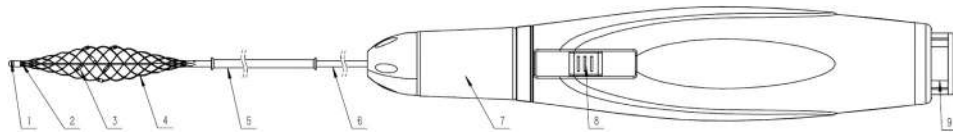


Figure E1. Structure diagram of the artery radiofrequency ablation catheter.

1, Wire with developing head; 2, mesh catheter connector; 3, electrode; 4, mesh catheter stent; 5, catheter sleeve; 6, seven-hole catheter; 7, handle shell; 8, moving part for button; 9, connector.

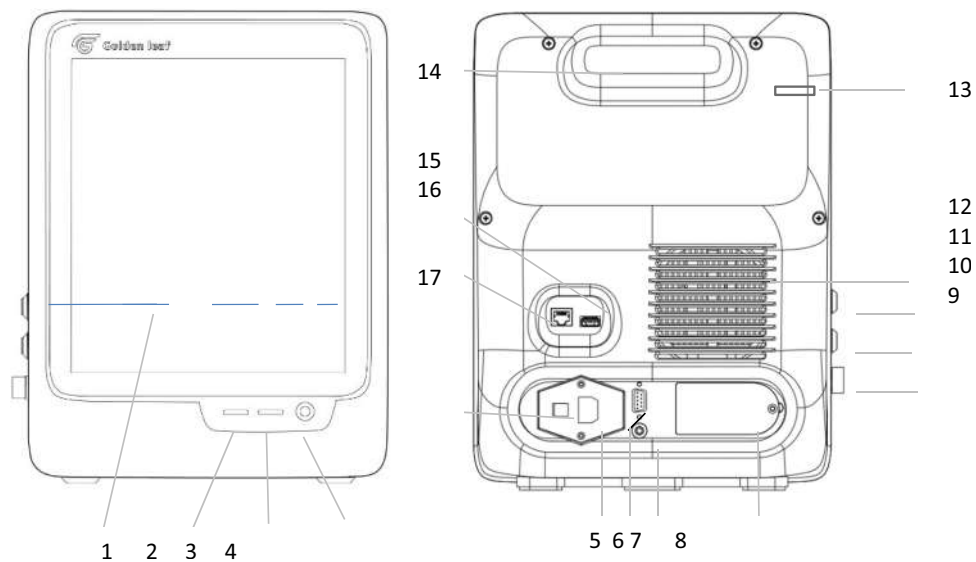


Figure E2. Structure diagram of the endovascular denervation radiofrequency generator.

1, Display screen; 2, RF working indicator; 3, alarm indicator; 4, RF start button; 5, power input socket; 6, RS232 serial port; 7, grounding screw post; 8, power circuit fuse; 9, conduit cable interface; 10, expansion interface; 11, body surface electrode interface; 12, cooling fan; 13, SD card socket; 14, handle; 15, USB foot pedal interface; 16, network cable interface; 17, power switch.