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Endoscopic duodenal mucosal resurfacing for nonalcoholic steatohepatitis (NASH): a pilot study

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ABSTRACT

Background and study aims Nonalcoholic steatohepatitis (NASH) is a leading cause of chronic liver disease worldwide with limited treatment options. Duodenal mucosal resurfacing (DMR) has been associated with improvement in glycaemic parameters and liver function tests (LFTs) in type 2 diabetes. This study aimed to assess the effect of DMR in patients with NASH.

Patients and methods This was a single-center, open-label pilot study. Patients with definite, biopsy-proven NASH (nonalcoholic fatty liver disease activity score [NAS] ≥ 4) underwent a single DMR procedure followed by a 2-week postprocedural diet, without lifestyle intervention. The primary outcome was either resolution of NASH with no worsening of fibrosis or improvement in fibrosis (≥ 1 stage) with no worsening of NASH at 12 months. Secondary outcomes were changes in key histological parameters of NASH, surrogate markers of fibrosis, LFTs, and metabolic factors at 12 months.

Results From 2017 to 2019, 14 patients underwent successful DMR, of whom 11 were included in the analysis. After 12 months, no resolution of NASH was observed, while three patients (27 %) had marginal improvement in fibrosis with no worsening of NASH. Serious adverse events related to the procedure were reported in two patients out of 14 (14 %). Neither weight loss nor improvement in NAS score, or in the other secondary outcomes, were observed at 12 months.

Conclusions In this small and heterogenous study population, we found that DMR, in the absence of lifestyle intervention, did not induce NASH resolution and marginally improved liver fibrosis at 12 months.

Introduction

Nonalcoholic fatty liver disease (NAFLD) affects up to 25 % of the worldwide population [1]. It is the leading cause of chronic liver disease in high-income countries and ranges from isolated steatosis to nonalcoholic steatohepatitis (NASH), which is characterized by hepatocyte injury and inflammation that can evolve to cirrhosis and/or hepatocellular carcinoma [2, 3]. The

main risk factors for NAFLD are obesity and type 2 diabetes mellitus (T2DM) [4]. More specifically, insulin resistance (IR) in peripheral tissues is considered to be one of the cornerstones of NASH, and this can be positively improved by weight loss [5], which is also the only validated treatment for NASH [6–9]. However, only a minority of patients can maintain and sustain long-term weight loss [6]. Despite numerous ongoing pharmaceutical trials, there is still an unmet need for a longstanding effective treatment to tackle NASH.

Duodenal mucosal resurfacing (DMR) is a recent novel endoscopic procedure involving the elective ablation of duodenal mucosa with hydrothermal energy followed by subsequent regeneration, with the aim of treating metabolic disorders [10]. The duodenal mucosa is involved in key metabolic pathways [11] but the underlying molecular mechanisms of this involvement are not fully understood. In a recent multicenter trial that assessed the impact of a single DMR procedure on patients with suboptimally controlled T2DM [12], significant improvement was reported in glycemia, IR, and liver transaminase levels 12 months after the procedure. In addition, noninvasive surrogate markers of liver fibrosis, such as the fibrosis-4 (Fib-4) score, and liver fat changes significantly improved at 6 months and 12 months, respectively, suggesting a potential effect on NAFLD/NASH [13]. Of note, these outcomes followed modest weight loss and no histopathological liver evaluation was available. Therefore, whether this procedure may also have a positive impact in NASH patients is currently unknown. In this pilot study, we aimed to evaluate the effect of DMR on histologic resolution of NASH and fibrosis improvement in patients with biopsy-confirmed NASH.

Patients and methods

Study design and patients

This pilot study was a single-center, single-arm, prospective study that evaluated the effect of a single DMR procedure in patients with biopsy-proven NASH. The study protocol was approved by the Medical Ethics Committee of CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium (P2017/302). The study was conducted in accordance with ICH Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written informed consent. Eligible patients were adults (aged ≥ 18 years) with histological evidence of definite steatohepatitis (per central expert pathologist reading of a liver biopsy obtained ≤ 6 months prior to the procedure) with an NAFLD activity score (NAS) of at least 4, including at least one point each for steatosis, lobular inflammation, and hepatocellular ballooning; and fibrosis stage, per Brunt stage, of F0 to F3. Main exclusion criteria were as follows: evidence of another cause of liver disease; history of sustained alcohol ingestion defined as daily alcohol consumption > 30 g/day for males and > 20 g/day for females; previous gastrointestinal surgery such as Billroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions; for subjects with T2DM, no current use of insulin or GLP-1 analogs; and for type 1 diabetes, probable insulin production failure defined as fasting C-peptide serum < 1 ng/mL.

The detailed study design, including inclusion and exclusion criteria, can be reviewed in Supplementary Table S1.

Study procedure

The DMR procedure was performed under general anesthesia by a single senior endoscopist with previous experience in > 20 cases and patients were hospitalized overnight per protocol. A screening gastroduodenoscopy was conducted first to ensure the absence of a contraindication to the procedure. The DMR device (Revita System; Fractyl Laboratories Inc., Lexington, Massachusetts, United States) (**Supplementary Fig. S1**) is a single-use catheter that allows submucosal injection and circumferential hydrothermal ablation of the duodenal mucosa, introduced over a guidewire under fluoroscopic visualization, alongside the endoscope, as previously described [12, 14]. Endoscopic images of the DMR procedure are presented in **Supplementary Fig. S2**. Patients were instructed to follow a 2-week diet after DMR in which clear liquids were progressively replaced by solid food. Proton pump inhibitors (40 mg once a day) were prescribed for 1 month. General dietary and lifestyle advice were provided before the DMR procedure, according to the European guidelines for the management of NAFLD [15] but no dietary counseling (provided by a dietician) was implemented during the study.

Assessments and outcome measurements

Follow-up

Follow-up visits were scheduled at 1, 3, 6, and 12 months after DMR in which clinical, anthropometric, biological, endoscopic, radiological, medication use, adverse event (AE), blood pressure, and liver biopsy (at 12 months) assessments were carried out.

Primary endpoint

The primary endpoint of this proof-of-concept-study was to assess liver histology 12 months after DMR. The primary endpoints were: 1) improvement of fibrosis (reduction of at least one stage) with no worsening of NASH (defined as no increase of hepatocellular ballooning, lobular inflammation, or steatosis); and 2) NASH resolution (defined as the overall histopathological interpretation of no fatty liver disease or fatty liver disease without steatohepatitis and an NAS of 0 or 0–1 for inflammation) with no worsening of fibrosis, as previously defined [18]. The assessment of liver biopsy was performed by an expert independent pathologist who was blinded to patient characteristics at baseline and 12 months after DMR.

Secondary endpoints

First, we evaluated several markers of liver damage. The levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined at each visit. Surrogate markers of liver fibrosis, including Fib-4 and NAFLD fibrosis score, were calculated at baseline and 6 and 12 months after DMR, as previously described [16], using the following formulas: [Age (years) × AST(IU/L)]/[plateletcount (× 109/L) × ALT(IU/L)1/2], for Fib-4, −1.675 + 0.037 − age (years) + 0.094 − BMI (kg/m^2) +

1.13 × IFG/diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio – 0.013 × platelet count (× 10^9/l) – 0.66 × albumin (g/dL), for NAFLD fibrosis score.

Magnetic resonance imaging (MRI) (clinical 1.5 Tesla scanner, Achieva, Phillips) was performed at baseline and 6 and 12 months to measure the liver proton density fat fraction (PDFF). All examinations were done by a single senior radiologist blinded to patient characteristics and colocalized regions of interest (ROIs) were used to assess longitudinal fat changes over time. One colocalized ROI was placed in each of nine liver segments and the mean of each ROI was calculated, as previously described [17].

Noninvasive liver stiffness was assessed using vibration-controlled transient elastography (VCTE) (Fibroscan, Echosens, Paris, France) for which 10 valid measurements and an interquartile range to median ratio < 30 % were considered to be reliable [16].

Second, we assessed several metabolic variables. At each follow-up visit, fasting laboratory assessments (i. e. fasting plasma glucose [FPG], glycated hemoglobin [HbA1c], insulin, and C-peptide) were performed and insulin resistance was estimated by the homeostatic model assessment index for insulin resistance (HOMA-IR), using the following formula: glucose (mg/dL) × insulin/405. A 75-g oral glucose tolerance test (OGTT) (Glucomedics, International Medical products, Belgium) was conducted at each follow-up visit, after a 12-hour overnight fast to evaluate whole-body glucose tolerance [18].

Histopathological evaluation

Liver and duodenal biopsies were fixed with 4 % formaldehyde and paraffin-embedded. Formalin-fixed paraffin sections were cut at 4 µm for liver and duodenal tissues. Liver tissue sections were stained with hematoxylin and eosin (H&E) and Masson's trichrome. A blinded expert pathologist performed histological grading of the liver tissue sections using the NASH-CRN scoring system. Formalin-fixed duodenal sections were stained with H&E. Histology images were obtained using a NanoZoomer HT Scan system (Hamamatsu Photonics, Japan).

Adverse events

Adverse events (AEs) and device-related AEs were recorded at each follow-up visit. Three months after DMR, a gastroduodenoscopy was performed to assess the eventual occurrence of any device-related AEs. Duodenal biopsies were collected before and 3 months after the DMR procedure (**Supplementary Fig. S2**).

Statistical analysis

Results for continuous variables are presented as medians (interquartile range) and categorical variables are summarized as frequencies and proportions. The Wilcoxon paired signed-rank test was used to analyze secondary endpoints. For OGTT, a linear mixed model test was used to compare plasma levels of glucose. Corrections for the multiple comparison tests made between time points. The Wilcoxon paired signed-rank test was used to compare two data points during the course of the OGTT. Data are expressed as median (IQR).

Statistical analyses were performed using R statistical analysis software (version 3.6.2, https://www.r-project.org/). All the statistical tests used were two-tailed, and $P < 0.05$ was considered statistically significant.

Results

Patients

Between 2017 and 2019, fourteen patients with biopsy-confirmed NASH were included in this study, two patients were excluded due to pregnancy and heavy alcohol consumption, respectively, and one patient was lost to follow-up (**Supplementary Fig. S3**). ▶ **Table 1** shows baseline and demographic characteristics for included patients (n = 11).

▶ **Table 1** Demographic and baseline clinical characteristics (N = 11).

Parameter	
Age, years	50 (47–60)
Male, n (%)	2 (18)
BMI kg/m^2	32.1 (28.6–34.8)
FPG, mg/dL	116 (95–141)
HbA1C (%)	6.5 (6.4–6.8)
HOMA	6.3 (4.5–8.2)
ALT, U/L	54 (39–90)
AST, U/L	44 (28–60)
CAP, dB/m	332 (304–344)
Elastometry, kPa	9.9 (8.3–14.1)
Fib-4	1.36 (1.06–1.54)
NAFLD fibrosis score	–1.14 (-1.89–0.32)
Cholesterol, mg/dL	194 (174–214)
Triglycerides, mg/dL	132 (120–158)
HDL, mg/dL	46 (42–54)
Patients with T2DM, n (%)	9 (82)
Fibrosis stage, n (%)	
▪ 0	2 (18)
▪ 1	2 (18)
▪ 2	4 (36)
▪ 3	2 (18)
▪ 4	1 (9.1)

Data are median (IQR) unless otherwise indicated. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; Fib-4, fibrosis-4 index; FPG, fasting plasma glucose; HbA1c: glycated hemoglobin; HDL, high density lipoprotein; HOMA: homeostatic model assessment of insulin resistance; NAFLD, nonalcoholic fatty liver disease fibrosis score; T2DM, type 2 diabetes mellitus.

Primary outcome

The primary endpoint of NASH resolution with no worsening of fibrosis was not met by any of the patients. The improvement in fibrosis (by at least one stage) with no worsening of NASH was met by three patients (27 %) (▶ **Table 2**). Among these three patients, two exhibited weight loss of 3 kg and 4 kg at 12 months. Based on these results, a theoretical sample size calculation was made to prove DMR efficacy in NASH patients (**Supplementary data, Appendix 1**).

Secondary outcomes

The other histological endpoints, including no worsening of fibrosis and NASH, improvement in NAS ≥ 2 with no worsening of fibrosis, improvement in fibrosis and resolution of NASH as a composite endpoint, improvement in fibrosis by ≥ 2 stages were not observed in any of the patients. However, improvement of at least one point in steatosis, lobular inflammation, and hepatocellular ballooning were detected in two (18 %), four (36 %), and three patients (27 %) patients, respectively (▶ **Table 2**).

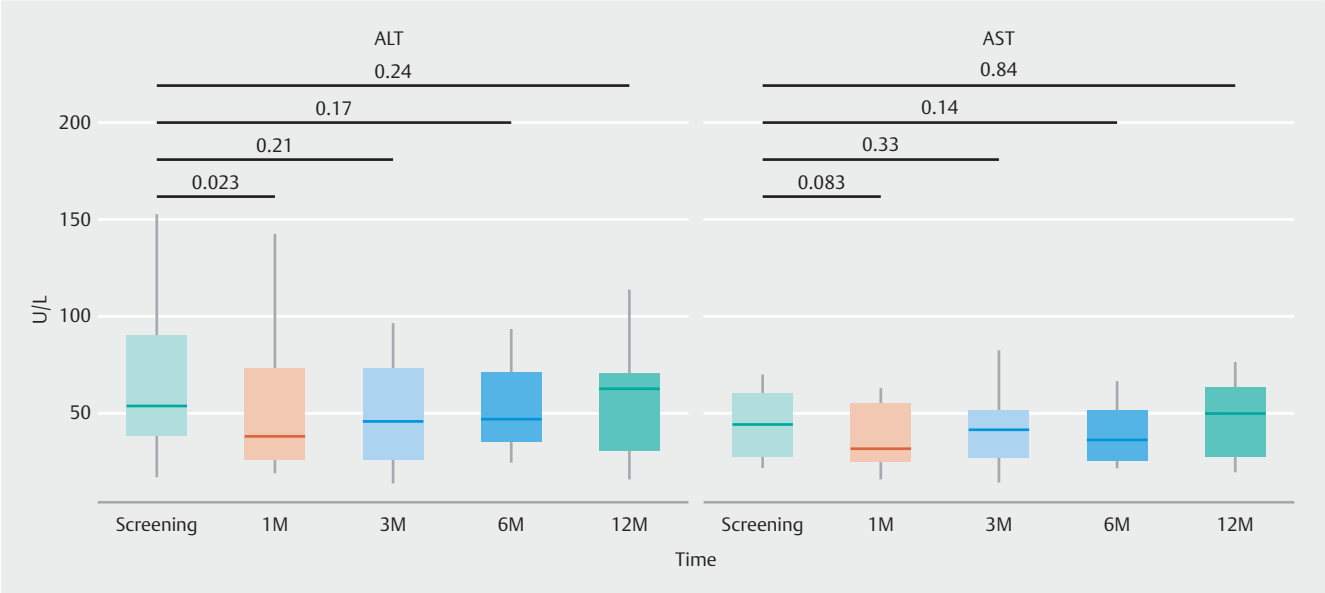
The median ALT level (IQR) decreased significantly from 54 U/L (39–90) to 44 U/L at 1 month ($P = 0.023$), but increased to levels of 46 U/L (31–74, $P = 0.21$), 47 U/L (36–71, $P = 0.17$), and 63 U/L (30–70, $P = 0.24$) at 3, 6, and 12 months, respectively (▶ **Fig. 1**). The median AST level (IQR) tended to decrease from 44 U/L (28–60) to 31 U/L (25–54, $P = 0.083$) at 1 month but remained unchanged from baseline at 3 (41 U/L (26–50, $P = 0.33$), 6 (36 U/L (26–48, $P = 0.14$), and 12 months (50 U/L (27–63, $P = 0.84$), respectively (▶ **Fig. 1**). At 12 months, the number of patients with an ALT level inferior to the upper limit of normal (ULN) (i. e. 40 U/L) was 36 (36 %) compared to 27 (27 %) at baseline, whereas an AST level inferior to the ULN was seen in 36 (36%) at 12 months compared to 45 (45 %) at baseline.

▶ **Table 2** Efficacy endpoints.

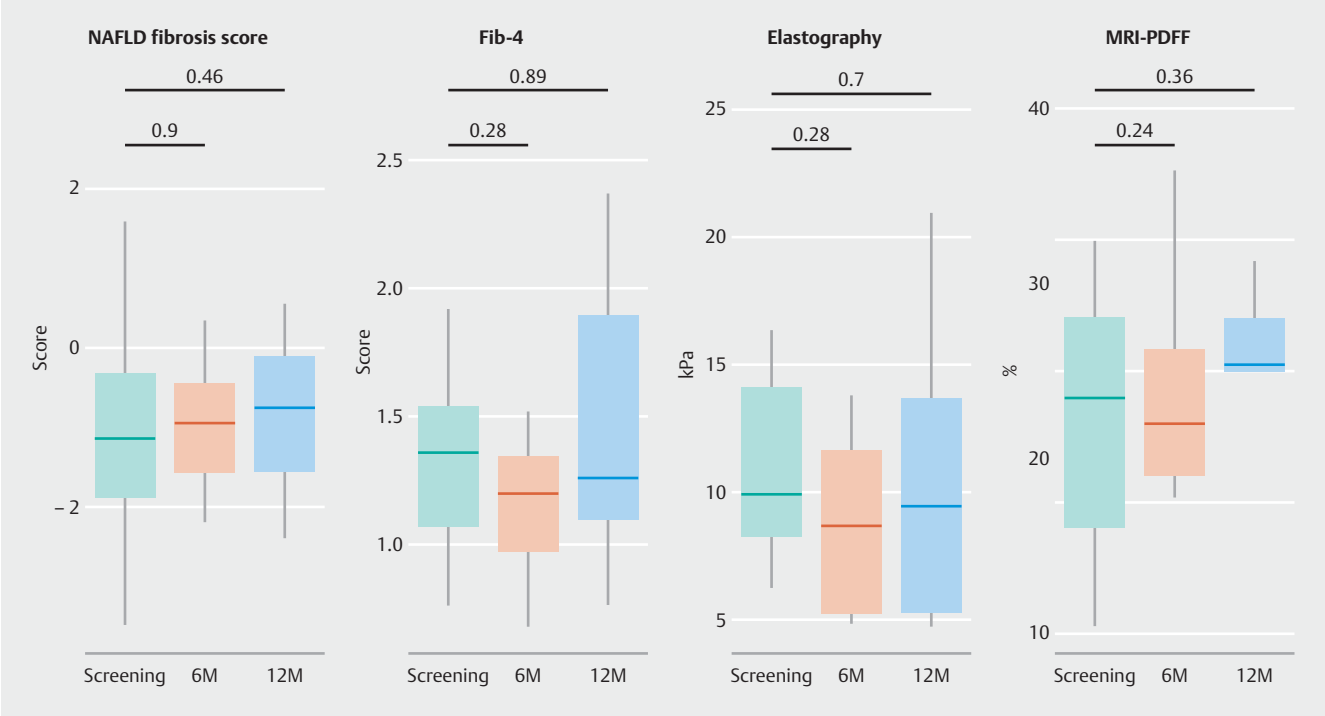
Primary endpoint, n (%)	
Improvement of fibrosis with no worsening of NASH	3 (27)
Resolution of NASH with no worsening of fibrosis	0
Secondary endpoints, n (%)	
Improvement of fibrosis by ≥ 1 stage or resolution of NASH without worsening of either	3 (27)
No worsening of fibrosis and no worsening of NASH	0
Improvement of NAS by ≥ 2 with no worsening of fibrosis	0
Improvement of fibrosis and resolution of NASH as a composite endpoint	0
Improvement in fibrosis by ≥ 2 stages	0
Resolution of fibrosis	0
≥ 1 point improvement in steatosis	2 (18)
≥ 1 point improvement in lobular inflammation	4 (36)
≥ 1 point improvement in hepatocellular ballooning	3 (27)

NAS, nonalcoholic fatty liver disease activity score; NASH, nonalcoholic steatohepatitis.

After DMR, the median Fib-4 score (IQR) slightly improved from 1.36 (1.06–1.54) to 1.20 (0.98–1.34) and 1.26 (1.09–1.90) at 6 and 12 months, respectively, but the median change was not significantly different (▶ **Fig. 2**). Similarly, there was no improvement in median NAFLD fibrosis score (IQR) which in-



▶ **Fig. 1** Change in liver transaminase levels over time. Change in liver biochemistry over time. Box plots of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at 1 month (1 M), 3 months (3 M); 6 months (6 M), and 12 months (12 M). Boxes indicate the 25th to 75th percentiles, the line within the boxes marks the median, whiskers (error bars) above and below the box indicate the 90th and 10th percentiles, while *P* values are indicated within the graph.



▶ **Fig. 2** Change in surrogate markers of liver fibrosis and steatosis over time. Change in surrogate markers of liver fibrosis and steatosis over time. Box plots of nonalcoholic fatty liver disease fibrosis score (NAFLD), fibrosis-4 score (Fib-4), elastometry, and magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) at 6 months (6 M) and 12 months (12 M). Boxes indicate the 25th to 75th percentiles, the line within the boxes marks the median, whiskers (error bars) above and below the box indicate the 90th and 10th percentiles, while *P* values are indicated within the graph.

creased from –1.14 (–1.89– –0.32) to –0.95 (–1.58– –0.46, *P* = 0.9) and –0.75 (–1.56– –0.10, *P* = 0.46) at 6 and 12 months, respectively (▶ **Fig. 2**). The median VCTE (IQR) also did not change significantly from 9.8 kPa (8.2– 14.1) to 8.6 kPa (5.2–11.6, *P* = 0.28) and 9.4 kPa (5.3–13.7, *P* = 0.7) at 6 and 12 months, respectively (▶ **Fig. 2**). The median MRI-PDFF (IQR) values did not reveal any change from 23 % (16–28) at baseline to 22 % (19–26, *P* = 0.24) at 6 months and 25 % (25–28, *P* = 0.46) 12 months after DMR, respectively (▶ **Fig. 2**). The median glycemic parameters derived from OGTT were statistically significant different (*P* = 0.06) compared to baseline values at 1 month (▶ **Fig. 3a**). The median plasma glucose level (IQR) decreased significantly from 230 mg/dL (210.5–307) to 199 mg/dL (161.5–277) 60 minutes after glucose load (*P* < 0.05) and from 231 mg/dL (206.5–315.5) to 214 mg/dL (177–297) 90 minutes after glucose load (*P* < 0.05).

Median weight (IQR) was similar at 1, 6, and 12 months after DMR while a significant weight loss was observed at 3-month follow-up (from 82 kg [76–94] to 80 kg [76–89]; *P* = 0.0083) (▶ **Fig. 3b**).

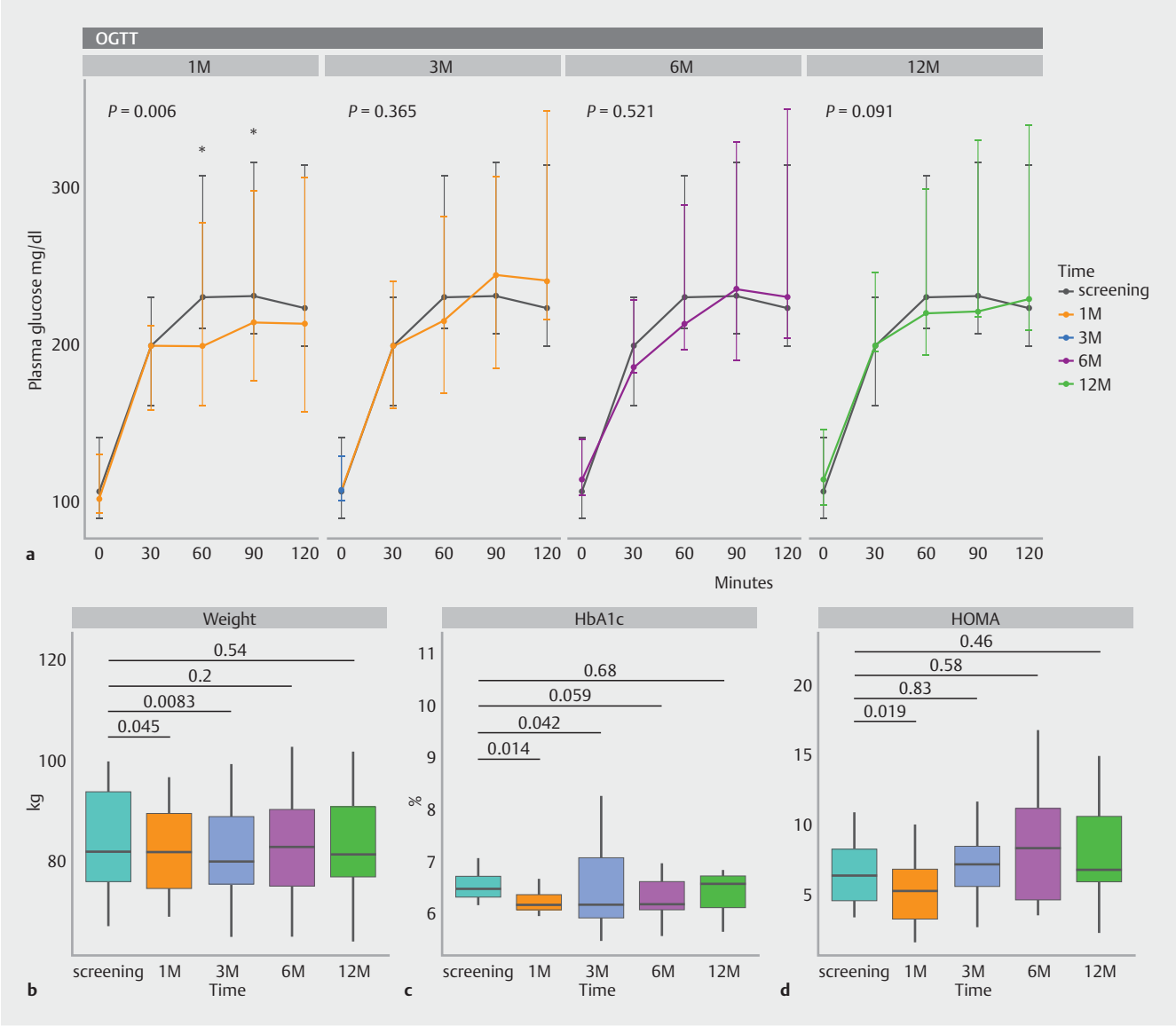
The median HbA1c level (IQR) significantly decreased 1 month after DMR, from 6.50 % (6.35–6.75) to 6.20 % (6.10–6.40, *P* = 0.014) and was sustained at 3 and 6 months, although the median change was not statistically different at these time points. This improvement was not sustained at 12 months where the median HbA1c level increased to 6.60 (6.15–6.75, *P* = 0.68) (▶ **Fig. 3c**).

The median HOMA index (IQR) significantly decreased 1 month after DMR, from 6.3 (4.5–8.2) to 5.2 (3.2–6.8, *P* = 0.019). Surprisingly, the median HOMA level increased at 3, 6, and 12 months compared to baseline value to 7.2 (5.5–8.4, *P* = 0.83), 8.3 (4.5–11.1, *P* = 0.58), and 6.8 (5.9–10.6, *P* = 0.46), respectively (▶ **Fig. 3d**).

Characteristics of DMR procedure and adverse events

The median DMR procedure time (IQR) was 62 minutes (54.5–68) whereas the median number of successive duodenal mucosal hydrothermal balloon ablations (IQR) was seven (6–8). All patients underwent a gastroscopy 3 months after DMR, with no findings of duodenal stenosis or gastroduodenal ulcers in any of the patients.

Overall, two serious AEs (SAEs) (14 %) related to the procedure occurred in this pilot study. One patient presented with moderate hypoxemia due to atelectasis of the right lower lobe of the lung and was successfully treated with oxygen and physiotherapy. The patient was discharged 2 days after the procedure. The second patient presented with epigastric pain associated with mild fever and moderate elevation in C-reactive protein. No microbiologically documented infections or local duodenal complications due to DMR were found on computed tomography scan. The evolution was spontaneously favorable and the patient was discharged 4 days after the procedure. Despite the absence of clear evidence, we cannot exclude that this latter event could be potentially related to the DMR procedure.



▶ **Fig. 3** Change in metabolic parameters over time. Change in metabolic parameters over time. **a** Oral glucose tolerance test (OGTT), plasma glucose at baseline and 30, 60, 90, 120 minutes (Min) after ingestion of 75 g of oral glucose. Data are expressed as median (IQR). Significance ($P<0.05$) between curves was assessed by mixed model test (p values indicated within the graph). *Indicates a $P<0.05$. N = 11, nine of whom had type 2 diabetes. **b**, **c**, **d** Box plots of weight, glycated hemoglobin (HbA1c), and homeostatic model of insulin resistance (HOMA) at screening at 1 month (1 M), 3 months (3 M), 6 months (6 M), and 12 months (12 M). Boxes indicate the 25th to 75th percentiles, the line within the boxes marks the median, whiskers (error bars) above and below the box indicate the 90th and 10th percentiles, while *P* values are indicated within the graph.

No unanticipated adverse device events (UADEs) were reported.

The most frequent AEs (▶ **Table 3**) were related to gastrointestinal disorders (36 %) and comprised the following symptoms: heartburn, constipation, chest wall pain, and epigastric pain. Two patients experienced hyperglycemia, one was mild and related to discontinuation of antidiabetic drugs and was resolved after resuming appropriate medication whereas the other patient needed to tailor their therapy by adding a second antidiabetic drug (i. e., gliclazide). Of note, this patient presented with decompensated diabetes, the latter being difficult to adapt despite tailoring antidiabetic drugs. The changes in oral antidiabetic medication are presented in **Supplementary Table S2**.

Discussion

This pilot study assessed, for the first time, the DMR procedure in patients with biopsy-confirmed NASH with histological evaluation at 1 year. Aside from a marginal improvement in fibrosis score, we found no resolution of NASH and no improvement in other liver histology or metabolic markers 12 months after the procedure. Similarly, MRI, PDFF, and VCTE also remained unchanged at 1 year. Of note, no intensive lifestyle follow-up was

▶ **Table 3** Summary of adverse events.

Adverse events	Number of patients (%) N = 14
Serious adverse events possibly or related to the procedure	2 (14)
Gastrointestinal disorders related to the procedure including heartburn, constipation, chest wall pain, epigastric pain	
▪ Mild	5 (36)
▪ Moderate	0
▪ Severe	1 (7)
Endocrine disorders not related to the procedure including hyperglycemia	
▪ Mild	1 (7)
▪ Moderate	1 (7)
▪ Severe	0
Musculoskeletal and connective tissue disorders not related to the procedure	
▪ Mild	1(7)
▪ Moderate	0
▪ Severe	0
Nervous system disorders not related to the procedure including falls without loss of consciousness	
▪ Mild	1(7)
▪ Moderate	0
▪ Severe	0
Respiratory, thoracic and mediastinal disorders related to the procedure including hypoxemia	
▪ Mild	0
▪ Moderate	0
▪ Severe	1 (7)

proposed during the study and patient weights remained unchanged at 1 year.

Our study population differs from the recent published REVITA-2 randomized clinical trial (RCT) [19] in which DMR was shown to be associated with improvement in metabolic factors. First, a greater reduction in HbA1c was reported in patients with high baseline FPG (≥180 mg/d) which contrasts with the demographic data for our study population. In addition, our study was designed to avoid the potential bias of weight loss because no intensive dietary intervention was implemented over the course of the trial and, as expected, no significant weight loss was observed 12 months after DMR. More specifically, comprehensive comparison of our study with REVITA-2 and the INSPIRE [20] studies is difficult because not only outcomes were evaluated at different timepoints, but mostly, especially for the INSPIRE study, the design was different emphasized by the implementation of another drug, i.e. glucagon-like peptide-1 receptor agonist. Liver fat content (measured by PDFF) was assessed at 3 months in the REVITA-2 study whereas long-term data (i.e. 12 months) were available in the INSPIRE study. Interestingly, the median baseline PDFF value was of 8.1 % (4.0–13.5) while our study reported a higher baseline value of 23 % (16–28). Moreover, liver fat content improvement reported in the INSPIRE study was associated with a significant weight loss whereas the level of weight change was not detailed at 3 months in the REVITA-2 study. These findings underscore that our study population is more severe compared to the published data and NAFLD is commonly known to be heterogenous [21]. In the other hand, weight loss achieved with a hypocaloric diet and/or increased physical activity is known to improve NASH-related histological endpoints [6, 15, 22] and metabolic factors such as HbA1c and HOMA-IR [23]. Controlling this important confounder was, therefore, critical to identifying a potential impact of DMR in NASH patients. Accordingly, most clinical trials in NASH have not provided nutritional counseling or an accurate description of lifestyle modifications [24]. Importantly, in a recent meta-analysis of placebo groups from 39 biopsy-proven NASH RCTs, 25 % of patients in the placebo groups had an improvement in NAS of ≥2 points and 21 % had an improved fibrosis score and these changes were correlated to changes in body mass index [25]. In this study, three patients (27 %) had an improved fibrosis score (by one stage) with no worsening of NASH; however, this might, at least in part, reflect the impact of weight loss observed in two of them. Thus, this apparently positive histological effect might be in line with the placebo response observed in large multicentric NASH clinical trials [25].

Furthermore, our pilot study population consisted of biopsy-confirmed NASH patients, more than 25 % of whom had advanced fibrosis, a feature that may also explain the discrepancies between our results and those reported in previous DMR trials performed in T2DM patients [12, 13]. Even though T2DM and NAFLD often co-exist [4], these findings support the fact that our population represents a more severe group, probably related to the selection of patients with biopsy-proven NASH. This could explain, at least in part, the negative results observed in this study.

No UADEs occurred in this pilot study and, more specifically, no duodenal stenosis, a factor that was a concern with the first published DMR trial [26]. Since then, further improvements were made to ensure proper mucosal lifting before ablation to avoid the aforementioned complications and a second-generation catheter was used in our study. The two SAEs related to the procedure (i.e. mild hypoxemia after extubation and transient fever) were not related to the device and resolved without further intervention within 1 to 3 days.

This pilot study has some limitations. The sample size was limited in the setting of a highly heterogeneous disease. However, the study was initially designed to evaluate, in a specific population of patients with biopsy-proven NASH whether DMR could have a positive effect on liver histology endpoints, the gold standard to prove a therapeutic role. The purpose of this pilot study was to evaluate whether at least a trend toward a

positive effect could be detected. This would have led to the conduct of a larger multicenter study to prove DMR efficacy in NASH patients, a project obviously abandoned given the current results. Other limitations are related to the observational design of the study and the high dropout rate. This study was also not designed to investigate the pathophysiological role of the duodenal mucosa. Further studies are required to better understand the underlying mechanisms induced by DMR and the possible synergistic effect of weight loss. Such explorations might be difficult to assess in humans, and in vitro and/or rodent models could be very helpful in this setting.

Conclusions

In conclusion, in this small and heterogenous study population, the DMR procedure in patients with biopsy-proven NASH did not improve liver histological endpoints, liver fat content, or any other metabolic marker at 12 months, in the absence of weight loss.

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Competing interests

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