Supplementary material

Figure S1.

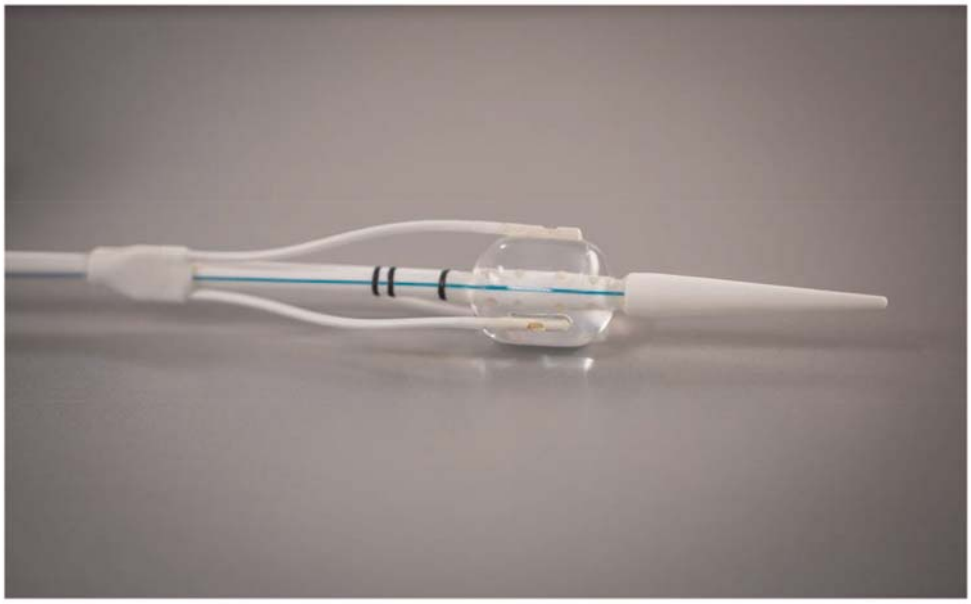


Fig S1. Duodenal mucosal resurfacing balloon catheter.
The three side catheters contain a needle to perform submucosal injection (through suction of the mucosal layer) before ablation. Hydrothermal ablation is performed through controlled perfusion of the balloon with hot water followed by rapid cooling.
Courtesy of Fractyl, Inc.

Supplementary material

Figure S2.

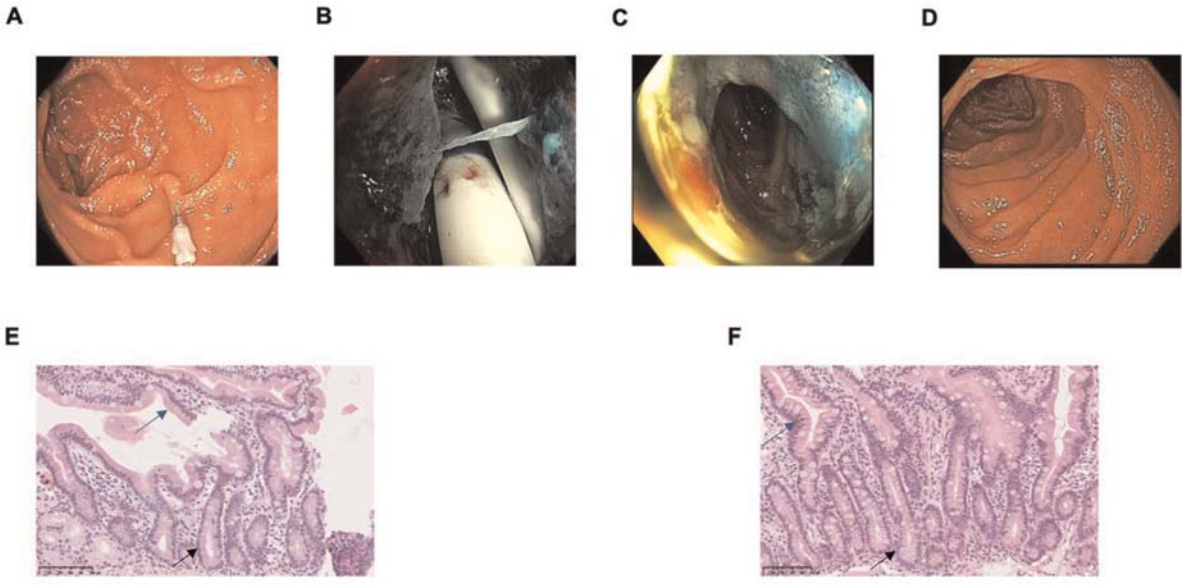
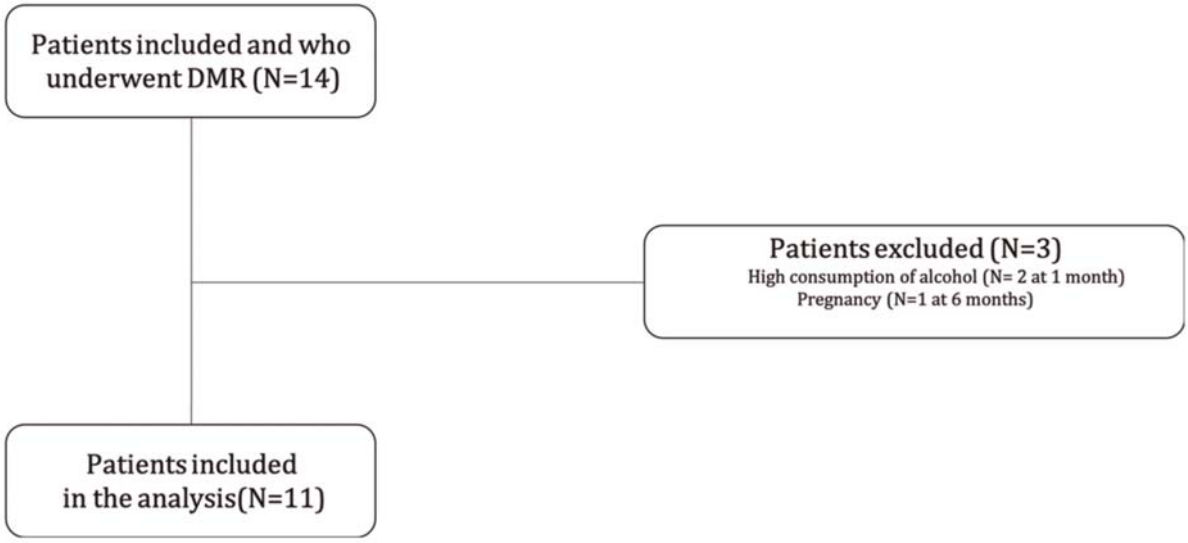


Figure S2. Endoscopic images of the DMR procedure and representative histology of duodenal mucosa. A. Hemoclip placed in the opposite site of the papilla to avoid thermal injury. B. Duodenal circumferential submucosal expansion with saline solution and methylene blue performed with a balloon catheter alongside the endoscope. C. Necrosis of the superficial layer of duodenal mucosa. E. Duodenal biopsy (before DMR) stained with hematoxylin and eosin. F. Duodenal biopsy (3 months after DMR) stained with hematoxylin and eosin. Black arrows indicate crypts, blue arrows indicate villi. Scale bars in E and F: 100 µm.

Supplementary material

Figure S3



Supplementary material

Supplementary Table S1.

INCLUSION CRITERIA
Adults subjects (male and female), aged 28 to 75 years
NASH histological diagnosis according to the currently accepted definition of both EASL and AASLD, requiring the combined presence of steatosis (any degree> 5%) + lobular inflammation of any degree + liver cell ballooning of any amount, on a liver biopsy performed ≤ 6 months before screening in the study and confirmed by central reading. a) SAF (steatosis, activity, fibrosis) activity score of 3 or 4 (>2) b) SAF steatosis score ≥ 1 c) SAF fibrosis score < 4
No other causes of chronic liver disease and compensated liver disease.
If applicable, have a type 2 diabetes with HbA1c <10.0 %
BMI (body mass index) ≥ 24 and ≤ 40 kg/m2.
Willing to sign an informed consent form.
Willing to comply with study requirements
EXCLUSION CRITERIA
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 subjects who have had Billroth 2, Roux-en-Y gastric bypass, or other similar procedures or conditions.
Known autoimmune disease, including celiac disease, or symptoms of systemic lupus eythematosus, sleroderma or other auto-immune connective tissue disorder.
For type 2 diabetes subjects, no current use of insulin or GLP-1 analogues.
Type 1 diabetes.
Probable insulin production failure defined as fasting C peptide serum < 1 ng/ml.
History of acute or chronic pancreatitis.
Active malignancy.
Persistent anemia defined as Hb < 10 g/dl.
Use of anticoagulation therapy which cannot be discontinued for 7 days before and 14 days after the procedure.
Use of P2Y12 inhibitors (clopidrogel, prasugrel, ticagrelor) which cannot be discontinued for 14 days before and14 days after the procedure.
History of coagulopathy or upper gastro-intestinal bleeding conditions likely to bleed.
Taking corticosteroids or drugs which possibly affect gastrointestinal motility or liver.
Unable to discontinue NSAIDs (non-steroidal anti- inflammatory drugs) during the treatment up to 4 weeks after procedure.
Use of weight loss medications.
Presence of liver cirrhosis (defined by histology)
Platelet count < 120 x 10^9/L.
Clinical evidence of hepatic decompensation or severe liver impairment as defined by the presence of any of the following abnormalities: a) Serum albumin < 32 g/L. 21. INR> 1.3. b) Direct bilirubin> 1.3 mg/L. c) ALT or AST > 5x ULN. d) Alkaline Phosphatase > 3x ULN.
History of esophageal varices, ascites or hepatic encephalopathy.
Splenomegaly.
Human immunodeficiency virus.
Contraindications to MRI as defined below.

Supplementary material

Supplementary Table S2: Change in oral antidiabetic medication from baseline to the end of the study (12 months, N=11).

	DMR (N=9)
Change in oral antidiabetic medication	
Increase	1(11)
Neutral	6(67)
Decrease	2(22)

Data from patients with type 2 diabetes (N=9) and with 12 months of follow-up are presented as n (%).
DMR, duodenal mucosal resurfacing.

Supplementary material

Supplementary Appendix 1: Sample size calculation.

Theoretical sample size calculation to prove DMR efficacy in NASH patients.

The following assumptions were made for the sample size calculation in case of a large multicentric trial assessing the effect of DMR on NASH resolution with no worsening of fibrosis and/ or fibrosis improvement with no worsening of NASH:

- α= 0.05
- Randomization ratio of 1:1
- Drop-out rate of 20%
- 20% response in the control group
- 27% response in the DMR group

The 20% response rate in the control group is based on the results of the previous study assessing the placebo effect in NASH clinical trials[1]. The 27% response rate in the DMR group is based on the results of this study. Accepting an alpha risk of 0.05 (two-sided), a beta risk of 0.2 and a loss rate of 20%, a sample size of 605 patients in each group is needed to achieve statistical significance.

References:

[1] Han MAT, Altayar O, Hamdeh S, et al. Rates of and Factors Associated With Placebo Response in Trials of Pharmacotherapies for Nonalcoholic Steatohepatitis: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2019; 17: 616-629.e26. doi:10.1016/j.cgh.2018.06.011