

Liver steatosis induces portal hypertension regardless of fibrosis in patients with NAFLD: A proof of concept case report



To the Editor:

Non-alcoholic fatty liver disease (NAFLD) affects 25-35% of adults in the general population, and it is closely related to metabolic diseases, particularly obesity and type 2 diabetes. The hallmark of NAFLD is the accumulation of lipid droplets in hepatocytes (so called steatosis). The pathophysiology of NAFLD is complex, and the clinical course is widely variable. The bulk of patients present with a mild non-progressive disease. However, in about 20-30%, lipid accumulation will promote cell death and oxidative stress, which will activate the cytokine cascade, promoting liver inflammation (non-alcoholic steatohepatitis [NASH]) that could trigger liver fibrosis and eventually cirrhosis and hepatocellular carcinoma.¹

Portal hypertension (PH) is the main driver of hepatic decompensation in advanced liver disease. It is defined as a multifactorial condition due to hemodynamic abnormalities of the portal venous system, related to increased intrahepatic vascular resistance and altered splanchnic blood flow. Nonetheless, several studies have suggested that PH can be present in the early stages of NASH, when fibrosis is far less advanced or even absent.²⁻⁸

We present the case of a 60-year-old Hispanic female with no alcohol consumption, a body mass index of 31.2 kg/m² and a waist circumference of 102 cm. The patient received proton-pump inhibitors due to gastroesophageal reflux disease and did not present any other medical history of interest. She was referred to our liver unit in 2020 due to a persistent alteration of liver enzymes and the presence of steatosis on abdominal ultrasound. After excluding other potential causes of liver disease, NAFLD was diagnosed. Liver stiffness measurement by vibration-

controlled transient elastography (VCTE) and controlled attenuation parameter values were 7.8 kPa and 333 dB/m, respectively, suggestive of severe steatosis without significant fibrosis. ALT and AST values were 102 and 82 IU/L, respectively, and liver function parameters (bilirubin, albumin) were within the normal range, as was platelet count (Table S1).

During follow-up, an upper gastrointestinal endoscopy (ordered for gastroesophageal reflux disease symptoms) showed small esophageal varices. The imaging techniques (ultrasound and contrast-enhanced scan) ruled out vascular disease and no architectural abnormalities in the liver or radiological signs of portal hypertension were found (spleen size 10.5 cm).

Due to the mismatch between endoscopic findings and imaging plus laboratory results, measurement of the hepatic venous pressure gradient (HVPG) and a transjugular liver biopsy were carried out. HVPG confirmed the presence of portal hypertension (6 mmHg) and the histological evaluation demonstrated an architectural lobular alteration due to severe steatosis and an increased hepatocyte size due to the accumulation of lipid droplets. The NAFLD activity score was 7/8 (steatosis 3; lobular inflammation 2; ballooning 2) with fibrosis stage 1a (Fig. 1A-B). The timeframe from endoscopy to VCTE and HVPG measurement/liver biopsy was 5 and 10 months, respectively. Of note, the patient had a stable weight, and no medication was added during that period.

PH plays a key role in the natural history of patients with liver disease. HVPG remains the gold standard, with a well-established threshold to define PH (≥ 6 mmHg) and clinically significant PH (CSPH; ≥ 10 mmHg), which is strongly associated with the presence of gastroesophageal varices and liver-related

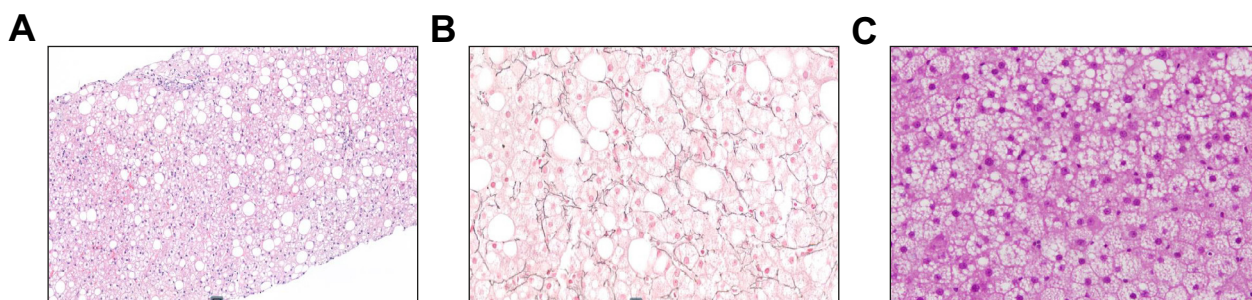


Fig. 1. Liver biopsy from a human with NAFLD and a rat model of NASH. (A,B) Individual with NAFLD and (C) rat model. Courtesy of Salcedo M. and Barberá A, respectively. Representative images showing NASH features in absence of fibrosis, stained with (A) H&E and (B) picrosirius red. (C) Representative image showing liver parenchyma stained with H&E in the murine model after 36 weeks of dietary intervention. NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis.

Keywords: Non-alcoholic fatty liver disease; Liver steatosis; Portal hypertension; Sinusoidal area; Non-alcoholic steatohepatitis.

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complications. Moreover, it has been shown that liver stiffness measurement ≤ 15 kPa + platelet count $\geq 150 \times 10^9$ rules out CSPH in compensated advanced liver disease.⁹ Nevertheless, some studies yielded unexpected results regarding the role of PH and the ability of HVPG and VCTE to address CSPH in NAFLD. On the one hand, it seems that the HVPG threshold to define CSPH is not specific enough for individuals with NAFLD,¹⁰ with liver events registered also at HVPG < 10 mmHg within this population.¹¹ On the other hand, the diagnostic accuracy of VCTE to rule in CSPH significantly decreases in individuals with obesity and NAFLD despite the utilization of the XL probe.¹² This gap was reflected in the Baveno VII expert consensus,⁹ where no specific recommendation in individuals with obesity and NAFLD was provided to rule in CSPH through non-invasive tests.

Interestingly, murine models suggested that both functional (*i.e.* endothelial dysfunction, imbalance in vasoactive

substances)^{2,3} and structural sinusoidal disturbances secondary to fatty liver changes could promote PH, even in the absence of fibrosis.^{4,5} Our group reported that steatosis was the main determinant of PH in a 36-week dietary NASH rat model.⁵ The main mechanism was the architectural distortion of the sinusoid area caused by accumulation of lipid droplets and morphological changes in hepatocytes, which led to sinusoidal compression and increased intrahepatic vascular resistance (Fig. 1C)

In summary, the present clinical case provides proof-of-concept of the major influence of liver steatosis on the physiopathology of PH in individuals with NAFLD. Further research is needed to elucidate the precise mechanisms of PH and to refine the diagnostic approach in obese individuals with NAFLD. Besides, the real prevalence of PH unrelated to fibrosis in individuals with NAFLD remains to be determined.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design; JRE, JMP, JG; Patient enrolment and acquisition of data JR, AB, MTS; Analysis and interpretation of data, JRE, AB, MTS; Drafting of the manuscript, JRE, JMP; Critical revision of the manuscript: JRE, AB, MTS, MM, JG, JMP. JRE is the guarantor of the article. All the authors approved the final draft which is being submitted.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2022.100618>.

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