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Review Article

Portal Hypertension in Nonalcoholic Fatty Liver Disease: Challenges and Paradigms

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Abstract

Portal hypertension in cirrhosis is defined as an increase in the portal pressure gradient (PPG) between the portal and hepatic veins and is traditionally estimated by the hepatic venous pressure gradient (HVPG), which is the difference in pressure between the free-floating and wedged positions of a balloon catheter in the hepatic vein. By convention, HVPG≥10 mmHg indicates clinically significant portal hypertension, which is associated with adverse clinical outcomes. Nonalcoholic fatty liver disease (NAFLD) is a common disorder with a heterogeneous clinical course, which includes the development of portal hypertension. There is increasing evidence that portal hypertension in NAFLD deserves special considerations. First, elevated PPG often precedes fibrosis in NAFLD, suggesting a bidirectional relationship between these pathological processes. Second, HVPG underestimates PPG in NAFLD, suggesting that portal hypertension is more prevalent in this condition than currently believed. Third, cellular mechanoresponses generated early in the pathogenesis of NAFLD provide a mechanistic explanation for the pressure-fibrosis paradigm. Finally, a better understanding of liver mechanobiology in NAFLD may aid in the development of novel pharmaceutical targets for prevention and management of this disease.

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Abbreviations: CSPH, clinically significant portal hypertension; ECM, extracellular matrix; FHVP, free hepatic venous pressure; HCV, hepatitis C virus; HSC, hepatic stellate cell; HVP, hepatic venous pressure; HVPG, hepatic venous pressure gradient; HVR, hepatic vascular resistance; KLF2, Kruppel-like factor 2; LSEC, liver sinusoidal endothelial cell; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PPG, portal pressure gradient; PVP, portal venous pressure; TAZ, transcriptional coactivator with PDZ-binding motif; TIPS, transjugular intrahepatic portosystemic shunt; WHVP, wedged hepatic venous pressure; YAP, Yes-associated protein.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) has become the most common liver disorder worldwide and is estimated to affect 25% of the US population.[1] NAFLD, which is considered a disease of metabolic dysfunction, is highly associated with obesity, type 2 diabetes mellitus, and dyslipidemia.[2] NAFLD manifests as steatosis or nonalcoholic steatohepatitis (NASH) and has the potential to progress to cirrhosis. The natural course of NAFLD is highly variable and the individual risk of developing advanced chronic liver disease is difficult to predict.[3,4] The severity of liver fibrosis is a key feature of disease progression and has been regarded as the most reliable predictor of liver-related and all-cause mortality in NAFLD.[5] Progression of fibrosis is increasingly associated with portal hypertension, which results from a profoundly disturbed liver microcirculation and leads to decompensating events, such as variceal bleeding, ascites, and hepatic encephalopathy.[6] These complications are primarily responsible for liver-related death in NAFLD, justifying major efforts to understand the pathogenesis of portal hypertension, improve early diagnosis of portal hypertension, and develop effective pharmacotherapy for the prevention and management of portal hypertension in NAFLD.[7]

The liver receives 25% of cardiac output, approximately 75–80% of which is supplied by the portal vein and the rest by the hepatic artery. Terminal branches of the portal vein and the hepatic artery merge into a unique capillary network of liver sinusoids.[8] Liver sinusoids are low-pressure, low-flow interconnected vascular channels that link the periportal area to the central vein. The portal pressure gradient (PPG) between the portal venous pressure (PVP) and the hepatic venous pressure (HVP) in the healthy liver is up to 5 mmHg.[6] The PPG is most often estimated by the hepatic venous pressure gradient (HVPG), which represents the pressure difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). The WHVP and FHVP are measured by a retrograde hepatic vein catheter in the wedged and free-floating positions, respectively.[6] By convention, an HVPG>5 mmHg indicates portal hypertension, and an HVPG≥10 mmHg indicates clinically significant portal hypertension (CSPH).[9,10] Portal hypertension may result from a variety of impediments to blood flow between the portal vein and the right atrium. In cirrhosis, portal hyperten-

sion most often stems from structural and functional changes in the sinusoids (i.e. sinusoidal portal hypertension), leading to increased hepatic vascular resistance (HVR) followed by splanchnic and systemic vasoregulatory disturbances and the formation of portosystemic collaterals.[6]

Portal hypertension associated with NAFLD has been addressed by several reviews, including an excellent summary recently published in this journal.[3,11–13] Here, we focus on selected aspects of this subject that represent major challenges and opportunities in the management of NAFLD. First, clinical and experimental evidence indicates that PPG begins to rise early in the course of NAFLD, and the presence of fibrosis is not a prerequisite to this process, which challenges our canonized concept of the sequence of pathological events in disease progression. Second, multiple observations confirm long-standing concerns that PPG in noncirrhotic NAFLD is underestimated by HVPG, suggesting that portal hypertension may be more prevalent in this condition than currently believed. Third, several laboratories have identified novel cellular and molecular mechanisms in early NAFLD that establish a causal relationship between elevated PPG and disease progression, making way for new paradigms in the pathogenesis of this disease. Finally, a better understanding of liver mechanobiology in NAFLD may aid in the identification of novel pharmaceutical targets for prevention and management of this disease.

Portal hypertension begins in precirrhotic NAFLD and may precede fibrosis

Sinusoidal portal hypertension originates from increased HVR, which is first and foremost a consequence of reduced sinusoidal space.[14,15] Early clinical and experimental observations provide evidence for the association between increased PVP and perisinusoidal and perivenular fibrosis in precirrhotic alcohol-induced liver injury.[16,17] Progression of experimentally induced fatty liver and human NAFLD into portal and periportal fibrosis involves profound architectural remodeling and formation of cirrhotic nodules, which represents obvious mechanical impediments to the hepatic microcirculation.[18,19] Increased thickness of fibrotic bands and smaller size of regenerative nodules reliably predict CSPH in patients with cirrhosis of different etiologies.[20] However, hemodynamic measurements in cirrhosis suggest that 20–30% of HVR is the result of functional changes, such as sinusoidal endothelial cell dysfunction and vascular deregulation, rather than fixed structural attributes.[21,22]

Whether portal hypertension can be initiated and sustained by nonfibrotic architectural and functional changes seen in steatosis or steatohepatitis is the subject of long-standing debate.[17,23–25] Numerous observations in animal models of NAFLD have suggested an association between steatosis and increased HVR. Impaired hepatic blood flow due to narrowing of the sinusoidal space has been demonstrated in rats fed choline-deficient diet,[26] New Zealand white rabbits fed high cholesterol diet,[27] the Zucker obese-rat model,[28] rats fed a methionine-choline deficient diet,[29,30] and in the rat model of human NAFLD using the cafeteria diet,[31] In all these reports, increased HVR developed in association with massive steatosis but without significant histological evidence of fibrosis, and without a significant increase in the expression of profibrotic genes,[32] Similarly, when steatohepatitis was induced in rats by high-fat glucose-fructose diet, increased PVP was demonstrated before significant fibrosis developed,[33,34] More recently, digital image analysis of hepatocellular fat and sinusoidal areas in the high-fat glucose-fructose diet model of NAFLD found an inverse correlation between vascular space and PVP.[35] Steatosis has also been associated with endothelial dysfunction and ineffective vasoregulation, implying that steatosis contributes to both the structural and dynamic components of increased HVR.[30–32]

Clinical studies provide additional evidence for the development of portal hypertension in precirrhotic NAFLD (Table 1).[36–41] When HVPG was measured in a study of 50 patients with biopsy-proven NAFLD, portal hypertension (HVPG>5 mmHg) was confirmed in 22% of patients with ≤F2 fibrosis. The severity of steatosis was the only histological parameter that correlated with the degree of portal hypertension.[36] In a prospective cohort that included 100 patients with biopsy-proven NAFLD and clinically evident portal hypertension, fibrosis was nonadvanced (≤F2) in 32% of the cases, suggesting that increased PPG may complicate nonfibrotic NAFLD if steatosis is sufficiently severe.[37] In another prospective cohort of 40 patients with obesity and noncirrhotic NAFLD undergoing transjugular liver biopsy, subclinical portal hypertension (HVPG>5 and <10 mmHg) was seen in 18% (7 of 40 patients) and CSPH (HVPG≥10 mmHg) was seen in one case of the cohort, indicating that even CSPH may occur in the absence of cirrhosis.[38] In a retrospective analysis of 89 patients with chronic liver disease of various causes, CSPH was suspected, and subsequently confirmed by HVPG in 75 cases with biopsy-proven cirrhosis, while the remaining 14 patients who also had HVPG≥10 mmHg had no cirrhosis; this subgroup included five cases of NAFLD.[39] In a brief report of 292 patients with NAFLD undergoing HVPG measurement, the number of cases with subclinical portal hypertension (HVPG>5 and <10 mmHg) increased in parallel with advancing stages of fibrosis from F0/F1 to F2 and to F3. Severe portal hypertension (HVPG>12 mmHg) was no detected in the absence of cirrhosis.[40] These data corroborate prior notions that increased portal pressure is a continuum that may mirror the severity of fibrosis in NAFLD.[42] Recent observations suggest that the severity of portal hypertension is an important risk of disease progression in NAFLD. In a European study, the 2-year cumulative incidence of hepatic decompensation in the setting of advanced fibrosis (≥F3) secondary to NAFLD was 3% in those with subclinical portal hypertension and 15% in those with CSPH. Furthermore, the cumulative incidence of hepatic decompensation after 5 years increased to 24% in those with subclinical portal hypertension, 39% in those with CSPH, and 50% in those severe portal hypertension (HVPG≥16 mmHg).[41] Thus, despite the nomenclature, the presence of subclinical portal hypertension in ≥F3 NAFLD is clinically significant, as nearly a quarter of these patients would be expected to decompensate over 5 years.

Altogether, it is reasonable to assume that portal hypertension serves as a feed-forward mechanism of disease progression in precirrhotic NAFLD, and there may be in fact no specific threshold value of abnormal PPG below which the risk for future events is negligible.[43–45] Timely detection and management of subclinical portal hypertension could therefore modify the natural course of NAFLD. As discussed later, this strategy is particularly promising if we target potentially reversible components of HVR, including hepatocellular steatosis, sinusoidal endothelial cell dysfunction, and vascular deregulation.[22,46]

Portal pressure in NAFLD is often underestimated

In current clinical practice, PVP is estimated by WHVP, based on the assumption that blood pressure detected at the tip of the wedged catheter represents the upstream pressure transmitted by a vascular column in which stasis has been achieved between the portal and hepatic veins.[47] There is ro-

Table 1. Clinical observations of subclinical portal hypertension in NAFLD

Author (year)	Study type (origin)	Study subjects	Major findings	Notes
Francque et al (2011)[36]	Prospective (Belgium)	50 patients with obesity and biopsy-proven NAFLD with F0 to F4 fibrosis	11 patients (22%) with ≤F2 fibrosis had portal hypertension (HVPG>5 mmHg)	Steatosis was the only histological parameter predicting portal hypertension
Mendes et al (2012)[37]	Retrospective (USA)	354 patients with biopsy-proven NAFLD and F0 to F4 fibrosis	23 of 100 patients (23%) with clinical evidence of portal hypertension (ascites, encephalopathy, varices, splenomegaly) had ≤F2 fibrosis	Steatosis was more severe in patients with NAFLD who had ≤F2 fibrosis but presented with portal hypertension
Vonghia et al (2015)[38]	Prospective (Belgium)	40 patients awaiting bariatric surgery with biopsy-proven NAFLD and F0 to F3 fibrosis	8 patients (20%) had portal hypertension (HVPG>5 mmHg)	Only five patients (12.5%) had ≥F3 fibrosis in the cohort and the other three patients (8%) with HVPG>5 mmHg had F0/F1 fibrosis
Rodrigues et al (2019)[39]	Retrospective (Switzerland)	157 patients with chronic liver disease of various etiology (including 45 patients with NAFLD and F0 to F4 fibrosis)	14 of 89 patients (23%) with clinically significant portal hypertension (HVPG≥10 mmHg) had ≤F3 fibrosis, five patients in this group had NASH	Details for patients with subclinical portal hypertension (HVPG 5.5 to 10 mmHg) were not reported
Moga et al (2021)[40]	Prospective (France)	297 patients with biopsy-proven NAFLD and F0 to F4 fibrosis	36 patients (17%) with ≤F3 fibrosis had portal hypertension (HVPG>5 mmHg), including 16 patients with ≤F2 fibrosis	Severe portal hypertension (HVPG>12 mmHg) was not detected in absence of cirrhosis
Paternostro et al (2021)[41]	Retrospective (Belgium, Austria)	109 patients with NAFLD and compensated advanced liver disease (≥F3 fibrosis)	10 of 42 patients (24%) with HVPG 5.5 to 10 mmHg at baseline developed decompensation events in 5 years	Cumulative incidence of decompensation is significant in those with subclinical portal hypertension

HVPG, hepatic venous pressure gradient; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

bust evidence to support this assumption in cirrhosis caused by alcohol or chronic viral hepatitis, as WHVP is almost identical to direct PVP measurement in these settings.[48–50] Whereas both WHVP and FHVP can be affected by fluctuations in intraabdominal pressure (e.g., owing to ascites), HVPG is not. HVPG is thus, calculated as a surrogate of the PPG. Indeed, HVPG has become the gold standard for diagnosing sinusoidal portal hypertension.[47,51] Additional studies have established that an HVPG≥10 mmHg is an excellent predictor of decompensation events in cirrhosis, and as such, this threshold is what defines CSPH.[9]

Given the rapid rise in the worldwide prevalence of NAFLD, HVPG is increasingly used to diagnose portal hypertension in this patient population. Several studies have analyzed the accuracy of this method and suggest that HVPG has undeniable benefits but also some limitations when applied to advanced NAFLD (Table 2).[9,52–56] A retrospective analysis of a cohort of patients with liver disease of various etiologies undergoing transjugular liver biopsy and hepatic vein pressure measurements indicated that WHVP and HVPG values were, on average, 4 mmHg lower in patients with NAFLD than in those with chronic hepatitis C virus (HCV) infection at every stage fibrosis.[52] In a recent prospective multicenter study, correlation between WHVP and direct PVP measurement was analyzed in 120 patients with decompensated cirrhosis of different etiologies (NASH, alcohol, and chronic HCV infection) who underwent transjugular intrahepatic portosystemic shunt (TIPS) placement.[53] Disagreement between WHVP and PVP (defined as a difference between WHVP and PVP of >10% of the PVP value) occurred more frequently in the NASH group (15 of 40 patients) compared with the non-NASH group (11 of 80 patients, 37.5% vs. 14%; p=0.003). For NASH cirrhosis, the disagreement between WHVP and PVP occurred because WHVP underestimated PVP (in 13 of 15 patients, with disagreement). In contrast, for non-NASH cirrhosis, the disagreement was evenly split between WHVP underestimation (6 of 11 patients) and overestimation (5 of 11 patients) of PVP. Overall, this study adds to concerns that WHVP underestimates PVP in NASH cirrhosis and that a different (lower) HVPG threshold may be required to predict decompensation.[53] Similar concerns emerged from the findings of an simtuzumab trial, in which an HVPG threshold of ≥10 mmHg reliably predicted decompensation in NASH cirrhosis but missed 14% of patients with an HVPG of <10 mmHg who developed decompensation events (variceal hemorrhage, ascites, and hepatic encephalopathy) within an average follow-up of <5months.[54]

The ability of HVPG to predict decompensation in advanced NAFLD was further analyzed in a large multicenter cohort of patients who either had steatosis and advanced (F3/F4) fibrosis on histology or steatosis on imaging and HVPG>5 mmHg compared with a control group of patients who had chronic advanced liver disease caused by chronic HCV infection with active viremia.[55] The prevalence of decompensa-

Table 2. Clinical observations of the use of HVPG in predicting liver-related outcomes associated with NAFLD

Author (year)	Study type (origin)	Study subjects	Major findings	Notes
Sourianarayanane et al (2017)[52]	Retrospective (USA)	142 patients with biopsy-proven chronic liver disease (including 35 patients with NASH and 52 patients with chronic HCV infection) undergoing HVPG assessment	HVPG was on average 4 mmHg lower in patients with NASH as compared to those with HCV for each stage of fibrosis	5 of 19 patients (26.3%) with NASH and 10 of 31 (32.4%) patients with chronic HCV infection had HVPG>6 mmHg in the presence of ≤F2 fibrosis
Sanyal et al (2019)[54]	Retrospective (80 centers in North America and Europe)	475 patients with NASH and F3 to F4 fibrosis previously enrolled in two clinical trials evaluating simtuzumab in NAFLD	Among the 50 patients who developed a major liver-related clinical event (e.g., ascites, encephalopathy, variceal bleed) over an average of 5 months of follow-up, HVPG was <10 mmHg in seven (14%)	HVPG-based prediction of decompensation in NAFLD is less reliable than seen in the landmark trial of 213 patients with cirrhosis of diverse etiologies by Ripoll et al.[9]
Ferrusquia-Acosta et al (2021)[53]	Cross-sectional (Spain, Italy)	120 patients with cirrhosis due to NASH (n=40), alcohol (n=40), and chronic HCV infection (n=40) undergoing HVPG measurement and TIPS placement	Discrepancy between indirect (via HVPG) and direct (via TIPS) measurement of portal pressure was independently associated with NASH etiology of cirrhosis	Lower HVPG threshold may be required to predict decompensation events in NAFLD-associated cirrhosis
Pons et al (2021)[56]	Retrospective (Spain, France, Romania, Italy, Austria, Canada, Switzerland, UK)	836 patients with compensated advanced chronic liver disease of various etiologies (including 248 patients with NAFLD) undergoing simultaneous HVPG and LSM	LSM predicted significantly lower prevalence of portal hypertension (HVPG>5 mmHg) in NAFLD (61%) vs. other etiologies (>90%)	Discrepancies in the use of LSM cutoffs to predict HVPG-based portal hypertension in NAFLD demonstrate need for additional studies to validate both methods in this setting
Bassegoda et al (2022)[55]	Cross-sectional (20 centers in Europe)	548 patients with advanced NAFLD and 444 patients with advanced chronic HCV infection undergoing HVPG measurement	15 of 166 patients (9%) with advanced NAFLD and HVPG 5.5 to 9 mmHg had evidence of decompensation	Patients with advanced NAFLD may experience decompensation even with subclinical portal hypertension, indicating the need for different HVPG cutoffs

HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TIPS, transjugular intrahepatic portosystemic shunt.

tion was higher in the NAFLD group than in controls for all different HVPG cutoffs analyzed in the study (<10, 10–12, and >12 mmHg). Moreover, decompensation was found in 15 cases (9%) in the NAFLD group with subclinical portal hypertension (defined as an HVPG of 5.5–9 mmHg), including six cases (4%) with large varices.[55]

These considerations also identify challenges for studies in which HVPG serves as a reference for validating other methods in the evaluation of portal hypertension. In a recent example, the ability of liver stiffness measurement (LSM) to predict portal hypertension was analyzed in an international study.[56] In that study, 836 patients with compensated liver disease of various etiologies and an LSM>10 kPa underwent hepatic vein pressure measurements to determine the best LSM cutoff for predicting CSPH. Interestingly, the prevalence of portal hypertension (HVPG>5 mmHg) and CSPH (HVPG≥10 mmHg) was significantly lower in the NASH group (61% and 39%, respectively) compared with chronic liver disease associated with alcohol (97% and 83%) and chronic HCV infection (90% and 59%), suggesting that LSM considerably overpredicts portal hypertension in NAFLD.[56] Moreover, obesity in that cohort was associated with even lower HVPG readings in NAFLD for every given LSM value compared with other etiologies, consistent with earlier observations.[57] In isolation, these data suggest that LSM has suboptimal performance in predicting the PPG in advanced NAFLD. However, given that HVPG has been shown to underestimate the PPG in NAFLD (as described above), the data beg the following question: does LSM really overpredict the PPG in NAFLD or is HVPG a flawed gold standard for assessing the true PPG in NAFLD?

Taken together, the findings suggest that the pathophysiology of portal hypertension in NAFLD-cirrhosis is sufficiently different from cirrhosis caused by alcohol or chronic HCV infection. Furthermore, the findings suggest that earlier established criteria for CSPH based on HVPG measurements may not fully apply to NAFLD. As mentioned above, the accuracy of HVPG hinges upon the assumption that WHVP very closely reflects PVP.[58] Indeed, the assumption that WHVP accurately estimates PVP is correct when HVR is increased at sinusoidal

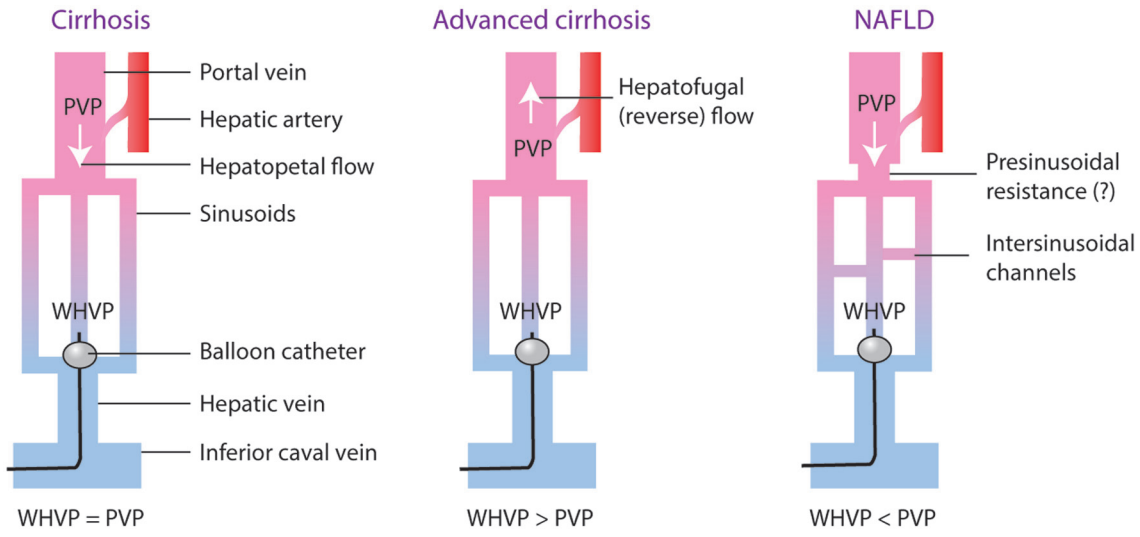

Fig. 1. Portal pressure measurement in NAFLD. Schematic illustration of sinusoidal circulation and a retrograde balloon-tipped catheter inserted into a hepatic vein branch for the assessment of portal venous pressure (PVP) by the wedged hepatic venous pressure (WHVP) in various liver conditions. (A) WHVP has an excellent correlation with directly measured PVP in cirrhosis, where the wedged catheter detects upstream pressure transmitted by a static vascular column created between the portal and hepatic veins. (B) In advanced cirrhosis, increased hepatic vascular resistance (HVR) may cause reverse (hepatofugal) blood flow in the portal vein, resulting in overestimation of PVP by WHVP. (C) By contrast, PVP is underestimated by WHVP in nonalcoholic fatty liver disease (NAFLD), which is likely due to the presence of intact intersinusoidal channels. These anastomoses allow pressure equilibration with adjacent areas in the noncirrhotic liver and may persist in cirrhotic NAFLD, accounting for diminished accuracy of indirect PVP assessment by WHVP. It has also been speculated that increased presinusoidal resistance in NAFLD may contribute to the underestimation of PVP. White arrows indicate the direction of blood flow in the portal vein. NAFLD, nonalcoholic fatty liver disease; PVP, portal venous pressure; WHVP, wedged hepatic venous pressure.

sites, which is the case in cirrhosis associated with sinusoidal portal hypertension (Fig. 1). It must be noted that WHVP may overestimate PVP in advanced cirrhosis when excessive HVR causes reverse (hepatofugal) blood flow in the portal vein or when large portosystemic shunts make sinusoidal blood flow become largely dependent on hepatic arterial perfusion.[53,59] By contrast, WHVP underestimates PVP when intersinusoidal anastomoses prevent the balloon catheter from creating a large area of stasis.[60] This is the case in healthy liver due to the generous presence of intersinusoidal channels. It has been speculated that these channels may be unevenly affected and/or more persistent in NAFLD-cirrhosis as compared to liver disease of other etiologies.[45] In precirrhotic NAFLD, intersinusoidal channels are presumably more preserved and similar to healthy liver, leading to dissipation of pressure and even less accurate HVPG readings.[50] Intact intersinusoidal channels may also mask the impact of presinusoidal factors associated with increased PVP in noncirrhotic idiopathic portal hypertension (now termed porto-sinusoidal vascular disease[61]), such as periportal fibrosis caused by Schistosoma infection, which is not 'seen' by the HVPG catheter.[48,62] It has been proposed that the distal segment of preterminal portal venules may serve as a quasi-sphincter and regulate redistribution of sinusoidal blood low in healthy liver,[63] while sinusoids have been identified as the primary site of vascular resistance in chronic liver disease.[64,65] To what extent presinusoidal factors contribute to increased portal pressure in NAFLD remains unclear.[45] Future research will need to focus on (1) the contribution of specific vascular changes to portal hypertension in NAFLD; and (2) the development and validation of easy, safe, and less invasive diagnostic tools for the measurement of portal pressure in precirrhotic NAFLD.

Portal pressure is a driver of NAFLD pathogenesis

The natural history of NAFLD has traditionally been viewed as a linear progression from steatosis to steatohepatitis to fibrosis and cirrhosis followed by portal hypertension and complications such as ascites, encephalopathy, and variceal bleeding.[4,66] However, progression along this continuum is highly heterogenous, and as discussed above, cirrhosis is not a prerequisite for portal hypertension in NAFLD. While there is strong evidence that fibrosis is a key determinant of adverse clinical outcomes, cellular and molecular mechanisms regulating disease severity in NAFLD have not been fully elucidated.[5,67] Specifically, it is unclear to what extent, and by what mechanisms, steatosis, and steatohepatitis are sufficient to generate subclinical portal hypertension that may precede fibrosis; furthermore, it remains unclear how subclinical portal hypertension may affect the progression of fibrosis in NAFLD,[43,45] In this section, we briefly review current evidence supporting the notion that mildly or moderately increased sinusoidal pressure modulates the pathogenesis of NAFLD.

Experimental and human data indicate that hepatic microcirculation is compromised early in the course of fatty liver disease.[27,68] These changes may disrupt sinusoidal perfusion and correlate with the degree of steatosis (Fig. 2). Sinusoids may be reduced to 50% of their normal size when circularly embraced by enlarged hepatocytes with accumulation of small or large lipid droplets.[69] In severe steatosis, compressed sinusoids appear tortuous and narrow, especially in the periportal region where leukocytes may become trapped and contribute to the obstruction of blood flow.[26,70,71] In addition, excessive growth of lipid droplets may result in extrusion of fat from dying hepatocytes (termed steatonecrosis), leading to the formation of lipid emboli within the sinusoidal channel and further impeding sinusoidal flow.[72] These mechanical events contribute to increased HVR from the very beginning of NAFLD.

Capillarization of liver sinusoidal endothelial cells (LSECs) is an additional architectural change of liver sinusoids associ-

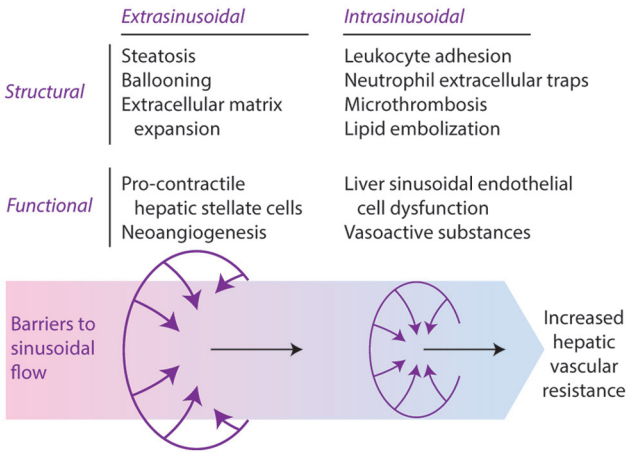

Fig. 2. Etiology of increased hepatic vascular resistance in NAFLD. Schematic illustration of extraluminal and intraluminal causes of impaired sinusoidal flow between the portal tract and the pericentral region that result in increased hepatic vascular resistance, which is the primary factor in the development of sinusoidal portal hypertension in advanced chronic liver disease. Barriers to sinusoidal flow may also be classified as structural and functional factors. Please see details in the main text. NAFLD, nonalcoholic fatty liver disease.

ated with steatosis, manifesting as the loss of unique fenestration and formation of a basal membrane.[73,74] Capillarization indicates endothelial dysfunction and occurs in response to excessive lipid exposure, engaging LSECs in complex cell-cell interactions from the earliest stages of NAFLD.[31,75,76] Dysfunctional LSECs worsen steatosis through multiple mechanisms, including: interfering with lipid transport across the sinusoidal membrane; disinhibiting hepatic stellate cells (HSCs) owing to reduced bioavailability of nitric oxide; stimulating inflammation by aiding in the activation of Kupffer cells and recruiting other immune cells; and promoting microthrombosis and neovascularization by secreting a multitude of cytokines and other bioactive substances.[77–79] LSECs themselves may swell and contract in response to vasoactive substances, further limiting blood flow.[71] With the onset of steatohepatitis, hepatocellular ballooning, and inflammatory expansion of interstitial fluids results in additional volumetric squeeze within the liver capsule, further reducing sinusoidal space and increasing liver tissue stiffness.[80,81] Steatohepatitis has also been associated with an increased number of pericentral arterioles, which are terminal hepatic arterioles that drain into distal, rather than proximal, sinusoidal segments; pericentral arterioles are not subject to the same pressure regulation mechanisms as periportal arterioles and are a source of fluid shear stress, as further discussed below.[82] While detailed discussion of the gut-liver axis is beyond the scope of this review, there is evidence of a complex interplay between the gut microbiota and the liver, indicating that dysbiosis-associated changes may contribute to the initiation of portal hypertension in early NAFLD by promoting endothelial dysfunction and pathologic cell-cell interactions in the sinusoids.[11,33]

Excessive buildup of lipids is associated with significant changes in the biomechanical properties of the liver, both at the single cell and organ levels. Single-cell force spectroscopy analysis of liver cells exposed to conditions that trigger steatosis in vitro has demonstrated a positive correlation between the size of lipid droplets and the relative elasticity or stiffness of the individual liver cell.[83] Cell biomechanics may represent a pivotal transducer connecting accumulation of lipid droplets and liver cell dysfunction (observed by abnormal expression of signaling molecules and other proteins).[84] Moreover, liver stiffness measured by acoustic radiation force impulse shear wave elastography has been associated with the severity of steatosis in a group of 60 patients with NAFLD but without significant fibrosis.[84] Corroborating earlier observations, these findings suggest that increased hepatocellular and liver stiffness can be a direct consequence of steatosis and enlarging lipid droplets in early stages of NAFLD.[84,85]

Altogether, multiple structural factors contribute to the disruption of sinusoidal homeostasis throughout the course of NAFLD. It is important to understand the mechanisms by which liver cells respond to changes in their physical environment (Fig. 3). Mechanotransduction is a term describing the process by which cells perceive mechanical cues, convert them into biochemical signals, and mount adaptive responses.[86,87] Various cell surface mechanosensors detect physical forces, such as hydrostatic pressure, stretch, and fluid shear, at interfaces with the extracellular matrix (ECM), bodily fluids, and each other.[88,89] Examples of cell surface mechanosensors include flow-responsive PIEZO ion channels, stretch-sensitive integrins and Notch receptors, and adherens junctions connecting neighboring cells, among others.[89,90] Propagation of mechanical signals from the cell surface to the nucleus occurs via biochemical signaling intermediates (mechanosignaling) and via the physical continuum of the cytoskeleton to the nucleoskeleton (mechanotransmission).[91] In recent years, we have seen major advances in unraveling the cellular and molecular pathways by which various types of liver cells respond to mechanical forces in health and disease. These data suggest that increased sinusoidal pressure is a major pathogenic player in the progression of NAFLD rather than simply an end-stage outcome in NAFLD.[92,93]

Several lines of evidence indicate that mechanical forces directly influence the behavior of liver cells. By virtue of lining the sinusoidal channels, LSECs are directly exposed to changes in the liver microcirculation, which may become turbulent and generate increased fluid shear stress when passages are narrowed due to vasoconstriction, external compression, or intraluminal obstacles (e.g., lipid emboli, adherent leukocytes, or microthrombi), as occurs in NAFLD.[94] As shown through experimentally induced sinusoidal congestion, stretch in LSECs activates Notch-dependent neutrophil chemotaxis and further aggravates portal hypertension by generating neutrophil extracellular traps.[95] Detection of shear stress by LSECs during the dramatic redirection of portal flow in the liver remnant has also been implicated in regenerative responses of the liver after partial hepatectomy.[96] Stiffness of the surrounding ECM is another key mechanical property detected by cells via integrins, which are mechanosensitive transmembrane components of the focal adhesion complexes that respond to stretch-induced conformational changes by initiating mechanoresponses and affecting key biological functions such as metabolism, motility, proliferation, and differentiation.[97,98] While fibrosis (collagen deposition) is the most significant component of tissue stiffness in liver disease, congestion, and inflammation, it may precede the development of fibrosis, and it also contributes to liver stiffness.[99] Increased ECM stiffness generates multiple mechanoresponses in liver cells, including altered metabolic functions in hepatocytes, capillarization of LSECs, and activation of HSCs into a procontractile and profibrogenic state; these mechanoresponses involve complex mechanisms of cell-ECM and cell-cell communication.[100–103]

Integration of cellular mechanoresponses occurs in the nucleus, which receives mechanical information through nuclear envelope complexes linked to the cytoskeleton and

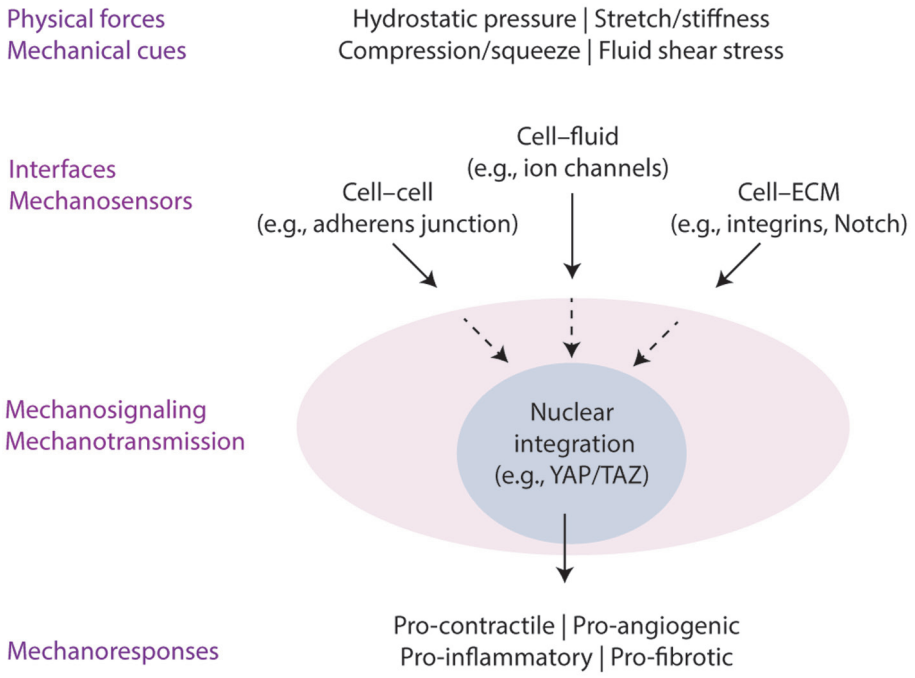

Fig. 3. Overview of cellular mechanotransduction. Mechanotransduction is a fundamental biological process by which cells perceive their physical environment and convert mechanical information into biological response. Key components of mechanotransduction include: physical forces that serve as mechanical cues; cell surface mechanosensors at interfaces of cells with other cells, bodily fluids, and ECM; intracellular spread of mechanical information via biochemical intermediates (mechanosignaling) and via the physical continuum between the cell membrane, the cytoskeleton, and the nucleus (mechanotransmission); and nuclear integration of this complex information with generation of a variety of mechanoresponses. In NAFLD, mechanoresponses have been implicated in disease progression. ECM, extracellular matrix, NAFLD, nonalcoholic fatty liver disease.

by using the nuclear pore complex to import transcriptional regulators, such as the paralog Yes-associated protein (YAP) and transcriptional coactivator with PDZ-binding motif (TAZ).[104,105] These pleiotropic molecules are involved in the control of cell functions such as motility, metabolism, differentiation, growth, and survival.[106] The mechanosensitive YAP/TAZ detect changes in matrix stiffness, fluid shear stress, and cell density in addition to responding to a variety of chemical and biological cues.[107] Evidence indicates that YAP/TAZ regulate the biological behavior of liver cells and coordinate the profibrotic response. In various experimental models of NAFLD, fibrosis is greatly reduced by cell-specific deletion of YAP/TAZ in hepatocytes and macrophages.[108–110] Recent research has implicated thrombospondin 1 in YAP-mediated profibrotic mechanoresponses in NAFLD.[111] Thrombospondins are secreted glycoproteins that bind integrins, Notch receptors, and other components of the ECM and regulate cellular adhesion, angiogenesis, inflammation, and fibrosis.[112] Elevated serum thrombospondin 1 has been described in NAFLD and have been associated with LSEC capillarization and HSC activation.[113] Similarly, thrombospondin 2 is involved in Notch signaling and has been identified as a promising biomarker of liver fibrosis.[114,115]

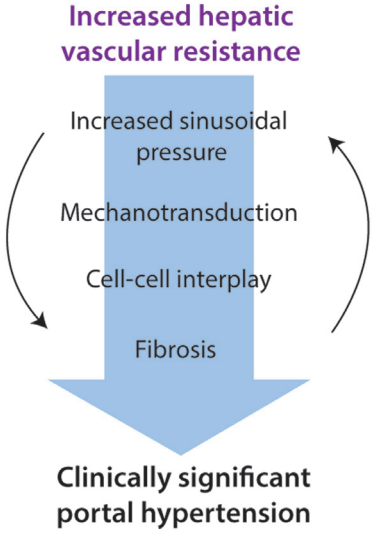

Fig. 4. Sinusoidal pressure-liver fibrosis paradigm. Schematic illustration of the bidirectional relationship between subclinical portal hypertension and fibrosis, implicating the contribution of mechanocrine signals, such as increased sinusoidal pressure, in the development and progression of fibrosis through cell-cell communication and self-amplification mechanisms, ultimately resulting in clinically significant portal hypertension. Further research is needed to explore the cellular and molecular details of this process.

Mechanobiology studies reveal new pharmacological targets in NAFLD

As we better understand the details of how liver cells respond to their changing mechanical environment during the progression of NAFLD, there is a promise of identifying new approaches in disease management. There are several excellent accounts reviewing current evidence that CSPH is not necessarily irreversible and that we have an increasing armamentarium of pharmacotherapy to halt or regress this process.[22,116,117] Here, we focus on two aspects of the field related to subclinical portal hypertension: (1) the paradigm of a bidirectional relationship between sinusoidal pressure

and liver fibrosis suggests that correcting sinusoidal microcirculation and HVR at early stages of NAFLD may reduce the impact of profibrogenic mechanotransduction pathways (Fig. 4); and (2) the prominent role of YAP/TAZ in converting mechanical cues of steatosis and steatohepatitis into profibrotic and pro-angiogenic cellular actions identifies these mechanosensitive transcriptional coactivators as potential targets in the management of NAFLD. Additional aspects and details of the cellular and molecular mechanisms related to liver mechanobiology that may assist in the prognostication and management of NAFLD have recently been discussed elsewhere.[93,118]

Plausibly, lifestyle, and medical interventions that aim to improve steatosis and steatohepatitis are the first line of therapy that may prevent or reduce the development of elevated sinusoidal pressure. However, sustained success through these measures is limited, indicating the need for drugs that specifically reduce HVR and prevent vicious pathogenic circles of worsening portal pressure and fibrosis in NAFLD. Improving the ability of LSECs to generate nitric oxide and restore the tonic control over HSCs is a major new indication for the use of statins in the management of chronic liver disease, including NAFLD.[119–122] In an animal model of steatohepatitis induced by a high-fat glucose-fructose diet and characterized by steatohepatitis without fibrosis but with increased PVP, administration of statins suppressed capillarization of LSECs, prevented activation of the procontractile phenotype in HSCs, halted the expression of genes associated with fluid shear stress, and reduced portal hypertension in these animals.[34] Statins exert their beneficial effects in NAFLD by multiple mechanisms that include interference with mevalonate synthesis and Rho/ROCK signaling, leading to diminished YAP/TAZ activity and preventing eNOS downregulation in the liver,[122] and enhanced hepatocellular expression of Kruppel-like factor 2 (KLF2), which has antifibrotic and vasoprotective effects.[119–121] Combined with their lipid-lowering activity, which is often desirable in liver-disease associated metabolic dysfunction, statins are poised to become standard therapy in the management of NAFLD.[123–126] In addition to statins, other medications currently used in clinical practice may have application in the management of NAFLD. In a recent report, administration of the sodium-glucose transporter-2 inhibitor empagliflozin significantly attenuated liver fibrosis in mice fed a choline-deficient, L-amino acid-defined, high-fat diet; this effect was associated with activation of the Hippo signaling pathway, preventing nuclear YAP translocation, and resulting in downregulation of profibrogenic genes in HSCs.[127]

Given the evidence that YAP/TAZ are involved in converting mechanocrine signals into pro-inflammatory, profibrotic, pro-angiogenic, and pro-oncogenic responses in NAFLD, these transcriptional regulators are a logical target for therapy in NAFLD. However, YAP/TAZ are also involved in a wide range of physiological mechanisms in the liver as well as other organs; as such, systemic blockade of YAP/TAZ for the management of NAFLD is likely to result in off-target effects.[128] For now, siRNA-mediated or pharmacological inhibition of YAP/TAZ in clinical practice is limited to oncological indications.[129] However, the potential benefits of cell-specific targeting of YAP/TAZ by genetic and pharmacological approaches has been reported in various *in vitro* and animal models using HSCs,[130,131] hepatocytes,[132] and macrophages[110] with improved cellular phenotypes, reversal of myofibroblast expansion, and reduced degrees of inflammation, extracellular matrix stiffness, and fibrosis. These findings are promising, but the feasibility of cell-selective YAP/TAZ inhibition in clinical practice will require additional pharmaceutical research.

Perspectives

The heterogeneity of NAFLD represents a remarkable need for understanding the pathogenesis and finding preventive and therapeutic approaches for this condition of increasing worldwide prevalence. Mounting evidence shows that steatosis is associated with biomechanical changes in hepatocytes and the surrounding sinusoidal architecture. Such changes can become early players in the development of steatohepatitis, fibrosis, and portal hypertension. The time-honored HVPG technique has provided essential guidance in advanced chronic liver disease by allowing better prediction of adverse clinical outcomes. HVPG has diminished accuracy in NAFLD, which may result from the persistence of intersinusoidal communications in this disease. Given that HVPG appears to underestimate the severity of portal hypertension in NAFLD and that subclinical portal hypertension appears to contribute to the pathogenesis of NAFLD, adjusted prognostic cutoffs for what constitutes 'clinically significant' portal hypertension in NAFLD are needed. We urge further studies on the onset, progression, and consequences of aberrant mechanosignaling in NAFLD. Specific targeting of mechanosensitive molecular regulators of procontractile, pro-inflammatory, pro-angiogenic, and profibrotic pathways may hold great promise for finding novel treatments for NAFLD.

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Conflict of interest

GB has been an associate editor of the *Journal of Clinical and Translational Hepatology* since 2020. EKM and PP have no conflict of interests related to this publication.

Author contributions

Study concept and design (GB), drafting of the manuscript (EKM, GB), critical revision of the manuscript for important intellectual content (EKM, PP, GB). All authors have made a significant contribution to this work and have approved the final manuscript.

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