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Review Article

Portal Hypertension in Nonalcoholic Fatty Liver Disease: From Pathogenesis to Clinical Practice

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Abstract

Portal hypertension in nonalcoholic fatty liver disease (NAFLD) mostly occur in cirrhotic stage. However, several experimental and clinical studies showed evidence of portal hypertension in NAFLD without significant or advance fibrosis. This early development of portal hypertension in NAFLD is associated with liver sinusoidal contraction by hepatocellular lipid accumulation and ballooning, which is also accompanied by capillarization and dysfunction of liver sinusoidal endothelial cells. Both of these impaired mechanical and molecular components can cause an increase in intrahepatic vascular resistance which lead to the increase of portal pressure in the absence of significant liver fibrosis. Extrahepatic factors such as insulin resistance and gut dysbiosis may also contribute to liver sinusoidal endothelial dysfunction and early portal hypertension in NAFLD. The clinical impact of early portal hypertension in NAFLD is still unclear. However, clinical tools for diagnosis and monitoring of portal hypertension in NAFLD are being investigated to predict high-risk patients and to guide therapy.

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Introduction

NAFLD is a growing problem in western countries as well as in Asian countries. The prevalence of NAFLD has shown an increasing trend globally. A systemic review and meta-analysis by Younossi *et al*.[1] estimated an overall 25.24% global prevalence of NAFLD. The highest prevalence was in the Middle East (31.79%) and South America (30.45%). Another systematic review and meta-analysis by Li *et al*.[2] focusing on Asian studies from 1999 to 2019, showed an increasing trend of NAFLD cases, from 25% in 1995–2005 to 34% in 2012–2017. A higher prevalence of around 51% was reported by a study in an urban population in Indonesia.[3] As NAFLD has a close association with multiple metabolic comorbidities, an updated definition using new terminology of metabolic dysfunction-associated fatty liver disease or MAFLD has been suggested. Using MAFLD criteria, a systemic review and meta-analysis by Liu *et al*.[4] showed that among overweight or obese patients, the estimated global prevalence of MAFLD was 50.7%.

Similar to viral or alcohol etiologies, NAFLD can progress to liver cirrhosis. Most patients are asymptomatic until complications of portal hypertension develop. A subset of NAFLD patients can progress to nonalcoholic steatohepatitis (NASH), which is a risk factor of cirrhosis progression and hepatocellular carcinoma (HCC) development.[5] According to survey data of the USA's National Health and Nutrition Examination Survey, there were 2.5-fold and 2-fold increases in the prevalence of NASH cirrhosis and NAFLD-associated advanced fibrosis, respectively, in 2009–2012 compared with 1999–2002.[6] Furthermore, in the USA, NASH and alcoholic liver disease are the most common etiologies among liver transplant waiting list registrant without any evidence of HCC.[7]

The reported prevalence of portal hypertension in compensated advanced liver disease (cALD) because of NASH, defined as a hepatic venous pressure gradient (HVPG) ≥5 mmHg, is 60.9%, while the prevalence of clinically significant portal hypertension (CSPH) defined as an HVPG ≥10 mmHg is 39.1%.[8] Mendes *et al*.[9] showed that complications related to CSPH, such as esophageal varices, splenomegaly, portosystemic encephalopathy, and ascites, were present in 25% of NAFLD patients, 88% of whom had already developed cirrhosis or advance fibrosis. Interestingly, it was reported that 12% of NAFLD patient with signs of portal hypertension had no significant fibrosis (F0–F2), but had severe-grade steatosis. In their retrospective analysis, Rodriques *et al*.[10] found that in 14 of 89 patients with CSPH, mostly were NASH or with nodular regenerative hyperplasia without cirrhosis but with perisinusoidal fibrosis and eight of them had hepatocyte ballooning. The presence of mild portal hypertension, an HVPG of 5–9 mmHg, has

Keywords: Portal hypertension; NAFLD; NASH; Metabolic.

Abbreviations: Ang II, angiotensin II; cALD, compensated advance liver disease; CSPH, clinically significant portal hypertension; eNOS, endothelial nitric oxide synthase; EUS-PPG, endoscopic ultrasound-portal pressure gradient; HFD, high-fat diet; HCC, hepatocellular carcinoma; HSC, hepatic stellate cells; HVPG, hepatic venous pressure gradient; IHVR, intrahepatic vascular resistance; LSEC, liver sinusoidal endothelial dysfunction; MAFLD, metabolic associated fatty liver disease; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NO, nitric oxide; NSBB, nonselective beta blocker; RCT, randomized controlled trial; SGLT2, sodium-glucose transport protein 2; SHAPE, Subharmonic aided pressure estimation; SSM, spleen stiffness measurement; SWE, shear wave elastography; TE, transient elastography; VPI, portal vein pulsatility index; vWF, von Willebrand factor.

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also been reported in a small number of noncirrhotic NAFLD patients, suggesting that steatosis *per se* also contributed to increased portal pressure.[11–13] The studies suggest that portal hypertension can develop early during the natural history of NAFLD before development of significant fibrosis or cirrhosis. In this review we look into the pathogenesis, diagnosis, and therapy of portal hypertension in NAFLD.

Pathogenesis

General pathogenesis of portal hypertension

Portal hypertension (PH) can be divided into three groups based on the site of resistance, which are presinusoidal, sinusoidal, and post-sinusoidal. Sinusoidal PH is the most common in advanced liver disease of any etiology. The primary change in sinusoidal PH is an increase in intrahepatic vascular resistance (IHVR). The IHVR is mainly caused by distortion of structural components such as fibrosis and regenerative nodules. The structural changes are accompanied by an increase in intrahepatic vascular tone because of endothelial dysfunction secondary to an imbalance of increased vasoconstrictors and decreased vasodilator stimuli. Furthermore, an increase in portal venous inflow because of splanchnic vasodilatation and increase in cardiac output further exacerbates the portal pressure. Increase in the portal pressure leads to formation of portosystemic collateral vessels and varices. The evidence suggest that angiogenesis also contributes to the formation of portosystemic collateral vessels.[14]

Liver steatosis contributes to the IHVR by sinusoidal compression and capillarization of endothelial cells

The main histopathological features of NAFLD include >5% steatotic hepatocytes with a centrilobular distribution, hepatocyte ballooning, lobular inflammation, and perisinusoidal fibrosis in NASH. With disease progression, fibrous septa, bridging fibrosis, and cirrhosis will eventually develop. Several clinical studies have shown a correlation between steatosis grade and portal pressure in NAFLD patients, and the data suggest that an early increase in portal pressure can occur without any evidence of significant fibrosis.[9,11,12] Steatotic changes in NAFLD can contribute to increased portal pressure by sinusoidal compression and reduced vascular compliance, as shown by measurement of portal venous pulsatile flow and flow velocity. Several studies have found a negative correlation between portal venous pulsatility and flow velocity with steatosis and fibrosis grade in NAFLD patients.[15–17] Using advanced tools such as intravital microscopy, Davis *et al*.[18] was able to show in real time that the sinusoidal diameter was significantly lower around steatotic hepatocytes in high-fat diet-fed C57BL/6 mice. Using a methionine choline-deficient diet to induce NASH in C57BL/6J mice, McCuskey *et al*.[19] reported a significant narrowing of the sinusoid lumen, especially in the centrilobular region in as early as 3 weeks after feeding began.[19] Morphological changes in liver sinusoidal endothelial cells (LSEC) in early NAFLD/NASH have also been reported. In healthy livers, LSECs are fenestrated, porous, and without a basement membrane. Miyao *et al*.[20] reported that as early as 1 week after starting a choline-deficient L-amino acid defined diet (early steatosis model) and 22 weeks after a high-fat diet in a mice (early NASH model), there was a capillarization or defenestration with reduction in porosity of the LSEC followed by Kupffer cell and HSC activation. In human NAFLD, using CD31 as a marker of LSEC capillarization, increased expression of CD31 was detected in the centrilobular area (zone 3).[21] Excessive dietary lipid or glucose may trigger LSEC capillarization in NAFLD. An *in vitro* study showed that when primary human LSECs were treated with ox-LDL, the fenestral diameter and porosity of LSECs were reduced, and the responses were mediated via the LOX1/ROS/NF-kB signaling pathway.[22] The defenestration of LSECs may then promote liver steatosis, creating a vicious cycle in NAFLD disease progression. Plasmalemma vesicle-associated protein (PLVAP), is an endothelial-specific integral membrane glycoprotein required for the formation of endothelial fenestrae. Mice deficient in PLVAP showed a reduced number of LSEC fenestration with impaired passage of chylomicron remnant from sinusoidal into hepatocytes. Lack of chylomicron remnants by the hepatocytes might then stimulate *de novo* lipogenesis or endogenous cholesterol biosynthesis.[23] That, in turn, further augments liver steatosis and an increase in the IHVR. Furthermore, restoration of LSEC porosity by returning to a normal diet or statin administration may reduce portal pressure.[24]

Liver steatosis contributes to IHVR through sinusoidal endothelial dysfunction

Sinusoidal endothelial dysfunction refers to the inability of LSEC to expand in response to the shear stress of blood flow. It is characterized by diminished bioavailability of vasodilators such as nitric oxide (NO) and increased synthesis of vasoconstrictors such as endothelin-1 (ET-1), resulting in increased intrahepatic vascular resistance (IHVR). Early NAFLD is associated with LSEC dysfunction and increased oxidative stress in the absence of inflammation or fibrosis.[25] Pasarin *et al*.[26] showed that when Wistar Kyoto rats were fed a diet rich in saturated fat for 1 month, the *in vivo* portal pressure was increased and the Akt-dependent endothelial nitric oxide synthase (eNOS) phosphorylation and NOS activity were decreased in the absence of liver inflammation and fibrosis. There was also a decreased response to vasodilator acetylcholine in isolated liver perfusion experiments. Similar results were also reported by Francque *et al*.[27] in methionine choline-deficient diet-fed rats. They showed that the liver expression of vasoconstrictor ET-1 was significantly increased. In healthy LSECs, NO keeps Kupffer cells and hepatic stellate cells (HSC) in a quiescent state. LSEC dysfunction with diminished NO bioavailability can lead to sinusoidal contraction by activated perisinusoidal HSCs and increased IHVR and portal pressure.[14] Diminished NO may in turn aggravate liver steatosis and further increase IHVR. NO can decrease liver steatosis by s-nitrosylation of very long chain acyl coenzyme A dehydrogenase, an enzyme in the liver that catalyzes the first committed step in fatty acid β-oxidation.[28] NO is also involved in fatty acid synthesis by controlling mitochondria enzymes, such as citrate synthase and NADH–cytochrome c oxidoreductase (KI+III) and inhibition of glycerol-3-phosphate acyltransferase (GPAT).[29.30] In addition to NO, hedgehog signaling, the expression TGFβ and VEGF by dysfunctional LSEC are also increased and augment HSC activation and sinusoidal contraction.[31]

Change of liver steatosis is associated with splanchnic vasodilatation

Francque *et al*.[32] showed that in Wistar rats fed a methionine choline-deficient diet, steatosis induced portal hypertension with an increase in mesenteric arterial and portal venous flow, arterial low responsiveness to vasoconstrictors, and decreased mean arterial blood pressure, indicat-

Table 1. NAFLD animal models with portal hypertension

Author (year)	Animal	Histopathology	Note
Dietary model			
Francque *et al*., 2012[27]	Male Wistar rats methionine choline-deficient diet for 4–8 weeks	Severe steatosis without marked inflammation & fibrosis	No feature of metabolic syndrome. Increased portal pressure
Pasarin *et al*., 2012[26]	Male Wistar Kyoto rats. Cafeteria diet (65% saturated fat) for 1 month	Steatosis without inflammation and fibrosis	With features of metabolic syndrome. Increased trend of portal pressure (not significant)
Garcia *et al*., 2018[34]	Male Sprague Dawley rats. High-fat high glucose-fructose diet (30% fat mainly saturated) for 8 weeks	Steatohepatitis with mild or absent fibrosis	With features of metabolic syndrome. Increased portal pressure
Transgenic mice			
Klein *et al*., 2019[35]	Transgenic TG (mRen2)27(Ren2) hypertensive rats with elevated tissue Angiotensin II	Renin induced liver injury. Steatohepatitis and mild fibrosis	Hypertensive rats, nonobese. Renin induced portal hypertension
Combined			
Cremonese *et al*., 2020[36]	TGR (mREN2)27 rats with Western diet for 2 or 4 weeks	Steatohepatitis and fibrosis	Obese. Increased portal pressure

NAFLD, nonalcoholic fatty liver disease.

ing the presence of splanchnic vasodilation and hyperdynamic circulation.[32]

Extrahepatic factors

Insulin resistance is associated with NAFLD through increased adipose tissue lipolysis, with the increase of free fatty acid delivery to hepatocytes. Insulin resistance may also play a role in LSEC dysfunction and contribute to IHVR and portal pressure. Pasarin *et al*.[33] in a study using a rat model of simple steatosis, showed that dose-dependent sinusoidal endothelium vasodilation was blunted in response to insulin in rats fed an HFD. Treatment with metformin, an insulin sensitizer, restored insulin-enhanced endothelium vasodilatation in the livers of the HFD-fed rats. In their analysis, Francque *et al*.[13] showed that the homeostatic model assessment for insulin resistance (HOMA-IR), as a parameter of insulin resistance, was significantly higher in NAFLD patients with PH than without PH, independent of liver steatosis and visceral fat.[13]

Gut dysbiosis has a role in NAFLD disease progression, including the development of portal hypertension. In rat model of NASH, 8 weeks of high-fat and high glucose-fructose feeding induced histological NASH without fibrosis, accompanied by endothelial dysfunction and increased portal pressure. In that rat model of NASH, intestinal microbiome diversity was reduced with significant increase in Firmicutes and decrease in Bacteroidetes. Furthermore, fecal transplantation from control rats reduced portal pressure and IHVR and improvement of endothelial dysfunction.[34]

Animal models

Several animal models have been used to study portal hypertension in NAFLD (Table 1).[26,27,34–36] The models show that portal pressure increases early in NAFLD or NASH in the absence of advanced fibrosis or cirrhosis. Unlike common animal models of cirrhotic portal hypertension, the presence of hyperdynamic circulation and increased portal vein inflow were not consistent evident in diet-induced model.

Clinical aspect

Diagnosis

Currently, hepatic venous pressure gradient (HVPG) is considered the main diagnostic tool for measuring the PPG and is considered the gold standard for measurement of CSPH.[37] HVPG is the difference between wedged and free hepatic venous pressure. Limitations of HVPG are invasiveness and availability limited to specialized centers. The reported prevalence of portal hypertension, defined as HVPG >5 mmHg, was lower in nonobese and obese NASH compared with other etiologies of compensated advanced chronic liver disease.[8] There was a weaker correlation between wedged hepatic venous pressure and portal pressure in decompensated NASH cirrhosis compared to alcohol or viral-related cirrhosis, suggesting that HVPG might underestimate the portal venous pressure [38] That might be associated with the presence of presinusoidal hypertension or the heterogenous distribution of steatosis and fibrosis within the liver parenchyma. Another study showed that portal hypertension-related decompensation was associated with lower HVPG levels in advanced NAFLD.[39] In NASH cirrhosis, a decrease in HVPG after nonselective beta blocker was not predictor of decompensation or long-term transplant free survival.[40] Therefore, routine HVPG measurement may not be an ideal tool for detection and monitoring of portal hypertension in NAFLD or different HVPG cutoff level should be established for NAFLD.

Some noninvasive tools have been developed for the detection of CSPH through measurement of liver or spleen tissue stiffness. According to the revised Baveno VII criteria, a combination of liver stiffness measurement by transient elastography (TE) ≤15 kPa and platelet count ≥150×10^9/L) have sensitivity and negative predictive values of >90% for ruling out CSPH in most etiologies of compensated advanced liver diseases (cALD, TE >10 kPa), including NASH. In viral- and alcohol-related cALD and also in nonobese NASH-related cALD, using a higher cutoff of TE ≥ 25kPa, we can rule in CSPH with specificity and positive predictive value >90%) but not in obese NASH.[37] While Baveno VI

criteria (TE <20 kPa + platelet count >150×10^3/mm^3) can be used to rule out high-risk esophageal varices.[41] However, obesity can overestimate liver stiffness measurement using TE, and obese patients have a lower prevalence of CSPH despite high liver stiffness.[37,42]

Splenomegaly in portal hypertension is associated with changes in spleen stiffness due to splenic congestion and spleen tissue hyperplasia and fibrosis. Spleen stiffness measurement (SSM) using several techniques such as TE, SWE, or MRE could predict portal hypertension and the presence of esophageal varices or high-risk varices.[43] In cALD patients of various etiologies, Colecchia *et al*.[44] showed that the combined model of Baveno VI criteria + SSM ≤46 kPa could rule out high-risk esophageal varices with high sensitivity and negative predictive value. A spleen-dedicated stiffness measurement, using a 100 Hz specific TE probe, has recently been shown to be more accurate for predicting varices or high-risk varices in chronic liver disease,[45,46] but further studies are needed to validate the findings in NAFLD/NASH. In early NAFLD/NASH, IHVR may not be accompanied by the splenomegaly and concomitant increase of splanchnic inflow. Therefore, the use of SSM for predicting portal hypertension in NAFLD may be limited to patients with advanced liver disease or cirrhosis.

Several Doppler ultrasound (US) parameters are associated with portal hypertension in chronic liver disease. However, definitive parameters for accurate prediction of portal hypertension in NAFLD are lacking. In NAFLD, steatosis grade is correlated with reduced portal venous blood velocity (lower peak maximum–minimum velocity, mean flow velocity, and portal vein pulsatility index (VPI) and compensatory increase of hepatic arterial flow (lower hepatic artery resistive index).[15,16,47,48] Using routine Doppler US**,** portal VPI can be calculated as (Vmax – Vmin) / Vmax, where Vmax is the maximum and Vmin is the minimum pulsed-wave Doppler ultrasound–estimated velocity of portal venous blood. Baikpour *et al*.[15] showed that lower portal vein pulsatility index (VPI) was associated with higher fibrosis stage in NAFLD and could be used to predict high-risk NAFLD (with ≥F2 stage liver fibrosis). Further study of VPI for predicting and monitoring portal hypertension in NAFLD is still needed.

Several novel methods have been developed to diagnose portal hypertension, such as subharmonic aided pressure estimation (SHAPE) using contrast enhanced ultrasonography, magnetic resonance (MR) methods, and the endoscopic ultrasound-portal pressure gradient (EUS-PPG). Gupta *et al*.[49] compared SHAPE to HVPG to diagnose portal hypertension. In 125 patients, 18% with NASH and most with chronic hepatitis C, they found that SHAPE had 95% accuracy for detecting CSPH or HVPG ≥12 mmHg.[49] MR elastography (MRE) has been studied in NAFLD. A multicenter retrospective study found that liver stiffness assessed by MRE had an area under the curve of 0.707 (95% CI: 0.511–0.902) for differentiating decompensated NAFLD-related cirrhosis, defined as ascites, hepatic encephalopathy or esophageal variceal bleeding, from compensated cirrhosis.[50] Recently, EUS-guided direct measurement of portal vein and hepatic vein pressure under the guidance has been developed. The mean difference of portal vein and hepatic vein pressure is then reported as the PPG. A human pilot study showed excellent correlation between EUS-PPG and HVPG (r=0.923).[51] The potential use of EUS-PPG for monitoring portal hypertension after endoscopic gastric plication in NASH-related cirrhosis has also been reported.[52]

Endothelial dysfunction contributes to intrahepatic resistance in NAFLD, and von Willebrand factor (VWF-Ag) is considered a marker of endothelial dysfunction. A retrospective study of 236 cirrhosis patients with various etiologies including NASH (12.3%) evaluated the diagnostic performance of VWF-Ag for predicting CSPH. At a cutoff of >226, VWF-Ag had an area under the curve (AUC) of 0.79 (95% CI: 0.72–0.87), a sensitivity of 76%, and a specificity of 71%. Using the VWF-Ag/thrombocyte ratio (VITRO score), there was the AUC increased to 0.86 (95% CI: 0.81–0.91), with a sensitivity of 80% and a specificity of 70% at a cutoff of >1.58 in predicting CSPH. The combination of TE and VITRO score further improved prediction for CSPH, with an AUC of 0.96 (95% CI: 0.91–0.98), a sensitivity of 91%, and a specificity of 93% at a cutoff of >0.71.[53]

Therapy

Lifestyle interventions including diet and physical exercise to reduce body weight is considered the first-line treatment for obese NAFLD. A target of 7–10% weight loss is associated with improvement in liver histology, including fibrosis. Obesity is a predictor of decompensation in compensated cirrhotic patients with various etiologies independent of HVPG and albumin or treatment with a beta blocker.[54] In the SportDiet study, a pilot study involving overweight/obese patients with compensated cirrhosis and an HVPG ≥ 6 mmHg, Berzigotti *et al*.[55] showed that a 16 week individualized hypocaloric normal-protein diet and 60 min/week of moderate exercise significantly reduced HVPG by 10–20%. The reduced HVPG was significantly associated with body weight loss. There were no episodes of decompensation during the short-term intervention, suggesting that calorie restriction while maintaining protein intake with moderate exercise is safe in compensated cirrhosis. Further study is needed to evaluate the long-term efficacy, feasibility, and safety of lifestyle interventions in cALD or cirrhosis.

Nonselective beta blockers (NSBBs) like propranolol, nadolol, or carvedilol are recommended in compensated cirrhosis with CSPH to prevent clinical decompensation and improve survival. NSBB reduces the risk of variceal bleeding not only by reducing the portal pressure, but also by improving intestinal permeability and reduced bacterial translocation.[56] Carvedilol is the preferred NSBB in compensated cirrhosis because of a greater reduction of portal pressure. Carvedilol does not adversely affect insulin sensitivity, glucose and lipid profile, which should be considered in NAFLD patients with metabolic comorbidities.[57]

Statin use is common in NAFLD with dyslipidemia or high cardiovascular risk. Several nonrandomized, controlled studies suggest beneficial effect of statin on NASH resolution and liver fibrosis. In an early NASH model with portal hypertension, statins decreased portal pressure by inducing recovery of LSEC capillarization and regression of HSC activation by upregulation of the hepatic endothelial expression of Kruppel-like factor 2, an endothelial transcription factor. Statins also decrease hepatic stellate cell activation by inhibition of RhoA / Rho-kinase signaling.[58] A study by Zafra *et al*.[59] showed that acute administration of 40 mg simvastatin in cirrhotic patients increased hepatic blood flow, decreased hepatic resistance, and increased NO products in hepatic venous blood.[59] That proof-of-concept study was followed by several randomized controlled trials (RCTs) that evaluated the effect of statins on HVPG levels. A meta-analysis of six RCTs showed that statin use was associated with reduction of portal hypertension >20% of baseline or <12 mmHg) at 1 month (RR=2.01; 95% CI: 1.31–3.10) but the difference was not significant at 3 months (RR=3.76; 95% CI: 0.36–39.77).[60] None of the studies specifically looked at NAFLD-related cirrhosis. Because of potential liver and muscle toxicity, we should be cautious on the use of statins in decompensated cirrhosis and it should be avoided Child-Pugh C patients.

Obeticholic acid, a farnesoid X receptor agonist, has been shown to improve the histological features of NASH.[61] In a

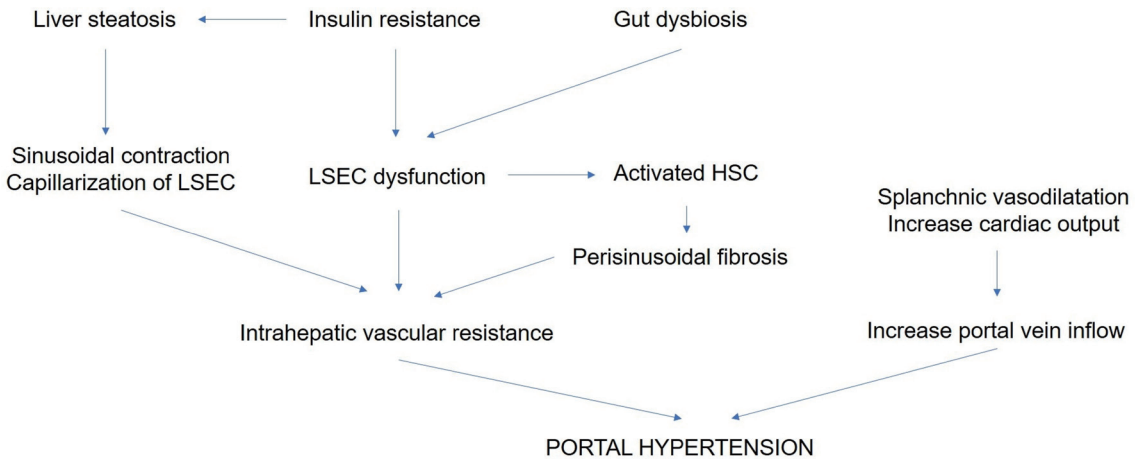

Fig. 1. Theoretical framework of portal hypertension in NAFLD. LSEC, liver sinusoidal endothelial cell; HSC, hepatic stellate cell; NAFLD, nonalcoholic fatty liver disease.

rat model of cirrhotic portal hypertension, it lowered IHVR associated with increased eNOS activity, down-regulation of Rho-kinase, upregulation of dimethylarginine dimethylaminohydrolase-2, and reduced asymmetric-dimethylarginine, an eNOS inhibitor.[62,63]

Sodium-glucose transport protein 2 (SGLT2) inhibitors are a class of antidiabetic agents that have also been studied in NAFLD or NASH. SGLT2 inhibitors reduce transaminase levels and improve liver fat content and body composition in NAFLD patients with type 2 diabetes mellitus.[64] SGLT2 inhibitors target the pathophysiology of portal hypertension. SGLT2 blockade inhibits glucose and sodium reabsorption in the proximal renal tubule, resulting in an increase in sodium delivery to the macula densa. Consequently, both renin secretion and angiotensin II level are reduced. SGLT2 inhibitors also reduce sympathetic nervous activity.[65] A recent observational study showed that SGLT2 inhibitors were well tolerated in a small sample of cirrhotic patients and type 2 DM.[66] Further studies are needed to evaluate the therapeutic effectiveness of SGLT2 inhibitors in portal hypertension.

The renin angiotensin system (RAS) is associated with disease progression in NAFLD. Experimental data has indicated that angiotensin II (Ang II) generation was associated with *de novo* lipogenesis, mitochondrial dysfunction, reactive oxygen species generation, pro-inflammatory cytokine production, and HSC activation.[67] Steatohepatitis with portal hypertension developed in transgenic TGR (mREN2)27 rats overexpressing mouse renin. Stimulation of angiotensin II type 1 receptor in HSCs by Ang II was found to induce fibrosis and portal hypertension via Janus kinase-2.[35,36] Clinical evidence of the therapeutic effectiveness of RAS inhibitors on the development of portal hypertension in NAFLD is still limited**.** However, several observational studies found a significant association of RAS inhibitors and disease regression in NAFLD patients with obesity or type 2 diabetes.[68,69]

Conclusion

Experimental and clinical evidence suggests that portal hypertension develop early in NAFLD through an increase in IHVR. Both the mechanical component of liver steatosis and the molecular component of liver sinusoidal endothelial dysfunction together with insulin resistance and gut dysbiosis in NAFLD augment IHVR. Furthermore, liver sinusoidal endothelial dysfunction activates HSCs and further augments IHVR via perisinusoidal fibrosis (Fig. 1). HVPG is recommended as the gold standard for diagnosing portal hypertension, but in advanced NAFLD, HVPG might underestimate portal pressure, and decompensation can still occur in a small number of patients with mild HVPG. Noninvasive liver stiffness measurement is considered an alternative to predict CSPH in NAFLD, but obesity might obscure the impact of liver stiffness on portal venous pressure. Further validation is needed for new biomarkers or other noninvasive tools specifically in NAFLD. Lifestyle modification is the first-line therapy for NAFLD and also to control comorbidities, with early data suggesting that body weight loss is also associated with reduction of HVPG levels. Similar to other etiologies, NSBB is also recommended to prevent decompensation and improve survival in NAFLD with CSPH, and statins may decrease portal venous pressure in addition to improvement of dyslipidemia and cardiovascular risk in NAFLD. Future drug development for NAFLD should also address portal hypertension as an important endpoint.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (CRAL), analysis and interpretation of data (SHHN, CRAL), drafting of the manuscript (SHHN, CRAL), critical revision of the manuscript for important intellectual content (SHHN, CRAL), and administrative, technical, or material support, study supervision (CRAL).

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