Invited Review

Portal Hypertension in NAFLD: Challenges and Perspectives

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Abbreviation List: NAFLD, non-alcoholic fatty liver disease; NAFL, non-alcoholic fatty liver; NASH, non-alcoholic steatohepatitis; MAFLD, metabolic dysfunction-associated fatty liver disease; PHT, portal hypertension; HVPG, hepatic vein pressure gradient; PVP, portal venous pressure; FHVP, free hepatic vein pressure; WHVP, wedged hepatic vein pressure; IHVR, increased intrahepatic vascular resistance; CSPH, significant portal hypertension; LSECs, Liver sinusoidal endothelial cells; HSCs, hepatic stellate cells; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; BMI, body mass index; EUS-PPG, endoscopic ultrasound-guided pressure measurement; FXR, farnesoid X nuclear receptor; PPAR, peroxisome proliferator–activated receptor.

Authors' contributions

(I) Conception and design: L Miao, MH Zheng, X Qi; (II) Collection and assembly of articles: L Miao; (III) Manuscript writing, intellectual input, critical evaluation and proofreading: All authors; (IV) Final approval of manuscript: All authors.

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Abstract

Non-alcoholic fatty liver disease (NAFLD) has become the most common chronic liver disease worldwide. NAFLD-related cirrhosis is often complicated with portal hypertension (PHT). Recent evidence showed that portal venous pressure starts to rise in the early stages of NAFLD, even in absence of advanced fibrosis or cirrhosis. However, the precise pathological mechanisms of this process are still poorly understood. Lipid accumulation, hepatocellular ballooning, sinusoidal endothelial cell dysfunction, capillarization, micro-thrombosis, increased angiogenesis and fibrosis may all play key roles in the development of increased portal venous pressure in NAFLD. Old measurements of PHT are invasive and impractical in non-cirrhotic NAFLD individuals, and may also underestimate its severity. Thus, novel non-invasive and more accurate measurements, including new serum biomarkers and scoring models and imaging techniques (such as ultrasonography, elastography, or magnetic resonance imaging) are urgently needed. With the increasing morbidity, challenges in the prevention and management of PHT in NAFLD are unprecedented. This review article aims to briefly discuss these challenges, and also summarize the mechanisms, diagnosis and emerging therapies for PHT, in people with NAFLD.

Key words: non-alcoholic fatty liver disease, metabolic dysfunction-associated fatty liver disease, portal hypertension, novel non-invasive measurement.

Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the commonest causes of chronic liver disease affecting up to 25-30% of the global population.[1-3] The histological spectrum of NAFLD ranges from non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis. [4] 10%~25% of patients with NASH progress to cirrhosis within 8~14 years, and the risks of developing portal hypertension (PHT), liver failure and hepatocellular carcinoma are significantly increased.[5] Increasing evidence suggests that patients with NAFLD may develop increased portal pressure even in the early stages of NAFLD when advanced fibrosis or cirrhosis are absent.[6-10] Recent evidence also suggests that increased portal venous pressure (PVP) can promote fibrosis development in NAFLD. [11,12] These data suggest that increased PVP is not just a consequence of NAFLD, but may also contribute to the pathogenesis of NAFLD.[8] However, the underlying pathophysiological mechanisms for portal hypertension (PHT) remain incompletely understood.

Measurement of hepatic venous pressure gradient (HVPG) is the most commonly used method for invasively detecting PHT, and HVPG is calculated as the difference between free hepatic vein pressure (FHVP) and wedged hepatic vein pressure (WHVP).[5,13] However, recent observations suggest that HVPG may underestimate the true PVP in patients NAFLD. [9,14] Therefore, this gold standard invasive method might not be accurate for assessing PHT in people with NAFLD. Thus, there are currently a

large amount of questions and challenges that arise in the detection of PHT in this patient population. These questions include: a) what is the underlying pathological mechanism? b) How does the increase in portal pressure contribute to NAFLD progression? c) How can subclinical portal hypertension be detected? d) How should patients with PHT be managed? e) What treatment is appropriate and what candidate drugs are available?

This review article briefly discusses and summarizes recently discovered mechanisms, novel measurements for assessment and therapies for PHT, and the review also provides our perspective as to how best to address these coming challenges.

1. Challenge in pathophysiology: the pathological mechanisms are unclear

The main pathophysiological mechanisms of PHT in NAFLD-related cirrhosis appear to be similar to other aetiologies of cirrhosis, such as viral hepatitis, autoimmune liver disease and schistosomiasis. [6] The increase in portal pressure is mainly due to increased intrahepatic vascular resistance (IHVR). [7] However, in contrast to other aetiologies, clinically significant portal hypertension (CSPH) may develop early in the natural history of NAFLD, even before the development of advanced fibrosis or cirrhosis. Changes in hepatic blood flow may also occur during the early stages of hepatic fibrosis in NAFLD patients, because of impaired of outflow in liver sinusoids.[15] Several mechanisms that may impair sinusoidal hemostasis and contribute

to the rise of IHVR in NAFLD are schematically illustrated in **Figure 1.**

1.1 Hepatocellular enlargement and sinusoidal narrowing

Hepatocellular enlargement, caused by lipid accumulation (steatosis) and ballooning, is thought to play a key role in the development of both increased IHVR and PHT in the early stages of NAFLD. This process of hepatocellular enlargement reduces the space of liver sinusoids hindering circulation from sinusoids to liver cells, because the diameter of swollen hepatocytes is enlarged about 1.5-2 times and cause sinusoidal narrowing, which may induce sinusoidal endothelial cell dysfunction. [8,16] Furthermore, steatotic hepatocytes can induce lipotoxicity, which affects several cellular signaling pathways, and induces reactive oxygen species formation and endoplasmic reticulum stress.[17] Furthermore, the ballooned hepatocytes, as a characteristic feature of lipotoxicity-induced NASH, may activate the sonic Hedgehog signaling pathway, which promotes increased liver fibrogenesis.[18]

1.2 Sinusoidal endothelial cell dysfunction

A disrupted balance between vasodilator and vasoconstrictor products of sinusoidal vessels has been observed in the early stages of NAFLD.[19-21] Liver sinusoidal endothelial cells (LSECs) play a key role in both sensing and regulating hepatic blood flow, not only regulating portal and hepatic vascular resistance, but also inhibiting the activation of Kupffer cells and hepatic stellate cells (HSCs).[22] Endothelial nitric oxide synthase (eNOS) is the key vasodilator that regulates sinusoidal blood flow, and

LSECs are the main source of nitric oxide (NO). [22] In an experimental study, Wistar Kyoto rats were fed with cafeteria diet (65% of fat) to develop liver steatosis and metabolic syndrome features. [8] Later, the cafeteria diet-fed rats developed higher in vivo hepatic vascular resistance and greater portal perfusion pressure. Because the decrease of endothelium-dependent vasodilation is due to a decrease of eNOS phosphorylation and NOS activity, the results of this experimental study suggest that liver steatosis may impair function of LSECs and limit NO release, causing endothelial cell dysfunction in the early stages of NASH.[8] HSCs, located in the space of Disse, are inhibited by NO release from LSECs in healthy livers.[23] HSCs are activated by liver injury, and cause contraction of the sinusoids and decrease sinusoidal blood flow. Kupffer cells may also regulate liver injury, inflammation and fibrosis, and participate in the pathogenesis of NAFLD.[24] Kupffer cells are also activated by injured hepatocytes and activate-HSCs.[23] Activated Kupffer cells release multiple chemokines, eicosanoid derivatives and reactive oxygen species that may further aggravate liver inflammation.[25]

1.3 Sinusoidal capillarization, fibrosis and angiogenesis

Sinusoidal capillarization of LSEC, as an early manifestation of endothelial dysfunction in NAFLD, happens before the synergistic activation of Kupffer cells and HSCs.[26] The capillarization of LSEC that leads to sinusoidal dysfunction may promote liver steatosis by blocking the transfer of chylomicron remnants from portal vessels to hepatocytes, potentially stimulating hepatic cholesterol and triglyceride

synthesis. [27] In response to liver injury, LSECs undergo gradual defenestration by forming a peri-sinusoidal basement membrane with deposits of extracellular matrix proteins, such as fibronectin and laminin, in the space of Disse. Capillarization impairs hepatic perfusion and induces chronic hypoxia, which may aggravate steatosis and promote the progression of NAFLD to NASH and cirrhosis, leading to activation of hypoxia-inducible factors and increased transcriptional gene regulation of angiogenesis and proliferation.[28-30] Increasing evidence suggests that sinusoidal capillarization and angiogenesis play a key role in the progression of NAFLD. Vascular endothelial growth factor is the key regulator in this process, which is activated by hypoxia inducible factor and may further promote fibrosis development.[16] Chronic hypoxia activates HSCs, collagen begins to accumulate in the space of Disse and with capillarization and hypoxia development, fibrous bridging occurs near the hepatic sinusoids, eventually leading to the formation of cirrhotic nodules.[28] Moreover, it is known that fibrosis in NAFLD usually begins to develop in the intercellular space around the central vein and in the peri-sinusoidal area of zone 3.[4,31] This fibrosis pattern is different from other forms of chronic liver disease, and potentially causes PHT before patients with NAFLD develop overt cirrhosis.[31]

1.4 Cell adhesion and micro-thrombosis

In NAFLD, enlarged hepatocytes (caused by steatosis and ballooning) initially reduce sinusoidal flow in zone 3, and this effect then spreads across the entire lobule, thereby resulting in increased shear stress in LSECs. Furthermore, LSECs respond by

facilitating adhesion of blood cells. When the sinusoids narrow enough to trap blood cells such as leucocytes, the effect usually occurs first in the centri-lobular region, constraining the sinusoidal space and exacerbating the negative impact of steatosis.[32]

It has been hypothesized that micro-thrombosis could also increase IHVR in NAFLD. In a cohort of obese/overweight individuals, it was found that patients with biopsy-proven NASH had higher plasma plasminogen activator inhibitor-1 (PAI-1) concentrations than those with normal livers ($P < 0.001$). [33] Levels of PAI-1 increased significantly with the histological severity of NAFLD, whereas other coagulation factors were unaltered. An increase in fibrinogen, factor VIII, and von Willebrand factor and decrease in anti-thrombin III were correlated with metabolic features, including fasting C-peptide and waist circumference, but not with liver histology. This finding might, in part, explain why micro-thrombosis and PHT are associated with NAFLD.[33]

1.5 Microbiota and gut-liver axis

Gut microbiota and bacterial translocation may also play an important role in the development of NAFLD-related cirrhosis and its complications, such as PHT, spontaneous bacterial peritonitis and hepatic encephalopathy.[34-36] Gut microbiota products, such as secondary bile acids, may affect intestinal permeability and PHT, mainly through the farnesoid-X receptor (FXR) and the G protein-coupled bile salt receptor-1, which mediate anti-steatotic, anti-inflammatory and anti-fibrotic effects. In

contrast, cirrhosis and PHT affect gut microbiota and increase translocation.[36] Therefore, pharmacological regulation of the gut-liver axis may be an effective strategy for the prevention and management of NAFLD-related PHT, although this needs to be tested in randomized clinical trials.

2. Challenge in the detection and assessment of PHT

In order to assess the degree of PHT, PVP is traditionally measured by an invasive method like HVPG that is costly and performed only in some specialized centers. [13] But there have been significant efforts to find novel diagnostic approaches for the assessment of PVP and replace traditional HVPG measurements, such less invasive or non-invasive techniques to indirectly estimate PVP (**Figure 2)**. But none of these non-invasive techniques have entered clinical practice as a substitute of HVPG with the exception of endoscopic ultrasound-guided pressure measurement (EUS-PPG).[37,38]

2.1 Shortage and inaccuracy of conventional measurements

Hepatic vein wedge pressure (WHVP) represents the hepatic sinusoid pressure, which indirectly reflects portal vein pressure in PHT.[13] Clinical signs of PHT maybe present in about 25% of patients when patients have advanced fibrosis or cirrhosis.[6] However, a recent study involving 40 patients with NAFLD-related cirrhosis treated with a trans-jugular intrahepatic portosystemic shunt in three European centers showed that discrepancies in the measurements of WHVP and portal pressure occurred in up to 15% of patients, thus suggesting that PVP could be significantly underestimated by

WHVP. These data suggest that WHVP in patients with NAFLD-related cirrhosis is not as accurate as in cirrhotic patients that is due to other aetiologies.[14]

HVPG is defined as the difference between WHVP and FHVP, and can better reflect PVP.[13] As early as 2005, the Baveno IV consensus proposed that monitoring HVPG can identify the beneficiaries of non-selective beta blockers.[39] The new Baveno VII consensus pointed out that HVPG ≥ 10 mmHg is still the gold standard for the diagnosis of clinically significant portal hypertension (CSPH).[13,40,41] This consensus also indicated that in patients with NAFLD-related cirrhosis, although an HVPG >10 mmHg is strongly associated with the presence of clinical signs of PHT such as esophageal varices[42], these signs can also be present in a small proportion of patients with HVPG values <10 mmHg.[13] In an observational study investigating the prevalence of, and the non-invasive predictors of PHT, in 354 patients with NAFLD, the authors found that signs of CSPH were present in about 25% of these patients at the time of diagnosis of NAFLD; and most of these patients had advanced fibrosis or cirrhosis. However, these authors also found that PHT could occur in a small proportion of patients with mild, or no fibrosis, and was associated with the extent of steatosis.[6] A discrepancy was found between HVPG and portal pressure gradient (PPG) in non-cirrhotic NAFLD.[14] A retrospective analysis showed that about 15% of patients with CSPH, whose HVPG was higher than 10 mmHg, did not have cirrhosis[7]. In two phase 2b, placebo-controlled trials of simtuzumab (combined) that involved a total of 475 individuals with NASH with bridging fibrosis or compensated cirrhosis

(F3 to F4 stage); the authors found that 7 patients with subclinical PHT (median HVPG, 7.5 mmHg; range, 4.0–9.5 mmHg) without cirrhosis developed the symptoms of decompensation, and patients with higher HVPG at baseline had the greater increase in HVPG over time.[43] All these observations suggest that HVPG may underestimate fibrosis stage and severity of NAFLD. Actually, the effects and manifestations of subclinical PHT, which was defined as HVPG ≥ 5 mmHg and HVPG□ 10mmHg, on the natural course of NAFLD are not well understood, and the effects of subclinical PHT may have been largely overlooked[44]. That said, measurements of WHVP and HVPG are invasive, and require technical expertise from the operator and equipment. Thus, these measurements are rarely used in clinical practice.

2.2 The novel invasive and non-invasive measurements

As shown in **Figure 2,** the EUS-PPG is one of the novel techniques that can directly measure the portal and hepatic vein pressure.[37] Theoretically, EUS-PPG is more accurate than WHVP and HVPG in patients with pre-sinusoidal PHT, because WHVP and HVPG tend to underestimate PVP in these patients. This ultrasound technique is suitable for patients with advanced NAFLD and for other patients with indications for endoscopy (e.g., surveillance of esophageal and gastric varices, portal hypertensive gastropathy screening, EUS-guided liver biopsy, or duodenal mucosal analysis by confocal endomicroscopy). Hence, other traditional techniques for portal pressure measurement that included intra-splenic puncture, trans-hepatic portal catheterization,

operative portal pressure measurements, and umbilical vein catheterization are now being gradually replaced. Thus, novel non-invasive measurements that accurately measure PVP in a safe and simple way are urgently needed.[38] Novel non-invasive measurements (**Figure 2)**, such as serum markers [45-50], the subharmonic-aided pressure estimation based, dynamic contrast-enhanced ultrasonography, liver and spleen stiffness elastography,[51-56] based on recent doppler ultrasound and imaging technology[57-61], contrast-enhanced computer tomography, [62,63] and multi-parametric MRI [64,65] require further investigation to test their utility in the investigation of PHT in NAFLD.

3. Challenge in prevention and management: there is no specific therapy

To date, there are no specific pharmacotherapies for NAFLD-related PHT. In non-cirrhotic NAFLD, prevention is usually the best therapeutic strategy, so lifestyle modifications are still the first-line recommended treatment.[42,66] In cirrhotic NAFLD-related PHT, current drugs used for management of PHT and its complications are substantially similar to those used for cirrhosis due to other aetiologies, such as prevention of variceal bleeding by using non-selective beta-blockers or vasoconstrictor drugs, such as terlipressin, vasopressin or octreotide.[13,40] However, these pharmacotherapies have not been yet tested for management of PH in the early stages of NAFLD. Most drug candidates for PHT management in early stages of NAFLD have only been tested in animal models.[67] However, there are some promising drugs for PHT in NAFLD as outlined below.

3.1 NO modulation

It is known that NO plays an important role in the modulation of IHVR in liver sinusoids, thus NO modulation might be a promising therapeutic option in the early stage of NAFLD. [8] In a pilot human study, vardenafil, i.e., a NO modulator that can prevent the breakdown of the NO mediator cGMP, was found to reduce HVPG. [68] In an animal model, portal pressure in cirrhotic rats was decreased by the use of tetrahydrobiopterin and AVE9488, which increase NOS transcription or activity. NO modulation may inhibit HSC activation. [69,70] However, NO donors might cause hypotension due to the decrease in systemic vascular resistance.[71] Thus, clinical trials in patients are needed to prove its effect on PHT and to investigate side effects.

3.2 Statins

Statins have been demonstrated to have some beneficial effects on steatosis, inflammation and fibrosis in NAFLD.[72] Furthermore, statins may lower portal venous pressure in patients with cirrhosis and reduce the increased postprandial portal pressure. [72,73] Some studies have shown that simvastatin had a positive effect on decreasing portal venous pressure in NAFLD. [68] This effect in NAFLD might be partially due to the statins' function to modulate IHVR by enhancing eNOS expression, which may improve endothelial dysfunction, and reduce HSC contractility.[68] Moreover, statins have been also reported to reduce angiogenesis that might also be beneficial on PHT.[74]

3.3 Farnesoid X nuclear receptor

Farnesoid X nuclear receptor (FXR), as a modulator of intrahepatic vascular resistance in NAFLD, affects bile acid metabolism, lipid metabolism, inflammation and fibrosis.[75] FXR agonists stimulate eNOS activity and inhibit the endothelin-1 (ET-1) mediated contraction of HSCs.[76] Obeticholic acid is a promising steroidal FXR agonist that may reduce PHT in rats by up-regulating eNOS and rho-kinase [77]. Another nonsteroidal FXR agonist PX20606 may reduce PHT by improving liver sinusoidal cell dysfunction, fibrosis, and vascular remodeling.[78] In addition, obeticholic acid has been shown to reduce bacterial translocation and intestinal inflammation in cirrhotic rats with ascites.[79] Therefore, FXR is now emerging as a promising therapeutic target for reducing PHT in NAFLD. However, the precise biological mechanisms of FXR-induced reduction of liver fibrosis need to be further explored.

3.4 Peroxisome proliferator–activated receptor agonists

Peroxisome proliferator–activated receptor (PPAR) agonists play a key role in fatty acid and lipid metabolism, inflammation and fibrogenesis. Promising agents such as pan-PPAR agonist (lanifibranor) showed some beneficial effect on liver fibrosis.[80-82] Moreover, the PPAR-α agonist fenofibrate could reduce PVP in cirrhotic rats by improving endothelial function mainly through increased NO bioavailability, and reduced leukocyte recruitment.[83] However, further research is needed to examine the

efficacy of PPAR agonists on PHT in humans.

Conclusions and future perspectives

PHT is the underlying cause of many liver-related complications that drive poor clinical outcomes. With the potential pathophysiological significance of increased PVP in NAFLD indicating that PHT may promote NAFLD/NASH fibrosis progression and vice versa, it is clinically important to find non-invasive and accurate methods that allow early detection and monitoring of PHT. The role of metabolic risk factors in the pathogenesis of PHT in the early stages of NAFLD is poorly studied and it worth further exploration. Likewise, we believe that the recently proposed change in the nomenclature from NAFLD to metabolic-dysfunction associated fatty liver disease (MAFLD) could help us to better understand the role of metabolic risk factors in PHT, and facilitate new drug development to reduce PVP and fibrosis in patients with NAFLD, possibly through the improvement of multiple metabolic pathways.

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Figure legends

Figure 1. Due to steatosis and hepatocellular ballooning, enlarged fatty hepatocytes reduce sinusoidal flow and promote endothelial dysfunction, contributing to further shear stress. In response to these structural and functional changes, LSECs become defenestrated and develop a basement membrane (capillarization) that causes hypoxia

and hepatocellular injury. HSCs reside in the space of Disse and Kupffer cells in the sinusoids. Defenestrated LSECs stimulate the contractility and transformation of HSCs into myofibroblasts leading to increased liver fibrogenesis and angiogenesis. Hepatocellular injury and apoptosis activate Kupffer cells leading to advancing inflammation, fibrosis and angiogenesis, which further narrowing the sinusoid. Augmented inflammatory changes include the recruitment of additional cellular components such as polymorphonuclear leukocytes promoting adhesion and micro-thrombosis.

Abbreviations: LSEC: liver sinusoidal endothelial cell, HSCs Hepatic stellate cells

Figure 2. Old and new invasive and non-invasive methods for the assessment of portal hypertension. Traditional methods (indicated by the blue area) include HVPG measurement, which uses a balloon-tipped central vein catheter inserted into a hepatic vein tributary that detects WHVP and FHVP. With development of endoscopy technology (indicated by red area), EUS-PPG is an emerging method to provide safe and direct measurement of portal pressure gradient (PPG). Analysis of mucosal vascular pattern and flow by confocal endomicroscopy is another novel method. Several non-invasive methods (indicated by the green area) e.g. serum biomarkers, models or risk scores, tissue stiffness assessment of the liver and spleen by elastography based on ultrasound or MR are in development.

Abbreviations: HVPG, hepatic venous pressure gradient; EUS-PPG, endoscopic ultrasound-guided pressure measurement; PPG, portal pressure gradient; WHVP, wedged hepatic venous pressure; FHVP, free hepatic venous pressure, EDG, endoscopy.