

Portal hypertension in patients with nonalcoholic fatty liver disease: Current knowledge and challenges

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Abstract

Portal hypertension (PH) has traditionally been observed as a consequence of significant fibrosis and cirrhosis in advanced non-alcoholic fatty liver disease (NAFLD). However, recent studies have provided evidence that PH may develop in earlier stages of NAFLD, suggesting that there are additional pathogenetic mechanisms at work in addition to liver fibrosis. The early development of PH in NAFLD is associated with hepatocellular lipid accumulation and ballooning, leading to the compression of liver sinusoids. External compression and intraluminal obstacles cause mechanical forces such as strain, shear stress and elevated hydrostatic pressure that in turn activate mechanotransduction pathways, resulting in endothelial dysfunction and the development of fibrosis. The spatial distribution of histological and functional changes in the periportal and perisinusoidal areas of the liver lobule are considered responsible for the pre-sinusoidal component of PH in patients with NAFLD. Thus, current diagnostic methods such as hepatic venous pressure gradient (HVPG) measurement tend to underestimate portal pressure (PP) in NAFLD patients, who might decompensate below the HVPG threshold of 10 mmHg, which is traditionally considered the most relevant indicator of clinically significant portal hypertension (CSPH). This creates further challenges in finding a reliable diagnostic method to stratify the prognostic risk in this population of patients. In theory, the measurement of the portal pressure gradient guided by endoscopic ultrasound might overcome the limitations of HVPG measurement by avoiding the influence of the pre-sinusoidal component, but more investigations are needed to test its clinical utility for this indication. Liver and spleen stiffness measurement in combination with platelet

count is currently the best-validated non-invasive approach for diagnosing CSPH and varices needing treatment. Lifestyle change remains the cornerstone of the treatment of PH in NAFLD, together with correcting the components of metabolic syndrome, using nonselective beta blockers, whereas emerging candidate drugs require more robust confirmation from clinical trials.

Key Words: Non-alcoholic fatty liver disease; Portal hypertension; Mechanotransduction; Endothelial dysfunction; Hepatic venous pressure gradient

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Core Tip: Portal hypertension (PH) occurs in patients with cirrhosis, but in non-alcoholic fatty liver disease (NAFLD) it is sometimes observed in non-cirrhotic stages due to perisinusoidal fibrosis and damage to liver microcirculation. The severity of PH tends to be underestimated by hepatic venous pressure gradient (HVPG) measurement in NAFLD, potentially due to the presence of pre-sinusoidal component, and some patients decompensate at HVPG < 10 mmHg. Liver elastography needs further validation in obese patients as it might overestimate the severity of PH. While candidate drugs for PH are currently in development, lifestyle changes and modulation of metabolic derangements remain the mainstay of treatment.

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INTRODUCTION

Portal hypertension (PH) plays a crucial prognostic role in chronic liver disease (CLD), including non-alcoholic fatty liver disease (NAFLD). PH develops during the evolution of CLD as a result of the increased accumulation of extracellular matrix in the liver, leading to elevated resistance to the portal blood flow, further aggravated by the distortion of the liver architecture and vascular network, which is caused by the formation of regenerative nodules. In addition to this static component, a reversible element of the heightened resistance derives from the contraction of hepatic stellate cells (HSCs) around the liver sinusoids, which is activated by the underlying pathogenetic process. This results in the development of PH at the sinusoidal level, which is typical for viral hepatitis and alcohol-related liver disease (ALD).

Current knowledge of the pathophysiology, diagnosis and treatment of PH relies predominantly on the data accumulated from the studies conducted regarding these two aetiologies of CLD. Considering the changing aetiological landscape of CLD, with NAFLD becoming the leading cause of liver-related morbidity, it is important to understand all aspects pertaining to the PH arising in the context of NAFLD. Based on recent reports, the development, diagnosis and prognosis of PH in NAFLD might not completely fit into the existing paradigms and rules established with chronic viral hepatitis and ALD. This article aims to describe the present understanding of the topic, as well as to highlight the unmet needs and controversial issues in the diagnosis and management of PH in patients with NAFLD.

PATHOPHYSIOLOGICAL BACKGROUND

General aspects of the development of portal hypertension in chronic liver diseases

Portal hypertension is defined as a clinical syndrome caused by elevated blood pressure in the portal venous system. Patients who suffer from advanced chronic liver disease (ACLD), especially cirrhosis, have an increased risk of developing PH[1,2]. Liver cirrhosis arises as the result of prolonged liver damage caused by various aetiological agents that finally lead to the replacement of the healthy parenchyma with fibrotic tissue, the formation of regenerative nodules and the distortion of the microarchitecture, including the liver vascular network[3,4]. In the portal tracts located at the periphery of the hepatic lobule (zone 1), terminal branches of both the hepatic artery and portal vein join into liver sinusoids and form a complex capillary network that drains into the centrilobular area of the central vein outflow (zone 3) [5,6]. Arteriolar inflow needs to be efficiently controlled to prevent damage and shear stress to liver sinusoids because of the very high arterial hydrostatic pressure, which is up to 40 times higher relative to that present in terminal branches of the portal vein[6-8]. Vasoregulatory changes in both intrahepatic and systemic circulation have an important role in the development and further aggravation of PH in individuals with cirrhosis. Hepatic causes of PH are essentially classified into three types according to the main location of the blood flow disturbance in the hepatic circulation: pre-sinusoidal, sinusoidal and post-sinusoidal[9,10]. Sinusoidal PH is the most common type, and it typically occurs in cirrhosis patients [11]. The principal causes of intrahepatic PH are depicted in [Table 1](#).

Table 1 Principal intrahepatic causes of portal hypertension (adapted based on references[1,9])

Pre-sinusoidal	Sinusoidal	Post-sinusoidal
Developmental abnormalities:	Fibrosis in the space of Disse:	Granulomatous phlebitis:
Adult polycystic liver disease	Metabolic cause: non-alcohol-associated fatty liver disease, Zellweger syndrome	Mycobacterium avium infection
Congenital hepatic fibrosis	Inflammatory cause: schistosomiasis, viral hepatitis B and C, chronic Q fever, cytomegalovirus	Mycobacterium intracellulare infection
Arteriovenous fistulas	Induced by drugs or toxins: amiodarone, methotrexate, alcohol, vinyl chloride, copper	Sarcoidosis
Porto-sinusoidal vascular disease:	Early alcohol-associated liver disease (defenestration)	Primary vascular malignancies:
Idiopathic non-cirrhotic portal hypertension		Epithelioid haemangioendothelioma
		Angiosarcoma
Granulomatous liver disease:	Microvesicular steatosis hypertrophied hepatocytes	Phlebosclerosis of hepatic veins:
Schistosomiasis (bilharzia)		Alcohol-associated liver disease
Mineral oil granuloma		Chronic radiation injury
Sarcoidosis		Hypervitaminosis A
Biliary diseases:	Infiltrative diseases:	Lipogranulomas:
Autoimmune cholangiopathy	Idiopathic myeloid metaplasia	Mineral oil granuloma
Primary sclerosing cholangitis	Gaucher disease	
Toxic biliary injury	Mastocytosis	
Biliary cholangitis		
Neoplastic occlusion of the intrahepatic portal vein	Amyloid or light-chain deposition in the space of Disse	Sinusoidal obstruction syndrome
	Acute hepatic injury	Budd-Chiari syndrome

The impact of lipid accumulation on PH development in early NAFLD

Hepatocyte ballooning occurs early in NAFLD pathogenesis because of the accumulation of cholesterol and fatty acids within the cytoplasm of hepatocytes[5,12]. Lipid-laden hepatocytes cause external sinusoidal compression, leading to increased intrahepatic vascular resistance (IHVR) and shear stress[5,13]. These sinusoids, which are deformed, tortuous and up to 50% narrower, are mostly located in the periportal region of hepatic lobules and impose a heightened resistance to portal blood flow before it enters the sinusoids[14,15]. Another structural change in NAFLD contributing to IHVR development is the formation of lipogranulomas commonly located near terminal hepatic venules, which are dispersed in portal tracts and the hepatic acinus[16,17]. Steatonecrosis, an event caused by the disintegration of hepatocytes due to excessive lipid accumulation[14,18], results in the liberation of lipid droplets which travel through the Disse space and the endothelium and fill the sinusoid as a sinusoidal lipid embolus[14].

The impact of the activation of neutrophils on PH development

The stretching of liver sinusoidal endothelial cells (LSECs) caused by the enlargement of hepatocytes activates Notch-dependent neutrophil chemotaxis[19]. Together with neutrophil chemotactic chemokines, which are produced by hepatocytes and HSCs, these signals have a crucial role in the recruitment of leukocytes and formation of neutrophil extracellular traps (NETs)[19], intraluminal web-like structures composed primarily of deoxyribonucleic acid (DNA)-histone complexes originating from neutrophils, which bind pathogens[20] and impose a barrier that leads to increased fluid shear stress at the level of sinusoids[21]. Thus, lipid accumulation in hepatocytes, with the consequent deformation of sinusoids, combined with the formation of lipogranulomas and NETs, as well as lipid emboli, contributes to sinusoid hypoperfusion[13,22,23], microvascular thrombosis[24] and the development of PH, with heightened presinusoidal resistance in NAFLD[13,25].

The principal mechanisms of portal hypertension development in NAFLD are illustrated in [Figure 1](#).

Animal models supporting the role of liver steatosis in the development of PH

The association between increased portal vein pressure (PVP) and steatosis has been observed in numerous animal experimental models. One of the oldest experiments confirming this connection was carried out almost 50 years ago. Donryu rats were fed a choline-deficient diet for eight to 38 weeks. Two thirds of the rats died during the feeding period and 27 developed a fatty liver (n = 7), some with fibrosis (n = 8) and others with cirrhosis (n = 12)[5,15]. The results showed a decrease in portal blood flow, an increase in PVP and a narrowing of sinusoids without visible abnormalities in

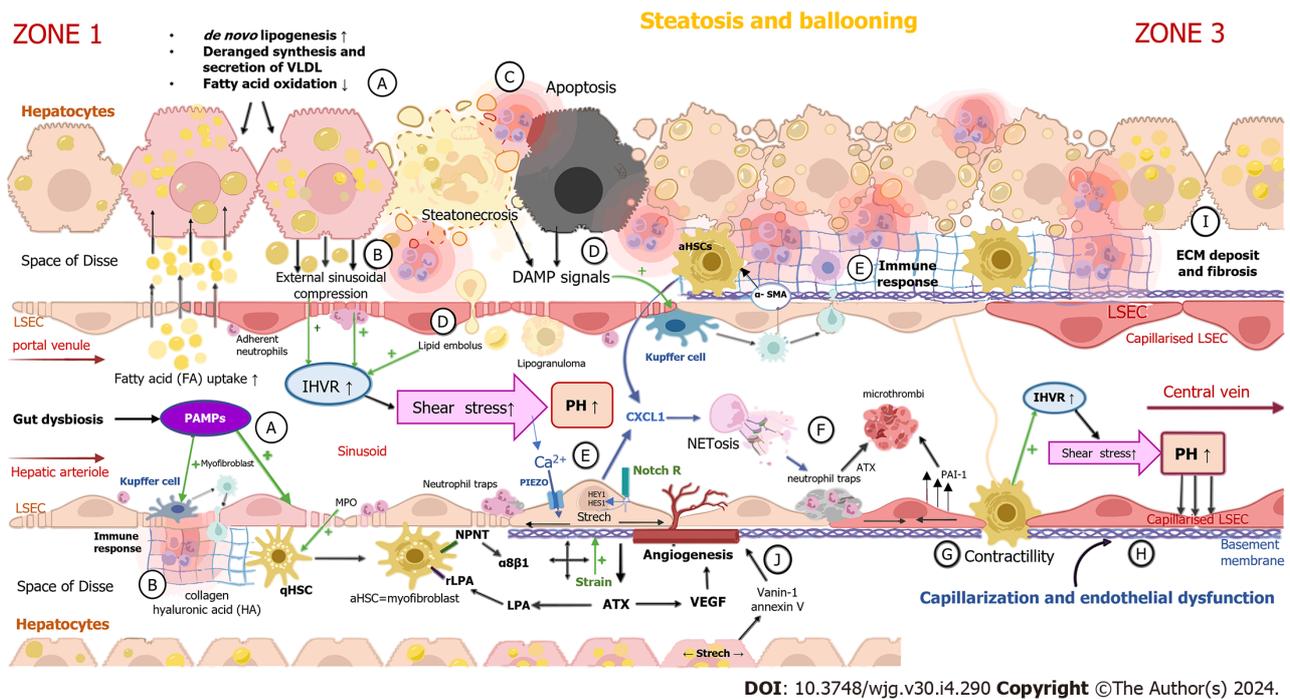


Figure 1 Development of portal hypertension in non-alcoholic fatty liver disease. A: Ballooning of hepatocytes are caused by excessive lipid uptake. Pathogen-associated molecular patterns (PAMPs), along with other products of intestinal dysbiosis, arrive at the liver via the portal blood flow and act on liver sinusoidal endothelial cells (LSECs) and Kupffer cells (KCs) from the luminal side of the sinusoid; B: Excessive lipid accumulation in hepatocytes and PAMPs trigger inflammation by cytokine secretion and immune cell infiltration; C: Immune cell infiltration leads to steatonecrosis, apoptosis and hepatic stellate cells (HSCs) activation; D: Hepatocytes dying by steatonecrosis and apoptosis release damage-associated molecular pattern molecules, causing the activation of KCs and subsequently HSCs. The destruction of lipid-laden hepatocytes incites lipid embolus liberation in the sinusoidal lumen. Lipid droplets participate in lipogranuloma formation, which interferes with sinusoidal blood flow and results in elevated intrahepatic vascular resistance (IHVR); E: Activated HSCs transdifferentiate to proliferative, contractile and collagen-producing myofibroblasts which secrete vascular endothelial growth factor (VEGF) and inflammatory chemokines such as neutrophil chemotactic chemokines and synthesize α -smooth muscle actin. Notch-dependent neutrophil chemotaxis is also activated by the stretching of LSECs caused by the enlargement of hepatocytes and the liver; F: Stretch-activated LSECs promote the creation of neutrophil extracellular traps (NETs), web-like structures composed primarily of DNA-histone complexes originating from neutrophils. NETs contribute to the creation of microthrombi; G: The activation of HSCs is a key event mediating the elevation of IHVR by contracting around the sinusoid. IHVR is also elevated by extrasinusoidal compression caused by swollen steatotic hepatocytes and increased shear stress produced by intraluminal obstacles such as NETs; H: Sinusoid capillarization and the endothelial dysfunction of LSECs are important events that promote the activation of HSCs and KCs, initiating liver fibrosis and inflammation promotion; I: Myofibroblasts and mechanical forces lead to collagen and hyaluronic acid deposition in the space of Disse, causing an excessive increase in extracellular matrix (ECM) stiffness. The cross-linking of ECM proteins and collagen leads to the formation of perisinusoidal fibrosis; J: Angiogenesis occurs as liver fibrosis progresses. Stretched lipid-laden hepatocytes, HSCs, portal myofibroblasts and macrophages stimulate angiogenesis by producing a greater amount of VEGF and other similar mediators as a response to shear stress, hypoxia and inflammation. qHSC: Quiescent hepatic stellate cell; aHSCs: Activated hepatic stellate cells; DAMPs: Damage-associated molecular pattern molecules; α SMA: α -smooth muscle actin; FA: Fatty acid; HA: Hyaluronic acid; CXCL: Chemokine (C-X-C motif) ligand 1; α -SMA: Alpha-smooth muscle actin; MPO: Myeloperoxidase; PAI-1: Plasminogen activator inhibitor-1; ATX: Autotaxin; LPA: Lysophosphatidic acid.

the pre- and post-sinusoidal vessels. All these findings were detected in rats with steatosis without fibrosis, suggesting that steatosis alone is sufficient for the formation of PH[5,10]. In another experimental NAFLD model, obese male Zucker rats with high-grade hepatic steatosis without cirrhosis were studied in comparison with lean rats aged 25 to 30 weeks ($n = 7$ vs 7). Compared to the control animals, an increment in IHVR and reductions of 35% to 38% in the total hepatic blood flow and portal venous flow were observed[5,26]. Francque et al[27] conducted a similar study on male Wistar rats given a methionine-choline-deficient (MCD) diet ($n = 30$) while another group was fed a control diet ($n = 30$) for four weeks. The two groups were compared through *in vivo* haemodynamic measurements and *in situ* perfusion experiments, as well as vascular corrosion and liver tissue and serum analysis. In the MCD diet group, the histopathology showed severe steatosis without evidence of inflammation or fibrosis, and the portal pressure gradient was significantly elevated, indicating an increased intrahepatic resistance, while vascular corrosion casts demonstrated a replacement of the regular sinusoidal anatomy by a sinusoidal wall with a disorganized pattern, in addition to vascular extensions and multiple interconnections. An increase in the expression of vasoconstrictor molecules and enzymes [thromboxane synthase and endothelin-1 (ET-1)] was also registered[27].

The impact of endothelial dysfunction on PH development in NAFLD

Endothelial dysfunction is defined as the loss of various key functions of the endothelium[28,29], chiefly characterized by a lower response of LSECs to the endothelium-dependent vasodilator acetylcholine[30] and a decrease in the production and release of endothelium-driven vasodilatory factors such as nitric oxide (NO)[31,32]. In a normal liver, hepatocytes release low levels of vascular endothelial growth factor (VEGF), which helps LSECs to generate NO through a cytosolic

calcium increase, leading to calmodulin binding and the activation of endothelial nitric oxide synthase (eNOS)[33,34]. To maintain physiological pressure in the sinusoids, shear stress induced by blood flow represents a constant stimulus of NO production in LSECs[35]. The first step in the development of endothelial dysfunction is the reduced production of NO [36] supplied by lessened protein kinase B (Akt)-dependent eNOS phosphorylation, causing diminished eNOS activity [30]. A very important molecule in the endothelial production of NO is insulin[37]. Insulin activates NO release through Akt *via* the Ca²⁺-independent pathway[37,38]. The disruption of insulin signaling observed in insulin resistance impairs the endothelial production of NO[38,39]. Decreased NO bioavailability[40] can also be generated by increased intracellular levels of reactive oxygen species[41] because of excessive lipid accumulation in the liver, endoplasmic reticular stress and mitochondrial dysfunction[10,42,43]. Elevated ROS concentrations reduce the amount of bioactive NO through direct chemical interactions, inducing the formation of toxic peroxynitrite[44]. The latter uncouples eNOS to become a dysfunctional superoxide-generating enzyme, which additionally contributes to vascular oxidative stress[44]. eNOS dysfunction is also caused by the formation of eNOS inhibitors[45] such as asymmetric dimethylarginine[46], a paracrine and a competitive inhibitor of eNOS. The reduced bioavailability of NO can lead to sinusoidal contraction through the activation of perisinusoidal HSCs, resulting in increased IHVR and the elevation of portal pressure[47]. Sinusoidal dysfunction and IHVR in NAFLD pathogenesis are represented in feedback loops and interactions between LSECs, hepatocytes, Kupffer cells, hepatic stellate cells and other immune system cells[10]. The chronology of changes in the structural and functional causes of IHVR is difficult to establish due to the complexity of cell-cell interactions[48].

The impact of vascular dysregulation on PH development in NAFLD

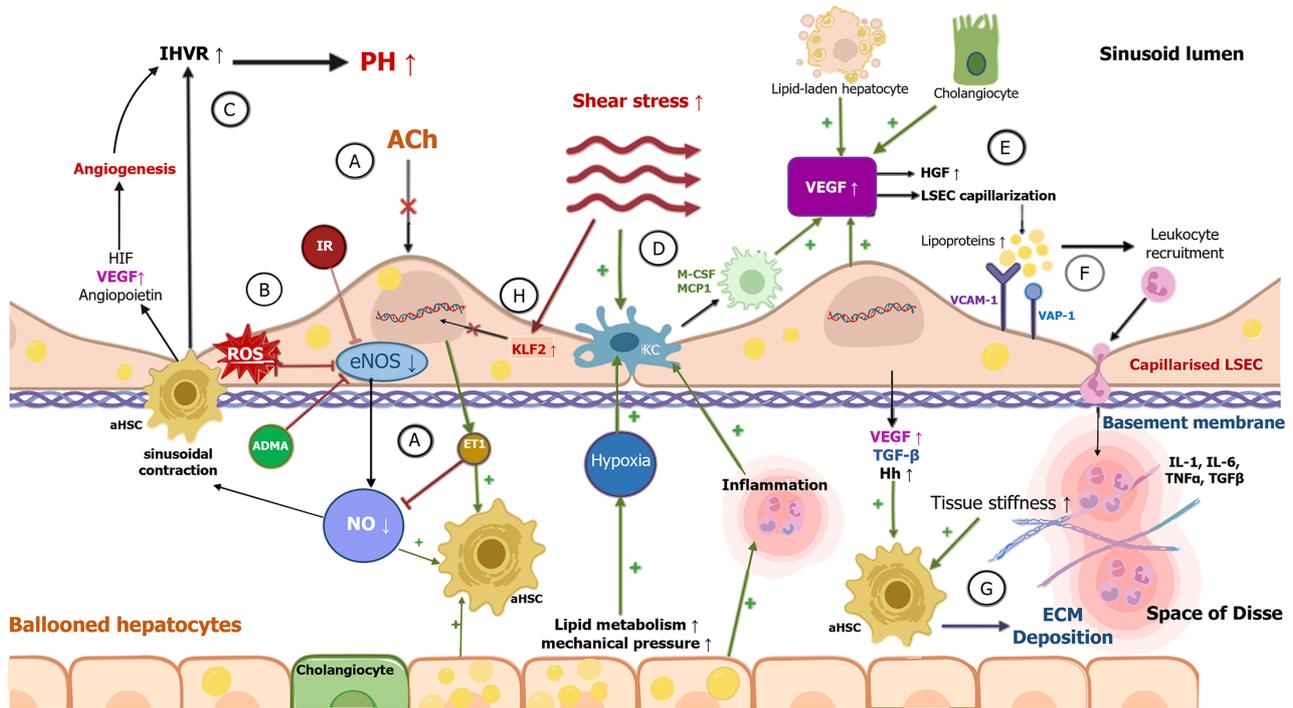
In NAFLD-ballooned hepatocytes, activated HSCs and macrophages stimulate angiogenesis by producing a greater amount of VEGF as a response to shear stress, hypoxia and inflammation[5,49]. Liver steatosis induces hypoxia by both a mechanical pressure on sinusoids and an excessive lipid metabolism which increases oxygen consumption[49]. Increased VEGF levels in NAFLD promote angiogenesis (the formation of new blood vessels)[50] and qualitative changes in liver vessels called vascular remodeling[49,51]. Sinusoidal capillarization, an early morphological feature of endothelial dysfunction, is marked by a dedifferentiation of LSECs, as well as the formation of the basal membrane and loss of fenestration, and represents an example of qualitative vascular remodeling[49,52]. Both angiogenesis and sinusoidal capillarization contribute to the distortion of the normal liver vascular network, blood shunting with consequent tissue hypoxia and deranged metabolic exchange across the endothelial interface[53]. The triggers of sinusoidal capillarization have not been fully elucidated[54], but it is believed that capillarization occurs as a result of the exposure of LSECs to extreme lipid accumulation in parenchymal cells and a surplus amount of circulating lipids in the sinusoidal blood flow [30]. As a response to disproportionate lipid exposure, LSECs express lipid-induced adhesion molecules, integrins (vascular cell adhesion molecule 1, intercellular adhesion molecule, E-selectin and vascular adhesion protein 1), leading to the induction of the recruitment of leukocytes and their translocation into the liver parenchyma[55]. The excessive exposure of LSECs to lipids may cause mitochondrial dysfunction, DNA damage in hepatocytes, endoplasmic reticulum stress and cytoskeleton alterations[56]. A perfusion of hepatic sinusoids can also be aggravated by functional impairments, such as the contracting and swelling of LSECs in response to vasoactive mediators produced by ballooned hepatocytes, *e.g.*, ET-1[23,57]. However, it is important to note that the main liver cells involved in controlling the sinusoidal diameter are perisinusoidal HSCs, also known as liver-specific pericytes[58,59]. Lipid-laden hepatocytes secrete microparticles that promote angiogenesis[60]. Examples of such molecules are vanin-1 and annexin V, which are isolated in the blood of perisinusoidal spaces and produced by stretched and/or compressed centrilobular hepatocytes[5, 60]. Damage in the periportal vascular area may also play an important pathogenic role in NAFLD-dependent PH[5,10]. A high degree of steatosis or periportal fibrosis leads to a poor regulation of arteriolar inflow and creates shear stress in liver sinusoids, which are low-pressure, low-flow vascular channels linking the periportal area of portal inflow (zone 1) to the centrilobular area of central vein outflow (zone 3)[5]. Between zone 1 and zone 3, intralobular arterioles occasionally drain to sinusoids[61]. The influence of “arterial twigs” on sinusoidal flow has not been fully clarified, but they may represent zones of higher pressure[61]. A recently conducted study showed that splanchnic vasodilatation in NAFLD also contributes to the rise in portal pressure long before the development of cirrhosis[62]. Splanchnic vasodilatation and hyperdynamic circulation in NAFLD-dependent PH are characterized by low arterial responsiveness to a vasoconstrictor mediator, a rise in portal venous and mesenteric arterial blood flow and a decrease in main arterial blood pressure[62,63]. Numerous vasoactive mediators (calcitonin gen-related peptide, glucagon, NO, platelet-activating factor, atrial natriuretic peptide and adrenomedullin, as well as bile salts and endocannabinoids) are involved in the arteriolar vasodilatation in the visceral vascular bed that drains into the portal circulation[11,64] and results in an increase in portal inflow and pressure[11,64].

The mechanisms that are important in the development of endothelial dysfunction and capillarization are shown in Figure 2. To summarize the information about early pathophysiological changes in the development of PH in NAFLD, external compression and intraluminal obstacles (*e.g.*, microthrombi, lipid emboli and neutrophil traps) caused by structural changes in NAFLD result in impaired sinusoidal blood flow and may contribute to the development of PH in early NAFLD. Mechanotransduction pathways activated by multiple mechanical forces such as strain, shear stress and hydrostatic pressure result in endothelial dysfunction and fibrosis development, contributing to the maintenance and progression of PH.

The role of increased portal pressure in NAFLD pathogenesis

PH in NAFLD begins to develop as a result of IHVR and the de-differentiation of liver cells[35]. The initial site of IHVR formation is the hepatic sinusoid[65], while the distal segment of the preterminal portal venule serves as a sphincter for blood redistribution[66]. IHVR has two components, which are structural[67] and functional[68], characterized by extrasinusoidal and intrasinusoidal disturbances[35]. Total available space within the liver capsule in NAFLD becomes

Endothelial dysfunction and capillarisation



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Figure 2 Development of endothelial dysfunction and capillarization. A: The initial step in the development of endothelial dysfunction is the reduced production of nitric oxide (NO) caused by decreased endothelial nitric-oxide synthase (eNOS) activity and the low response of liver sinusoidal endothelial cells (LSECs) to acetylcholine; B: Reduced NO bioavailability can be caused by insulin resistance, heightened intracellular levels of reactive oxygen species and the formation of eNOS, paracrine and competitive inhibitors such as asymmetric dimethylarginine; C: Low levels of NO paired with increased endothelin 1 (ET-1) synthesis lead to sinusoidal contraction through the activation of perisinusoidal hepatic stellate cells (HSCs), resulting in elevated intrahepatic vascular resistance and the elevation of portal pressure; D: As a response to shear stress, hypoxia and inflammation, lipid-laden hepatocytes, cholangiocytes, LSECs, activated HSCs and Kupffer cells stimulate angiogenesis by producing an excessive amount of vascular endothelial growth factor (VEGF); E: Hypoxia in fatty liver is induced by mechanical pressure on sinusoids and increased lipid metabolism. Elevated VEGF concentrations lead to the promotion of angiogenesis and fibrogenesis by the increased fibrogenic functions of HSC, as well as LSEC capillarization and the secretion of hepatocyte growth factor. Capillarization, marked by the formation of the basal membrane and loss of fenestration, occurs as a result of LSECs exposure to lipid accumulation in parenchymal cells and a great amount of circulating lipids in the blood; F: As a response to excessive lipid exposure, LSECs express lipid-induced adhesion molecules (VCAM-1, VAP-1, etc.), activate Kupffer cells through the secretion of pro-inflammatory cytokines and induce leukocyte recruitment and their translocation into the liver parenchyma; G: Capillarized LSECs also activate HSCs through the release of angiocrine signals such as VEGF, transforming growth factor and hedgehog signals. Activated HSCs begin to deposit extracellular matrix, which increases tissue stiffness, further stimulating HSC activation; H: Shear stress downregulates the expression of ET-1 via Krüppel-like factors 2 (KLF2) activation. LSECs overexpress KLF2 to maintain HSCs in a quiescent state as a compensatory mechanism to manage vascular dysfunction. Unfortunately, this is an insufficient mechanism for preventing portal hypertension development. ACh: Acetylcholine; aHSC: Activated hepatic stellate cell; KC: Kupffer cell; ROS: Reactive oxygen species; HIF: Hypoxia-inducible factor; M-CSF: Macrophage colony-stimulating factor; MCP1: Monocyte chemoattractant protein-1; IR: Insulin resistance; ADMA: Asymmetric dimethylarginine; HGF: Hepatocyte growth factor; VCAM-1: Vascular cell adhesion molecule 1; VAP-1: Vascular adhesion protein-1; IL-1: Interleukin-1; IL-6: Interleukin-6; TNF α : Tumor necrosis factor α ; TGF- β : Transforming growth factor; Hh: Hedgehog signals.

restricted as a result of lipid accumulation and hepatocellular swelling, leading to a volumetric squeeze and consequently to a reduction in the sinusoidal spaces and a drop in blood flow [15,69,70]. Mechanical forces taking place in the sinusoidal microenvironment of NAFLD (such as increased hydrostatic pressure, strain and shear stress) cause the deformation of cellular structures such as caveolae and plasma membrane lipid rafts, and result in an excessive extracellular matrix (ECM) deposition in the perisinusoidal space of Disse as well as sinusoidal hypercontractility. They also modify the conductivity of ion channels, expose new protein-binding sites and change the activity of transmembrane receptors [35,71,72]. The increase in ECM stiffness that results from the cross-linking of ECM proteins and collagen [73,74] is detected by integrins, mechanosensitive transmembrane proteins that initiate key biological processes upon stretch-induced conformational changes [74,75]. These are also involved in the binding and recruitment of cytoskeleton linker proteins [76], the activation of the transforming growth factor- β (TGF- β) signaling pathway [77] and the conformational alteration of ion channels [78]. Structural changes caused by steatosis in connection with mechanical forces induced by ECM accumulation and haemodynamic changes, as described previously, lead to the compression and/or stretching of liver cells and stimulation of signaling pathways [35], including the contraction and relaxation of the actin filament of the hepatocyte cytoskeleton that result in increased intracellular tension [35,79,80]. Intracellular tension pulls ECM-bound integrins, which then organize into focal adhesions and, together with adaptor proteins, strengthen the ECM-cytoskeleton connection [35,79,80]. The tension generated in the cytoskeleton is transmitted through the linker of the nucleus and cytoskeleton complex [35,79,80]. The deformation of the nucleus, which is proportional to the stiffness of the ECM

[81], affects the change in the gene expression by changing the permeability of the nuclear membrane and altering the rheology of chromatin[35]. This causes the translocation of transcription factors and co-factors[79] such as the yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ)[82]. The co-factors YAP/TAZ are mechanosensitive and can detect fluid shear stress, as well as increases in liver cell density and changes in ECM stiffness [83]. YAP/TAZ regulate the biological behavior of liver cells and the profibrotic response through an insufficiently elucidated mechanism[84,85], resulting in the further accumulation of fibrosis[86,87]. Other important transcription factors are myocardin-related transcription factor-A[88] and *zyxin*, part of the mechanosensing FA complex[89]. These factors translocate to the nucleus as a result of cell stretching and regulate the expression of genes related to inflammation, proliferation and cell apoptosis[35,76,89-91].

In conclusion, disrupted mechanical homeostasis in liver sinusoids is the key contributor to the pathogenesis of NAFLD, caused by intracellular lipid accumulation, enhanced ECM stiffness and altered functions in the contractile cytoskeleton that finally lead to further fibrosis accumulation and cellular contractility, representing the positive feedback loop mediated through the mechanotransduction pathways.

The development of fibrosis and its impact on PH

In NAFLD, excessive lipid accumulation triggers inflammation through cytokine secretion and immune cell infiltration [92]. The initiation of the inflammatory response leads to hepatocyte necrosis, apoptosis[93] and HSC activation[94,95] as the characteristic features of non-alcoholic steatohepatitis (NASH), in which a large amount of free fatty acids released from the injured hepatocytes, as well as damage-associated molecular patterns (DAMPs), are removed by Kupffer cells [96-98]. The latter release profibrogenic growth factors (TGF- β and platelet-derived growth factor)[99] that, in conjunction with ROS, pro-inflammatory cytokines (interleukin-6, interleukin-10 and tumor necrosis factor α)[100,101] and products of lipid peroxidation[102], along with endothelin and fibronectin produced by capillarized LSECs, result in HSC activation[5]. Activated HSCs transdifferentiate from the quiescent phenotype to proliferative, contractile and collagen-producing myofibroblasts[103]. These cause the synthesis of ECM through the production of collagen (types I, III and V) and hyaluronic acid[103]. In addition to the ECM products, myofibroblasts also synthesize α -smooth muscle actin[104], a hallmark of HSC activation[105], and release VEGF and chemokines such as macrophage colony-stimulating factor and monocyte chemoattractant protein-1. Collagen is deposited in the space of Disse as an early phenomenon in NAFLD that generates the formation of perisinusoidal fibrosis and narrowing of the sinusoidal lumen[5]. Fibrosis in NAFLD develops in the pericellular space around the central veins and in the perisinusoidal space of zone 3[106], whereas the fibrosis pattern in other chronic liver diseases initially shows a portal instead of a pericentral distribution[107]. Due to the specific distribution of fibrosis in patients with NAFLD, PH may occur before the development of cirrhosis[107]. Increased ECM stiffness sends a positive feedback signal to HSCs, contributing to the further progression of liver fibrosis[35]. This results in the remodeling of the liver architecture and the formation of cirrhotic nodules with the additional distortion of hepatic microcirculation[108,109]. Both the structural component, represented by accumulated fibrosis with narrowed sinusoids and a distorted microvascular network, and the dynamic one resulting from endothelial dysfunction and myofibroblast contraction (with the latter considered responsible for 20%-30% of the IHVR) contribute to the rise in portal pressure[110, 111].

In conclusion, the development of liver fibrosis has a fundamental influence on the advancement and further aggravation of PH, not only as the structural barrier to the intrahepatic blood flow, but also by inducing the secretion of local vasoactive mediators. This leads to vascular dysregulation and the functional deterioration of endothelial dysfunction that additionally aggravates IHVR[5,35].

PORTAL HYPERTENSION IN RELATION TO THE STAGE OF LIVER FIBROSIS AND GRADE OF STEATOSIS: CLINICAL DATA

Large-scale epidemiological investigations focused on the prevalence of PH among the NAFLD patients are lacking. However, several clinical studies have been conducted to investigate the relationship between the development and severity of PH and the histological and clinical features of NAFLD. In a cohort of 50 overweight patients who underwent transjugular liver biopsy (TJLB) coupled with HVPG measurements, PH (HVPG > 5 mmHg) was diagnosed in 14 (28%) of subjects and the only histological parameter that differed between them and those without PH was a higher grade of steatosis ($P = 0.016$). In the group with PH, only 21% of patients had advanced fibrosis/cirrhosis. The independent clinical predictors of PH were waist circumference ($P = 0.008$) and the homeostatic model assessment for insulin resistance (HOMA IR; $P = 0.043$)[112]. In a prospective cohort study that included 40 obese patients who underwent TJLB (30% with diabetes, 70% with NASH) and HVPG measurements, PH was found in eight (20%) patients, and none had cirrhosis. The presence of PH positively correlated with the proinflammatory blood cytokine profile as well as with microvascular changes in the form of sinusoidal dilatation, previously reported as an early histological change in severe steatosis even in the absence of advanced fibrosis[27,113]. In an observational investigation, in a cohort of 354 subjects with biopsy-confirmed NAFLD, 100 patients exhibited clinical signs of PH (the presence of at least one of esophageal varices (EV), portosystemic encephalopathy, splenomegaly or ascites). Among them, 77 had liver cirrhosis and 11 had bridging fibrosis (stage F3). However, signs of PH were also present even in 12 (12%) patients who had no or only mild fibrosis (stages F0-F2)[107]. PH was increasingly detected in patients at a more advanced stage of fibrosis ($r = 0.48$, $P = 0.006$). In the F0-F2 subgroup ($n = 204$), a comparison between those with PH ($n = 12$) and those without PH ($n = 192$) was made, and the only histological feature that was significantly different between the groups was a higher grade of liver steatosis in patients with PH (mean grade 2.3 ± 0.5 vs 1.9 ± 0.7 , $P = 0.03$). This work provides evidence that even clinically significant PH may

exist before liver fibrosis enters an advanced stage, which is classically considered the threshold for PH development, and this might be caused by fat overload leading to the progressive enlargement of hepatocytes and reduction of the sinusoidal lumen[10,107].

In another investigation, 14/89 (16%) patients with clinically significant portal hypertension (CSPH) diagnosed by HVPG measurement were found to not have cirrhosis, and seven had stages F0-F2 (five were diagnosed with NASH). All these patients had perisinusoidal fibrosis and 8/14 had hepatocyte ballooning[114]. Based on these results, it becomes clear that patients with NAFLD may have PH and even CSPH without cirrhosis. Somewhat different results came from a study that investigated the prevalence of PH in a cohort of 292 NAFLD patients with metabolic syndrome associated with a liver stiffness measurement (LSM) > 8 kPa and/or liver blood test abnormalities (alanine aminotransferase > upper limit of normal), with no prior liver decompensation events. These patients were referred for TJLB and HVPG measurements, and 75/292 had liver cirrhosis. Among the 217 non-cirrhotic patients, 36 had PH (only one had CSPH), and there was no difference in steatosis or inflammatory grade between the patients with and without PH[115]. The only patient who presented with CSPH in the non-cirrhotic group was a young woman with Alström syndrome, severe type 2 diabetes, arterial hypertension and obesity. To compare, in the group of 75 patients with cirrhosis, PH was present in 53 (71%), CSPH in 38 (51%) and severe PH in 29 (39%). Accordingly, whereas PH might appear even in a non-cirrhotic liver, severe PH was not observed in NAFLD patients in the absence of cirrhosis[115].

Portal hypertension and advanced cirrhosis, regardless of aetiology, are traditionally associated with splenomegaly [116]. Interestingly, the results of a recent retrospective study in a large population of patients with biopsy-proven NAFLD revealed a strong correlation between splenomegaly and increased body weight, whereas none between splenomegaly and the histological degree of the underlying disease could be confirmed[117]. Thus, splenomegaly might be considered a consequence of visceral lipid deposition in the spleen and not necessarily a sign of PH. This view is further supported by the results from some other investigations demonstrating an enlarged spleen size in people with NAFLD with no other signs of PH, as well as in otherwise healthy individuals with a higher body height and weight[118,119].

THE PROGNOSTIC PROPERTIES OF THE HVPG IN NAFLD

In terms of stratifying the risk of hepatic decompensation, the prognostic properties of the HVPG have mostly been derived from investigations conducted in patients with viral and alcoholic aetiologies of chronic liver disease, where they have demonstrated robust predictive values. The normal HVPG value is 1-5 mmHg, and values of 6-9 mmHg are considered subclinical PH, while an HVPG ≥ 10 mmHg represents CSPH, as from this threshold all major complications related to PH start to develop, including the formation EV, ascites accumulation and portal encephalopathy[120-123]. Esophageal varices bleed at an HVPG ≥ 12 mmHg, and the risk of death increases significantly in patients with an HVPG ≥ 16 mmHg[120,121,123]. Given the complexity of the histological presentation and pathogenesis of PH in NAFLD, the HVPG cut-off values that are used in other aetiologies might not be appropriate for this purpose in NAFLD. To further elucidate this issue, a multicentric cross-sectional study was conducted with a cohort of 548 patients with advanced NAFLD and 444 with advanced hepatitis C (aHCV), who underwent detailed PH evaluation including HVPG measurement, TJLB, gastroscopy and abdominal imaging. Advanced chronic liver disease was defined either clinically by the presence of PH (HVPG > 5 mmHg) or histologically by the presence of stage 3 or 4 of liver fibrosis, and the majority of patients had compensated ACLD (cACLD; 71%). The median HVPG was lower in patients with advanced non-alcoholic fatty liver disease (aNAFLD; 13 mmHg vs 15 mmHg), although the indicators of liver function were similar between them and the aHCV group, whereas decompensation rates were higher among aNAFLD patients (32% vs 25%, $P = 0.019$), suggesting that NAFLD patients decompensated at lower HVPG levels[124]. According to the classic HVPG thresholds, clinical decompensation appeared in both groups at an HVPG > 10 mmHg, while no signs were detected in aHCV patients with an HVPG < 10 mmHg. Interestingly, some NAFLD patients experienced decompensation even when the HVPG was < 10 mmHg[124]. Further insights into this issue were provided from a study that investigated the agreement between wedge hepatic vein pressure (WHVP) and portal pressure (PP) in patients with decompensated NASH cirrhosis ($n = 40$), as well as those with alcohol-related ($n = 40$) and HCV-related decompensated cirrhosis ($n = 40$). All the patients were treated with a transjugular intrahepatic portosystemic shunt and the results revealed an excellent correlation between WHVP and PP in those with alcohol-related or HCV-related cirrhosis ($r = 0.92$; $P < 0.001$; intraclass correlation coefficient (ICC) 0.96; $P < 0.001$) whereas it was only moderate in the NASH group ($r = 0.61$; $P < 0.001$; ICC 0.74; $P < 0.001$). When the WHVP differed by > 10% from PP, this was regarded as a disagreement between the two, and this occurred more frequently in the NASH group (37.5% vs 14%; $P = 0.003$)[125], where WHVP tended to underestimate PP. Data from a simtuzumab trial revealed that 14% of patients with NASH cirrhosis and an HVPG < 10 mmHg developed liver decompensation during a median follow-up of 4.7 mo. Nevertheless, an HVPG ≥ 10 mmHg maintained its prognostic properties in terms of predicting the liver decompensation in the overall group of patients with NASH cirrhosis, in comparison to those who had an HVPG < 10 mmHg (hazard ratio 2.83; 95% confidence interval, 1.33-6.02; $P = 0.007$)[126].

Based on these studies, there is strong evidence for the underestimation of portal pressure in NAFLD patients by HVPG, probably due to the presence of a pre-sinusoidal component. In this line, portal inflammation and ductular reaction in the portal tracts were described in patients with advanced NASH[127,128], and it may be plausible that biliary injury contributes to increased presinusoidal pressure, and therefore favors PP underestimation. Whether periportal fibrosis and/or biliary injury may contribute to increase vascular tone and resistance to blood flow at the level of the portal venules remains to be elucidated.

INNOVATIVE DIAGNOSTIC APPROACHES TO DIAGNOSING PORTAL HYPERTENSION IN NAFLD: A CONCEPT OF ENDO-HEPATOLOGY

The hepatic venous pressure gradient (HVPG) represents the gold standard for diagnosing and grading PH[2,121,123,129]. However, it is invasive, expensive and not widely available[130,131]. Among the most serious drawbacks of the HVPG is its inability to detect pre-sinusoidal PH, which obviously takes place in patients with NAFLD, and thus the HVPG might not reliably rule out CSPH in this group. These objective limitations of the HVPG have influenced the search for other methods to be invented and used for diagnosing PH.

Endoscopic ultrasound-guided portal pressure gradient (EUS-PPG) measurement represents a new diagnostic approach to direct PVP assessment. This new method is currently being tested in correlation to traditional HVPG measurement[10]. Under EUS guidance, a modified 25-gauge fine-needle aspiration needle connected to a digital manometer, a self-calibrating compact pressure transducer, is inserted through the liver parenchyma directly into a hepatic vein branch and the portal vein[10,132]. After three consecutive measurements, the mean value is calculated and recorded as the EUS-PPG. In theory, this method could overcome limitations from the HVPG as it measures EUS-PPG, and thus it might more reliably assess the PH grade even in the presence of a pre-sinusoidal component. The first EUS-guided portal vein puncture with portography and pressure measurement was performed on a pig model in 2004[133]. In further animal models, an excellent correlation between EUS-PPG and HVPG measurements ($r = 0.99$) was demonstrated [132]. In a human pilot study conducted in 28 patients with chronic liver disease, EUS-PPG demonstrated a 100% feasibility of accessing all targeted vessels, with no adverse events. In addition, the EUS-PPG results were highly correlated with the presence of clinical signs of PH (no HVPG measurements were available)[134]. Although it has exhibited promising results, this method needs to be further tested over a larger cohort of patients with different aetiologies of chronic liver disease. Moreover, the issue of how to validate its accuracy in patients with presinusoidal PH, in the absence of a gold diagnostic standard (because the HVPG might not be considered as such in this scenario), still remains. Another limitation of EUS-PPG is that sedation must be used to achieve reliable EUS-PPG measurements, but this heavily influences the hepato-portal haemodynamic and thus probably the results of EUS-PPG measurements as well. The direct measurement of portal pressure is also possible through a surgical approach, which is obviously not acceptable for wider clinical use[10,135].

THE NON-INVASIVE DIAGNOSIS OF PORTAL HYPERTENSION IN NAFLD

In addition to the HVPG as an invasive assessment of PVP, numerous non-invasive diagnostic methods have been investigated, and some of them are currently utilized in clinical practice. Ultrasound-based methods have been the most frequently evaluated and are widely implemented in hepatology practices, as they are harmless, with no ionizing radiation, easy to use and supported by a large body of scientific evidence. By employing conventional ultrasound, it is possible to detect morphological signs of PH, such as splenomegaly, the presence of ascites or portosystemic collaterals, which is also achievable through other imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI). The last two are either ionizing (CT), or not that readily available (MRI). However, morphological signs of PH detected by imaging methods indicate the presence of CSPH, whereas the goal should be to detect the existence of CSPH as early as possible before the signs of the advanced stage develop. In this line, elastography represents one of the most promising candidates, and has become probably the most influential non-invasive diagnostic tool applied in everyday hepatology practice, including the assessment of PH. Most data have been accumulated with the use of transient elastography (TE), but significant evidence also exists for other ultrasound-based methods such as point shear wave elastography and two-dimensional shear wave elastography[136,137]. The pivotal study testing the diagnostic performance of TE for CSPH was published in 2021 and included an international cohort of 836 patients with CLD of mixed aetiology (including 248 with NAFLD), paired LSM and HVPG measurements and no history of liver decompensation. All patients had an LSM ≥ 10 kPa, and the overall prevalence of PH and CSPH was 83% and 59%, respectively. At the LSM cut-off ≥ 25 kPa, TE had a $\geq 90\%$ positive predictive value (PPV) for ruling in CSPH in all aetiologies except for NAFLD, where only 77% of patients with an LSM over this threshold had CSPH according to the HVPG measurements. For non-obese NAFLD patients, the PPV of LSM over 25 kPa was better, with 91.7% of these patients having CSPH. The PPV for obese patients with NAFLD was lower, but the specificity was similar, and the reduced PPV was due to a lower prevalence of CSPH. For ruling CSPH out, a combination of LSM ≤ 15 kPa and platelet count $\geq 150 \times 10^9/L$ had a $\geq 90\%$ negative predictive value for all aetiologies of CLD including NAFLD, except for hepatitis B, due to the very low number of tested participants. In an attempt to improve the prediction of CSPH in NAFLD patients, the authors constructed a nomogram by using LSM, body mass index (BMI) and platelet count, and demonstrated that at a certain LSM the probability of CSPH is much lower in obese patients compared to their non-obese counterparts[138]. These results were considered by the Baveno VII consensus, which issued recommendations for the non-invasive evaluation of PH utilizing the cut-off values of LSM and platelet count as obtained in this work[139]. To validate these non-invasive criteria for diagnosing CSPH, a retrospective cohort study on 76 cACLD patients (23 with NAFLD) was conducted, and the results revealed that the LSM ≥ 25 kPa criterion had 88.9% specificity and 87.1% PPV for ruling in CSPH, whereas the LSM ≤ 15 kPa and Plt ≥ 150 criterion had 100% sensitivity and a negative predictive value (NPV) for ruling out CSPH. This paper also confirmed that with an increasing BMI, for any given level of platelet count, higher LSM values were needed for a certain probability of having CSPH[140]. According to the Baveno criteria, patients with platelet count $> 150 \times 10^9$ cells/L and LSM < 20 kPa exhibit a very low risk of having high-risk varices and can safely avoid screening endoscopy[139,141].

A spleen stiffness measurement (SSM) that demonstrated high accuracy in classifying patients according to the presence of varices needing treatment (VNT) and CSPH might be helpful in borderline cases, as it reflects an increased resistance to portal blood flow, and the SSM is not affected by liver steatosis[142-145]. Accordingly, the Baveno VII consensus issued recommendations that an SSM > 50 kPa measured by TE might be applied to rule in CSPH, and an SSM < 21 kPa to exclude it in patients with viral hepatitis[139]. A combined approach in which two out of three criteria (LSM \geq 25 kPa, SSM > 40 kPa and Plt < $150 \times 10^9/L$) were employed in cACLD patients to non-invasively identify those with CSPH correctly classified 88% of patients in a recent individual patient data meta-analysis[146]. Whereas the respective PPVs were 91% and 93% in the subgroups with obesity and a non-viral aetiology, the corresponding specificities were 71% and 85%. The combination of two criteria (LSM \leq 15 kPa, SSM \leq 40 kPa and Plt count \geq $150 \times 10^9/L$) demonstrated a suboptimal NPV (67%) for ruling out CSPH in non-viral aetiology, whereas the NPV was 91% if SSM < 21 kPa was utilized instead. Whether the performance of these cut-offs is limited to patients with NAFLD remains to be further validated. Some promising initial results were published using contrast-enhanced ultrasound, specifically the subharmonic aided pressure estimation method[147], but these results require further validation.

Beside imaging methods, biomarker(s) from blood or stool would be welcome for early detection of PH in NAFLD patients, as this approach could potentially have wider applicability. Given that NAFLD is closely related to type 2 diabetes, postprandial blood glucose (PPG) has been studied as an important blood biomarker for assessing the progression of liver disease from steatosis to fibrosis[148-150]. Elevated PPG during NAFLD occurs prior to fibrosis, indicating a bidirectional relationship between postprandial dysfunction in NAFLD and fibrosis development[149,150]. The results of a recent study on a Chinese NAFLD population showed an independent association between elevated PPG and progression of liver fibrosis[148]. Whereas some investigations described distinctive metabolomic blood/stool signature of advanced fibrosis/cirrhosis in comparison to simple steatosis or mild fibrosis, they still have not revealed reliable single biomarker or biomarker combination specific for PH, and thus further research in this regard is warranted [151,152].

NON-INVASIVE DIAGNOSIS OF HIGH-RISK ESOPHAGEAL VARICES IN NAFLD

Progression of liver cirrhosis and PH leads to the development of CSPH and its complications in the form of EV, ascites accumulation, portal encephalopathy and EV[9,11,153,154]. Esophago-gastro-duodenoscopy (EGD) represents the gold standard method for diagnosing and assessing the degree of EV, and it offers the possibility of treating EV at the same time[155,156]. However, EGD is an invasive procedure, associated with some risks, including damage to the gut wall, bleeding and perforation, and it is not very well accepted by some patients. Therefore, non-invasive approaches to the diagnosing of EV have been extensively investigated during the last decade. By using non-invasive methods, such as TE in the first place, liver disease is more frequently detected at an early stage, which significantly increases the number of unnecessary endoscopies[157]. Non-invasive Baveno VI (LSM < 20 kPa, Plt > $150 \times 10^9/L$) and expanded Baveno VI criteria (LSM < 25 kPa, Plt > $110 \times 10^9/L$) have proven to be efficient in ruling out high-risk VNT[141,158]. According to the original report, it was possible to safely avoid 40% of EGDs at the cost of missing only 1.6% of VNT by applying expanded Baveno VI criteria[159]. However, only a minority of patients included in these investigations had NAFLD, whereas the data referred mostly to patients with alcohol-related cirrhosis and viral cirrhosis. Therefore, NAFLD cirrhosis criteria were proposed by Petta *et al*[160] based on a multicentric international study that included 790 patients with compensated NAFLD cirrhosis who underwent EGD and LSM by TE no more than six months apart. Accordingly, the best performing criteria for ruling out VNT by utilizing an M probe were an LSM < 30 kPa and platelet count > $110000/mm^3$, whereas the corresponding values if an XL probe was employed were an LSM < 25 kPa and platelet count > $110000/mm^3$, the latter identical to the expanded Baveno VI criteria[160].

Based on these data, an algorithmic approach to ruling out VNT in patients with NAFLD cirrhosis was finally proposed: if LSM could be reliably assessed by an M probe, then Baveno VI criteria should be applied to non-obese subjects, and NAFLD cirrhosis criteria to obese ones. If the XL probe had to be used, again Baveno VI criteria should be applied to non-obese subjects, and NAFLD cirrhosis criteria (extended Baveno VI) to obese ones[160,161]. In a retrospective cohort study from China, the authors investigated the diagnostic performance of Baveno VI and extended the Baveno VI criteria for ruling out VNT in a cohort of 224 patients with biopsy- or clinically proven compensated NAFLD cirrhosis. It should be highlighted that 60.7% patients had coexisting hepatitis B, 15.6% hepatitis C and 8.9% alcohol-related chronic liver disease. The mean LSM was 18.1 ± 13.9 kPa and the authors did not declare which probe(s) they utilized. By employing Baveno VI and expanded Baveno VI criteria, it was possible to avoid endoscopy in 37.5% and 56.7% patients, with the respective risk of missing VNT in 1.19% and 3.15% patients[162]. Obviously, the dilemma regarding the steatosis influence on LSM is still an open issue, in terms of both its impact on the accuracy of non-invasive staging of liver fibrosis in NAFLD patients, as well as in assessing the severity and complications of PH[138,163,164]. Measuring spleen stiffness might also be helpful in this clinical scenario, as it was demonstrated that in patients who were outside Baveno VI criteria based on LSM and platelet count assessment, an SSM \leq 46 kPa had a 98% NPV for ruling out VNT[165]. Accordingly, the Baveno VII consensus issued a recommendation that endoscopy could be safely avoided in patients who do not meet LSM/platelet criteria if their SSM is \leq 40 kPa[139]. Again, this recommendation relies on the data obtained mostly from patients with viral hepatitis and thus should be further validated in those with NAFLD.

A SPECIFIC TREATMENT FOR PH IN PATIENTS WITH NAFLD: NOT THERE YET

The numerous molecular and cellular pathophysiological processes that contribute to IHVR in patients with NAFLD represent potential therapeutic targets for PH[5,10,166]. Nonselective beta blockers like carvedilol and propranolol are utilized for the prevention of clinical decompensation in patients with compensated cirrhosis and CSPH[167]. Statins have been demonstrated to stimulate the eNOS-NO-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate pathway with increased intrahepatic NO production, the upregulation of a transcription factor (Krüppel-like transcription factor) and the inhibition of the RhoA/Rho-associated coiled-coil-containing kinase pathway that is important for the development of LSEC capillarization and vasoconstrictive effects[166,168]. Multikinase inhibitors (sorafenib) were investigated for attenuating pathological angiogenesis in the course of chronic liver disease[166,169,170]. Immunomodulatory drugs (thalidomide), caspase inhibitors (emricasan), antioxidative drugs, radical scavengers, cyclooxygenase inhibitors and antibiotics (rifaximin)[166] were used to reduce hepatic inflammation and bacterial translocation as important steps in preventing the progression of PH. Farnesoid X receptor agonists were demonstrated to decrease IHVR by stimulating eNOS[171] activity in a rat model of cirrhotic PH[172].

However, despite ongoing research efforts, there are still no specific agents approved for the treatment of PH caused by NAFLD[173]. Therefore, general guidelines for PH should be followed in patients with NAFLD, while lifestyle changes (reduction in caloric intake, weight loss and daily exercise) remain the mainstay of the treatment approach[10].

CONCLUSION

The development of clinically significant portal hypertension mostly occurs in patients with cirrhotic NAFLD. Despite this fact, multiple lines of evidence confirm the early elevation of portal vein pressure and onset of PH in non-cirrhotic NAFLD patients. Increased IHVR is the main cause of PH in NAFLD and arises because of perisinusoidal fibrosis and microcirculation damage. HVPG as an invasive diagnostic method underestimates portal pressure in patients with NAFLD and some patients develop liver decompensation below an HVPG of 10 mmHg, which is traditionally considered the threshold for CSPH. Obesity seems to reduce the diagnostic accuracy of LSM, leading to the overestimation of PH severity. Baveno VII criteria might be used for non-invasive ruling out, but they have suboptimal diagnostic performance for ruling in CSPH in obese NAFLD patients. Similarly, Baveno criteria are reliable for ruling out VNT in non-obese NAFLD patients, whereas in obese patients NAFLD cirrhosis criteria might work better. Recent advances in understanding the pathophysiological background of NAFLD and related PH have resulted in several candidate molecules and pathways that might serve as the targets for pharmacological compounds, but this is still an area of ongoing research, and currently we still lack specific drugs for PH in NAFLD. Nevertheless, it is unrealistic to expect that a single medication could reverse all pathological changes taking place along the complex pathways of PH development in NAFLD, and thus a combination of lifestyle changes, liver-targeted therapies and modulation of metabolic derangements would probably represent the solution to this problem.

FOOTNOTES

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