World Journal of Hepatology

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DOI: 10.4254/wjh.v7.i3.443

World J Hepatol 2015 March 27; 7(3): 443-459
ISSN 1948-5182 (online)

REVIEW

Endothelial dysfunction in cirrhosis: Role of inflammation and oxidative stress

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Author contributions: Vairappan B solely contributed this work.
Supported by The Department of Biotechnology-Ramalingaswami Fellowship 5 years grant from the Government of India.
Conflict-of-interest: Vairappan B declares that he has no conflict of interest.

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Received: August 29, 2014
Peer-review started: August 30, 2014
First decision: November 1, 2014
Revised: November 8, 2014
Accepted: November 27, 2014
Article in press: November 27, 2014
Published online: March 27, 2015

Abstract

This review describes the recent developments in the pathobiology of endothelial dysfunction (ED) in the context of cirrhosis with portal hypertension and defines novel strategies and potential targets for therapy. ED has prognostic implications by predicting unfavourable early hepatic events and mortality in patients with portal hypertension and advanced liver diseases. ED characterised by an impaired bioactivity of nitric oxide (NO) within the hepatic circulation and is mainly due to decreased bioavailability of NO and accelerated degradation of NO with reactive oxygen species. Furthermore, elevated inflammatory markers also inhibit NO synthesis and causes ED in cirrhotic liver. Therefore, improvement of NO availability in the hepatic circulation can be beneficial for the improvement of endothelial dysfunction and associated portal hypertension in patients with cirrhosis. Furthermore, therapeutic agents that are identified in increasing NO bioavailability through improvement of hepatic endothelial nitric oxide synthase (eNOS) activity and reduction in hepatic asymmetric dimethylarginine, an endogenous modulator of eNOS and a key mediator of elevated intrahepatic vascular tone in cirrhosis would be interesting therapeutic approaches in patients with endothelial dysfunction and portal hypertension in advanced liver diseases.

Key words: Asymmetric dimethylarginine; Endothelial function; Nitric oxide; Portal hypertension; Hepatic cirrhosis, Reactive oxygen species; Inflammation

Core tip: Endothelial dysfunction (ED) is a key and early relentless event in patients suffering from gastrointestinal bleeding in cirrhosis and involves in response to both vasoactive and vasoconstrictor substances. The one such vasoactive molecule, nitric oxide (NO) plays a prime role in maintaining normal hepatic vascular function and if there any defect in NO availability leads to ED and portal hypertension (PHT) could be of great utility in preventing and curing complications of PHT.

Vairappan B. Endothelial dysfunction in cirrhosis: Role of inflammation and oxidative stress. *World J Hepatol* 2015;

7(3):443-459 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i3/443.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i3.443

INTRODUCTION

The endothelium is the largest organ and encompasses > 10^{13} endothelial cells in the body can able to generate both vasodilator [nitric oxide (NO), endothelium derived hyperpolarising factor (EDHF) and prostacyclin] and vasoconstrictor (endothelin-1, norepinephrine, leukotriene, thromboxane A_2 and angiotensin Ⅱ) substances and is essential for hepatic vascular homeostasis. Endothelium serves as a barrier to separate blood from the underlined tissue and thus maintains homeostasis at the vascular wall during physiological condition[1,2]. The salient features of normal healthy endothelium which including, regulation of vascular permeability, decrease in vascular tone, reduce in platelets adhesion and aggregation, prevention of thrombosis, inhibition of smooth muscle cell proliferation, inflammation and restricting leukocyte adhesion[3]. Indeed, many of these functions are mediated by endothelium driven NO[4]. The term endothelial dysfunction (ED) implicate a loss of function of numerous activities of the endothelium[5], mainly characterised by impairment of the production and release of endothelium driven vasodilatory factors including NO[4,6]. The hepatic vascular bed of cirrhotic liver exhibits ED and is now considered to play a key role in the initiation and advancement of liver cirrhosis[7]. The intrahepatic vasculature also displays increased sensitivity to vasoconstrictors in cirrhosis[8]. Furthermore, ED is also a common index for a wide variety of pathological conditions such as chronic renal failure, atherosclerosis, hypercholesterolemia, hypertension, diabetes and coronary artery disease[9,10].

HEPATIC CIRRHOSIS

Cirrhosis is a complication of many forms of chronic liver diseases and is a late stage of fibrosis, in which regenerative nodular formation surrounded by fibrous bands of the liver. The development of portal hypertension (PHT) (elevated pressure within the hepatic circulation) heralds the onset of most fatal complications of cirrhosis, which carry a poor prognosis and represent the first cause of death and need for liver transplantation in patients with cirrhosis[8,11]. The pathogenesis of PHT is predominantly related to a combination of structural and dynamic components that cause an increase in hepatic vascular resistance to portal blood flow[12]. The structural components such as fibrosis, regenerative nodule formation and vascular remodelling[13].

INTRAHEPATIC ENDOTHELIAL DYSFUNCTION IN CIRRHOSIS

Impaired endothelial dependent relaxation in the hepatic microcirculation due to reduced bioavailability of vasodilator, NO in cirrhotic liver contributes to increasing intra-hepatic vascular resistance, which culminating portal hypertension[14]. By contrast, in the splanchnic vascular bed, overproduction of NO contributes to increased endothelium dependent relaxation, leading to hyperdynamic circulatory disturbances, which observed in cirrhosis with portal hypertension[15,16]. Furthermore, increased vasoconstrictor agents such as thromboxane A_2 (TX A_2), a COX-1 derived prostanoids, and endothelin-1 are thought to associated with the pathogenesis of the dynamic component of the augmented intra-hepatic resistance and play a major role in the intrahepatic endothelial dysfunction of the cirrhotic liver[7,17]. Such imbalance between endogenous vasoconstrictor and vasodilator factors observed in the cirrhotic liver is thought to be similar to that found in other cardiovascular diseases[18]. The assessment of NO concentration in cirrhotic liver and systemic circulation is considered to be the prime indicative of endothelial dysfunction (ED).

NO AND ENDOTHELIAL DYSFUNCTION IN CIRRHOSIS

Endothelial dysfunction is thought to be a key event in the development of distinct human vascular diseases, including liver cirrhosis, hypertension, diabetes and atherosclerosis. Classically, ED has been considered to be the result of a decrease in bioavailability of NO in cirrhosis[14,19]. The amino acid, L-arginine, is the substrate of eNOS, the enzyme responsible for NO synthesis (Figure 1). Endothelial nitric oxide synthase (eNOS) driven nitric oxide (NO) is a potent vasodilator that plays a substantial role in maintaining vascular homeostasis in the normal intact liver[14,19], however when the liver fails, reduced intrahepatic eNOS activity triggers endothelial dysfunction contributes to the pathogenesis of PHT (Figure 1)[20]. It is an early and relentless event occurring after all forms of liver injury that leads to substantial morbidity and mortality in individuals with cirrhosis[11,21]. Reduced NO bioavailability makes a major contribution to endothelial dysfunction and is mainly due to reduced NO production or increased NO breakdown due to the chemical reaction with oxidant radicals[22]. Inflammation and oxidative stress are other important pathophysiological consequences that causes endothelial dysfunction and reduced NO bioavailability[22], which make an important contribution to the vascular structural changes in cirrhosis[23]. Furthermore, treatment with exogenous L-arginine

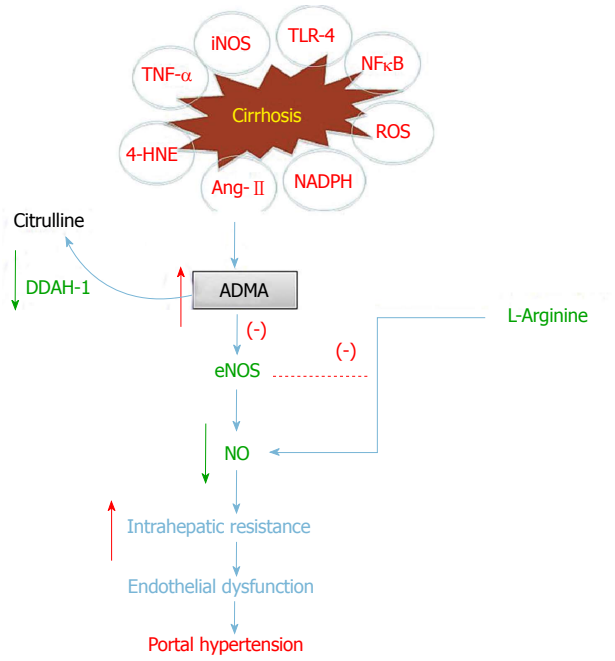

Figure 1 Schematic representation of the proposed role of inflammation and oxidative stress in mediating hepatic endothelial dysfunction in cirrhosis. Inflammation and oxidative stress are synergistically triggers accumulation of ADMA in the systemic circulation and the liver. Increased ADMA endogenously inhibits eNOS results in decreased hepatic NO production, which causes increased intrahepatic vascular resistance and endothelial dysfunction thus, portal hypertension in the context of cirrhosis. Inflammation and oxidative stress also inhibit ADMA hydrolysing enzyme, DDAH activity and promote methylarginine concentrations in the liver. L-arginine is the source for eNOS enzyme for NO production and is vasoprotective. TNF-α: Tumor necrosis factor α; NFkB; Nuclear factor kappa B; TLR: Toll like receptor; Ang II: Angiotensin II; NO: Nitric oxide; ADMA: Asymmetric dimethylarginine; eNOS: Endothelial nitric oxide synthase; DDAH: Dimethylarginine diaminohydrolase; iNOS: Inducible nitric oxide synthase; 4-HNE: 4-hydroxy-2-nonenal; NADPH; Nicotinamide adenine dinucleotide phosphate-oxidase; ROS: Reactive oxygen species.

has been shown to improve vascular function in liver cirrhosis suggesting that decreased substrate availability contributes to endothelial dysfunction[24]. Thus, impaired vascular uptake of L-arginine may play a key role in the pathogenesis of endothelial dysfunction in cirrhosis and should be explored as a potential therapeutic target[25].

Endogenous negative eNOS regulators

Several mechanisms are involved in regulating NO production following eNOS activation. Studies in relation to decreased hepatic eNOS activity have, to date, focused on inhibitors of eNOS activity such as asymmetric dimethylarginine (ADMA)[26,27] and caveolin-1 (major coat protein of endothelial caveolae)[28], or on the process affecting the post translational modification of eNOS[29]. Furthermore, trafficking and proper subcellular localization of eNOS are also critical for regulation of its activity[29,30]. One such protein, eNOS trafficking inducer (NOSTRIN), identified in a yeast two-hybrid approach, has been demonstrated to interact physically with eNOS *via* its C-terminal SH3 domain and regulated its function[29-31].

An emerging body of evidence indicated that ADMA, a deleterious endogenous inhibitor of NO synthases and thus presumed to be a marker of hepatic dysfunction in cirrhosis with PHT. One mechanism thought to be partially responsible for the reduction in NO and resultant ED in liver disease is an increase in the levels of the endogenous inhibitor of NOS, ADMA[19,32]. In this regard, our previous studies have shown evidence that increased ADMA contributes to reduced hepatic NO biosynthesis as a consequence of altered hepatic vascular function in cirrhosis[26,27,33]. In critically ill patients to whom admitted in ICU, hepatic dysfunction was associated with elevated ADMA levels and was identified as an independent predictor of mortality[34]. Furthermore, increased plasma ADMA was reported recently in biopsy proven non-alcoholic fatty liver disease (NAFLD) patients[35], hepatic vein of patients with compensated cirrhosis[36] and decreased following liver transplantation; thus the significant improvement of liver function[37] propose an important role for ADMA in clinical medicine. Elevated plasma ADMA has also recognised as an important risk factor for cardiovascular disease[38], coronary heart disease[39] and chronic renal failure[40]. Consequently, increased ADMA may be related to elevated activity of protein methyltransferase (PRMT), which is responsible for the methylation of arginine residues in cellular proteins[41]. Moreover, increased ADMA level was correlated with the severity of inflammation and levels of increased proinflammatory cytokine such as tumor necrosis factor (TNF)[42,43]. Laleman *et al*[44] showed in cirrhotic animals infusion of ADMA and NG-nitro-L-arginine methyl ester (L-NAME), other known inhibitors of NOS synergistically aggravated and resulted in paradoxical vasoconstriction, which associated with a further decrease in NOx levels. The pathophysiological increase in hepatic ADMA concentration observed in cirrhotic rats manifest decrease of hepatic eNOS activity.

Dimethylarginine diaminohydrolase

Furthermore, the intracellular levels of these methylated arginines are regulated through their metabolism to citrulline and dimethylamine by its hepatic specific enzyme called, dimethylarginine diaminohydrolase (DDAH)[41,45] (Figure 1). Two isoforms of DDAH have been identified and are widely expressed in human and rodent liver. DDAH 1 is an important isoform for the regulation of hepatic and systemic ADMA concentration and is present higher levels in tissue that expressing neuronal NOS (nNOS)[41,45]. The other DDAH isoform (DDAH 2) has an important effect in regulating NO activity, and is mainly found in tissue expressing eNOS and inducible NOS (iNOS)[41,45,46]. It is well known that increased intracellular DDAH plays a critical role in regulating tissue ADMA concentration[26,27,33,47], therefore alterations of DDAH activity and expression lead to change in intracellular ADMA concentrations and concomitant NO synthesis. *In vitro*, human umbilical vein endothelial cells (HUVECS) exposed to prolonged (48 h) TNF-α show eight fold increase of

ADMA, compared to control medium and associated DDAH activity was decreased to almost 60% of baseline values[48]. DDAH is a redox sensitive enzyme and is thus subject to inhibition by oxidants derived from endothelial superoxide[47,49], and antioxidant treatment corrects DDAH inhibition in *in vivo*[33,50]. Cirrhotic rat livers showed an increased O_2^- content compared to control rat livers and was ameliorated by adenoviral gene delivery of superoxide dismutase, increases NO bioavailability, improves intrahepatic endothelial function and reduces portal pressure[51]. In contrast to ADMA, SDMA, its vasoactive stereoisomer, has no effect on inhibition of NO synthases but competes with arginine for cellular transport across the y+ transporter[38,52]. Recently, Siroen and co-workers have shown that the human liver takes up substantial amounts of SDMA from the portal and systemic circulation and suggested that high plasma levels of SDMA may have hemodynamic consequences similar to those reported for ADMA[53]. However, in patients with alcoholic cirrhosis, noted plasma SDMA level was within the normal limit[54].

OXIDATIVE STRESS AND ENDOTHELIAL DYSFUNCTION IN CIRRHOSIS

In cirrhosis, oxidative stress induced mainly by an overproduction of reactive oxygen species (ROS)[55], which is a critical determinant of endothelial dysfunction and is due to disturbed balance between oxidant and antioxidant enzymes. Increased superoxide formation in the presence of equimolar concentrations of NO will lead to the formation of the potent ROS and reactive nitrogen species[56]. Furthermore, decreased NO bioavailability within the cirrhotic liver is mainly attributed by endothelial dysfunction and is mainly due to diminished eNOS activity as well as NO scavenging by increased release of superoxide (O_2^-)[55]. NO also binds to superoxide anion (O_2^-) to produce the most powerful oxidant peroxynitrite ($ONOO^-$). Consequently, peroxynitrite can cause oxidative damage, protein nitration and S-nitrosylation of biomolecules such as proteins, lipids and DNA[57,58]. In fact, peroxynitrite can also oxidise tetrahydrobiopterin (BH_4), an essential cofactor for eNOS to trihydrobiopterin radical (BH_3)[59], which can further disproportionate to dihydrobiopterin (BH_2). As a consequence, functional endothelial NOS is converted into a dysfunctional O_2^- generating enzyme[60] termed as eNOS uncoupling, contributes to ROS overproduction within the intrahepatic circulation. The generation of ROS and superoxide are the key mediators of damage to endothelial cells in cirrhosis[23,61]. BH_4 administration to cirrhotic rats increased hepatic NOS activity and cyclic guanosine monophosphate (cGMP) levels and significantly reduced ED, and subsequent portal pressure may represent a new therapy for ED in patients with cirrhosis[62,63]. Overwhelming evidences have also indicate that in cirrhosis with bacterial endotoxemia, excessive NO production by iNOS reacts with molecular oxygen (O_2^-), leading to the formation of peroxynitrite radical and causes massive hepatic tissue damage as well as fall in blood pressure induced in the vascular wall[27,64]. Furthermore, eNOS uncoupling is also caused by L-arginine depletion, increased endogenous eNOS inhibitors and S-glutathionylation of eNOS[65,66].

HEPATIC INFLAMMATION AND ENDOTHELIAL DYSFUNCTION IN CIRRHOSIS

Hepatic inflammation is a common trigger of liver diseases, associated with ED and causes increased hepatic vascular risk in cirrhosis[67]. There are several inflammatory mediators involved in downregulation of eNOS activity and NO bioavailability within the hepatic circulation resulting increased intrahepatic resistance and ED thus, PHT in patients with cirrhosis (Table 1).

TNF-α

TNF-α, a proinflammatory cytokine with the broad spectrum of deleterious effects is believed to exert vascular effects by increasing vascular permeability and causing vasodilatation, which mediated through NO dependent pathways[68]. In cirrhosis, increased systemic and hepatic TNF-α concentration has shown to associate with overwhelming NO production[47]. Interestingly, in cultured endothelial cells, TNF-α reduces NO bioavailability[48], and *in vivo* TNF-α may also directly alter endothelial vasomotor function[69]. Moreover, Plasma TNF-α concentration was shown to be significantly higher in alcoholic hepatitis (AH) patients who subsequently died than those who survived[70]. Patients with AH had significantly higher plasma TNF-α concentration than did patients with inactive cirrhosis or alcoholics having no liver disease[71,72]. It has also shown that lipopolysaccharide (LPS), a component of the gram-negative bacterial cell wall, induces a marked TNF-α production *in vivo* in cirrhotic rats[73] and *ex vivo* in monocytes from cirrhotic patients[74]. Infliximab (anti-TNF antibody) treatment has been shown to reduce systemic TNF-α and a concomitant drop in portal pressure in alcoholic hepatitis patients with severe ED[75]. Our previous study also supported the above notion that treatment with anti-TNF improved hepatic DDAH enzyme function by decreasing ADMA level and a concomitant increase of hepatic eNOS activity and NO bioavailability in a bile duct-ligated cirrhotic rat[42]. Infliximab treatment also shown to beneficial in CCl_4, and high fat diet induced liver disease models[76,77]. Furthermore, anti-TNF treatment to the portal vein ligated rats significantly blunts the development of the hyperdynamic circulation and reduces portal pressure[75].

Nuclear factor-κB

Nuclear factor-κB (NFκB) is a ubiquitous transcription

Table 1 Factors affecting endothelial dysfunction in cirrhosis

Marker	Endothelial dysfunction	Ref.
Inflammatory marker		
TNF-α	Inhibition of NO synthesis	[47,75,78,84,99,104]
NFκB	Increase of ADMA	
TLR	Increase of Caveolin-1	
Ang II	Reduction of eNOS activity	
	Inhibition of DDAH enzyme	
	Upregulation of iNOS	
	Increase of superoxide production	
	Reduction of antioxidant capacity	
Oxidative marker		
4-HNE	Reduction of DDAH enzyme activity	[42,78,104]
NADPH	Decrease of NO bioavailability	
	Increase of ADMA levels	
	Increase of ROS generation	
Cyclooxygenase -derived prostanoids		
TXA_2	Reduction of intrahepatic nitrate/ nitrite	[110-112]
PGI_2	Upregulation of iNOS expression	
	Increase of intrahepatic resistance	
Other marker		
ET-1	Increase of inflammation	[122,130,138,139, 145]
LOX-1	Stimulation of ROS generation	
PARs		
Adiponectin		
Palmitic acid		

TNF-α: Tumor necrosis factor-α; NFκB; Nuclear factor kappa B; TLR: Toll like receptor; Ang II: Angiotensin II; NO: Nitric oxide; ADMA: Asymmetric dimethylarginine; eNOS: Endothelial nitric oxide synthase; DDAH: Dimethyl arginine diaminohydrolase; iNOS: Inducible nitric oxide synthase; 4-HNE: 4-hydroxy-2-nonenal; NADPH; Nicotinamide adenine dinucleotide phosphate-oxidase; ROS: Reactive oxygen species; TXA2: Thromboxane A2; PGI2: Prostaglandin I2; ET-1: Endothelin -1; LOX-1: Lectin-like oxidized low-density lipoprotein receptor-1; PARs: Protease activated receptors.

factor that activated by a variety of cytokines which including TNF α and is thought to be a key regulator of genes involved in inflammation[47,78]. In BDL cirrhotic rats, elevated plasma F2-isoprostanes correlated with an increase of TNF-α and constitutive activation of NFκB[79]. Osanai *et al*[80] showed in HUVECs that synthesised ADMA by PRMT-1 was further stimulated by shear stress *via* activation of the NFκB pathway. Recently ADMA induces TNF-α production *via* ROS/ NFκB dependent pathway also reported in human monocytes[81]. Activation of NFκB also increased in the liver of chronically HCV-infected patients compared with controls[82], which is in line with our previous observation that increased NFκB protein expression in BDL cirrhotic rats was downregulated following Infliximab treatment[47,78]. TNF-α facilitates the translocation of free NFκB from cytosol to the nucleus and the induction of iNOS gene expression. The overproduction of NO by iNOS is important in inflammation and causes ED and may associate with hyperdynamic circulation in cirrhosis[27,83,84]. In this context, recently Jalan *et al*[84] observed that an incubation of cirrhotic patient plasma or LPS with HUVECS showing increased iNOS activity. Thus, transjugular intrahepatic stent-shunt insertion (TIPSS) induced endotoxemia results in upregulation of the iNOS pathway in the endothelium of critically ill cirrhotic patients[84]. Hence, increased iNOS driven NO is marker for the treatment of inflammatory disorders, and its prevention is a target for the design of new drugs acting on iNOS[85,86]. In fact, inhibition of NFκB activation was initially considered important for designing NOS inhibitors, since NFκB mainly involved in iNOS expression during inflammatory conditions[47,85,86]. Therefore, the regulation of iNOS *via* the NFκB pathway is an important mechanism in inflammatory processes and potential site for intervention in inflammatory diseases.

Toll-like receptors

Toll-like receptors (TLRs) belong to the family of transmembrane pattern-recognition receptors that recognize pathogen-associated molecular patterns, which including LPS[87]. TLR4 expressed on both parenchymal and non-parenchymal cell types in the liver and its activation trigger hepatic innate immune signaling, and may contribute to endothelial dysfunction and intrahepatic vascular tone in patients with cirrhosis[8,87,88]. In addition, the potential role of TLR4 in mediating renal injury in patients with cirrhosis was described recently[89]. The seminal observations made in this study were that the renal expression of TLR4 and the excretion of TLR4 protein was significantly higher in patients with cirrhosis who presented with acute deterioration and had renal dysfunction compared with those that did not[89]. Furthermore, urinary TLR4 was associated with significantly greater risk of death in patients with renal dysfunction and in those with superimposed inflammation[89]. TLR4 expressed on the surface of several cell types, including endothelial cells and its activation shown to reduce NO concentration, resulting ED[90]. Accordingly, anti-TLR4 treatment improved endothelium-dependent relaxation, and improved NO[91]. TLR4 also contributes to the increased ROS production and ED in hypertension, diabetes and obesity[92]. Recently, Benhamou *et al*[93] revealed that both TLR2 and TLR4 in mediating endothelial dysfunction and vascular remodeling in primary arterial antiphospholipid syndrome. TRL4 signalling leads to activation of NF-κB[94], a pathway associated with endothelial injury[95], and increased TLR4 expression has also shown in advanced liver disease[89,96]. LPS induced TLR4 mediated proinflammatory signalling has also showed in human hepatic stellate cells (HSC)[97], and functional expression of TLR9 has detected in sinusoidal hepatic endothelial cells and hepatocytes[98]. Furthermore, several animal studies support the importance of TLR4 in hepatic fibrosis, and TLR4 knockout mice showing less fibrosis induced by BDL or carbon tetrachloride (CCl_4) compared to wild type[99].

These results suggested an important function of TLRs on the development of inflammatory pathology in hepatic cirrhosis. Stadlbauer *et al*[96] observed that in AH patients, the increased TLR 2, 4 and 9 expressions correlated with neutrophil dysfunction and endotoxemia, albumin an endotoxin scavenger attenuated these complaints by decreasing TLRs expression. Several lines of evidence exist implicating gut derived endotoxemia in the pathogenesis of portal hypertension[100]. Administration of norfloxacin, a selective gut decontaminant prophylactic reduced endotoxin levels, TLR4 expression and decreased NO-mediated forearm vasodilatation and improved survival in cirrhosis[94,101].

Angiotensin Ⅱ

The renin-angiotensin system (RAS) plays a key physiological role in regulating vascular function. In the pathophysiology, RAS has also shown to promote vascular injury by triggering ED, vascular remodelling and vascular inflammation[102,103]. Angiotensin (Ang) Ⅱ the core composition of the RAS involved in many chronic diseases, which including hepatic cirrhosis[104]. Increased Ang Ⅱ causes endothelial dysfunction, vasoconstriction, sodium water retention, elevated blood pressure, ROS generation, inflammatory mediators and pro-fibrotic cytokines[105]. The adverse effects of Ang II induced ED is mediated by interaction with the plasma membrane AT 1 receptors (Ang Ⅱ type 1 receptors) and causes NO reduction by inducing eNOS enzyme dysfunction and promoting NOS uncoupling. Thus, pharmacological inhibition of the production or actions of Ang Ⅱ receptor blockers now represents an effective strategy to delay the progression of endothelial dysfunction in experimental models and humans[105,106]. In this context, previous clinical studies have shown evidence that RAS play an important role in the elevation of the ADMA concentration in hypertensive patients, and blockade of Ang Ⅱ by ACEI or Ang Ⅱ receptor blocker (ARB) significantly attenuates the elevated level of ADMA, resulting in endothelial protection[107,108]. Pharmacological blockade of angiotensin Ⅱ receptors using the drug Candesartan cilextil (CC) may attenuate the progression of liver cirrhosis and endothelial dysfunction. In HUVECS, CC increased the eNOS protein level, inhibited the expression of nicotinamide adenine dinucleotide phosphate oxidase (Nox) subunits and Ang Ⅱ induced intracellular ROS and nitric oxide, and promoted the extracellular release of nitric oxide[109] suggesting that it augmented the bioavailability of nitric oxide. Thus, CC administration may attenuate ED and for the future therapeutic approach in portal hypertensive patients with cirrhosis. Ang Ⅱ can also activate NADPH oxidase (Nox), leading to increased ROS generation and commencing ED in cirrhosis[104].

VASOCONSTRICTORS AND ENDOTHELIAL DYSFUNCTION

Thromboxane

TXA_2, a vasoactive prostanoid and COX metabolite, increased intrahepatic vascular tone in cirrhosis, more specifically in the phenomenon of hyper responsiveness to vasoconstrictors and caused intrahepatic ED[110,111]. Administration of COX inhibitors such as flurbiprofen and nitroflurbiprofen (NO releasing COX inhibitor) to cirrhotic rats result in decreased hepatic TXA_2 production and an increased intrahepatic nitrate/nitrite (an index of NO synthesis) concentration thereby by attenuating intrahepatic vascular resistance, endothelial dysfunction, and hepatic hyper reactivity to vasoconstrictors[111]. TXA_2 and PGI_2, the other COX 2 derivatives may act simultaneously, producing a compensatory effect that reduces NO release and may limit the hyperdynamic circulation in cirrhosis[112]. The use of indomethacin, a COX inhibitor has shown to prevent liver fibrosis, and rise in portal hypertension in liver cirrhosis[113]. Indeed, study also shows that COX inhibitors could worsen the hyperdynamic circulation associated with liver cirrhosis[112]. TXA_2 induces vasoconstriction by activating the TXA_2/prostaglandin-endoperoxide (TP) receptor[114]. TP receptor ligands include TXA_2, PGH_2, and isoprostanes[115,116]. TXA_2 acts through its G-protein-coupled receptor leading to vasoconstriction by activating the RhoA/Rho-kinase pathway, and by increasing calcium levels in HSC[117]. Oral administration of terutroban, a specific antagonist of the TP-receptor[118] has shown to attenuates inflammation and oxidative stress and reduce RhoA/Rho-kinase-dependent signaling and restore NO bioavailability in endothelial cells[119] may represent a useful agent in the treatment of endothelial dysfunction in cirrhosis with portal hypertension.

Endothelin-1

A most potent vasoconstrictor endothelin (ET) -1 regarded as a key player in ED, primarily binding to G-protein coupled receptors such as ETA and ETB and acts in a paracrine fashion[120]. Previous study has shown that ETB receptors present in endothelial cell can elicit endothelium-dependent relaxation by improving NO release by contrast, ETA and ETB receptors present on the fibroblasts and smooth muscle cells trigger vasoconstriction and inflammation[121]. Cirrhotic rats with diabetes showed higher intrahepatic ET-1 vasoresponsiveness than normoglycemic cirrhotic rats[122]. ED also found in patients with insulin resistance (IR)[123,124]. In this context, IR can be triggered by ET-1 infusion in rats by activating phosphatidylinositol (PI) 3-kinase activity in smooth muscle cells in an ETA dependent manner and treatment with ETA receptor antagonists results in improvement of insulin sensitivity and associated

endothelial function *via* an inhibition of PI 3-kinase activity[125]. In this context, a very recent study pointed out that LPS stimulation to portal hypertensive rats showed enhanced renal vascular response to ET-1 through ETA overexpression[126].

OTHER MARKERS OF ENDOTHELIAL DYSFUNCTION

Lectin-like oxidised LDL receptor-1

Lectin-like oxidised LDL receptor-1 (LOX1) is a key receptor for oxidised low-density lipoprotein (Ox-LDL) and identified in endothelial cells, and considered as a marker of ED in various pathological setting[127,128]. LOX-1 promotes ROS generation augments endothelial adhesiveness to monocytes and inhibits NO synthesis[129]. The recent review by Lubrano *et al*[130] described in detail about the relationship between LOX1 and ROS. Furthermore, increased expression of LOX1 was found in the placenta of women with intrahepatic cholestasis during pregnancy[131]. LOX-1 polymorphism also associated with liver disease severity in non-alcoholic steatohepatitis[132] and could be a biomarker for patients with endothelial dysfunction in liver cirrhosis.

Protease activated receptors

Protease activated receptors (PARs) are G protein-coupled receptors which, mediating cellular effects of some proteases of the activated coagulation system such as thrombin, trypsin or metalloproteinase[133]. ECs express PAR1, PAR2 and PAR4[134]. Endothelial PARs play important roles in the crosstalk between coagulation and inflammation in sepsis[133]. Acute PAR1 activation causes an increase in vascular permeability, presumably due to direct endothelial contractile responses[133]. PAR1 deficiency and blockade has shown to reduce inflammation in a mouse model of colitis[135]. Moreover, activation of protease through its receptor following thrombus formation, hemorrhage and inflammation led to the conversion of ECs to a proinflammatory phenotype and may result in vascular lesion development[133]. Garcia *et al*[136] have shown in cultured ECs, PAR1 activation stimulates the production of prostacyclin and NO, consisting with other reports shown in *in vivo* that PAR1 activators cause hypotension when injected intravenously and cause NO mediated vasodilation[137]. In this context, Knight *et al*[138] and Sakata *et al*[139] reported that PAR2 promotes experimental liver fibrosis by increase of TGF β production in mice and to induce a profibrogenic phenotype in human HSCs. Thus, targeting PARs and using its antagonists in endothelial dysfunction with cirrhosis may represent a novel therapeutic approach in preventing portal hypertension in cirrhosis.

Adiponectin

Adiponectin is a protein hormone synthesized by adipose tissue. Plasma physiological concentration of adiponectin represents 0.05% of all plasma proteins and is a key component in the relationship between adiposity, inflammation and insulin resistance[140]. Previous studies have shown evidence that the association between hypoadiponectinemia and ED[141,142]. Wang *et al*[142] showed in ECs that adiponectin stimulating NO synthesis by activating AMPK mediated pathway. Furthermore, adiponectin knockout mice exhibited impaired endothelium dependent vasodilation and NO production[143]. Earlier published studies have pointed out that adiponectin administration significantly increases NO production by regulating eNOS enzyme activity and its phosphorylation and maintain endothelial function[141]. However, despite the hepatoprotective effect of adiponectin have shown in NAFLD and other chronic liver ailments, the plasma concentration of which increased in patients with cirrhosis of different aetiologies. Indeed, the factors related to elevated levels of adiponectin in cirrhosis are not yet completely understood. In this context, Tietge *et al*[144] showed an evidence that increased adiponectin levels in cirrhotic patients correlate exclusively with reduced liver function and altered hepatic haemodynamics. Furthermore, Salman *et al*[145] and Tacke *et al*[146] reported that an elevated adiponectin correlated with inflammation and liver damage and high levels were found in human cholestasis as well as in an animal model of cirrhosis[145,146]. Thus, adiponectin may serve as a novel biomarker for cholestasis in liver cirrhosis and agents that modifying adiponectin concentration in liver cirrhosis may use as a potential diagnostic tool but also as therapeutic target for ED in cirrhosis.

Free fatty acid

Liver plays a significant role in lipid homeostasis including several stages of lipid synthesis and transportation. Thus, it is reasonable to anticipate an abnormal lipid profile associated with the progression of hepatic dysfunction. Furthermore, hyperlipidaemia is main risk factor for ED, which is a common indicator in patients with hepatic cirrhosis[147]. Accumulated evidence indicates that increased hepatic and plasma free fatty acid (FFA) concentration led to hyperlipidemia and may cause ED in cirrhosis. Previously it has been shown that FFA trigger HUVECs apoptosis and inhibit cell cycle progression[148]. In this regard, palmitic acid a key FFA in the bloodstream, exposure to ECs causes cell necrosis and the release of proinflammatory cytokines[149,150] consistent with other report showing in cultured bovine retinal pericytes, in which palmitate can induce apoptosis by promoting oxidative stress[151]. Recently Ristic-Medic *et al*[152] observed in cirrhotic patients, increased levels of palmitic acid and total saturated fatty acids when compared to healthy controls. Thus, FFA play an important role in cirrhosis with ED and agents that reduce palmitic acid concentration would be used as a possible future target for therapy. One such agent,

Table 2 Classic and novel therapeutic strategies directing to improvement of endothelial dysfunction in cirrhosis

Therapeutic agent	Endothelial function	Ref.
Anti-inflammatory agents	Increase of NO bioavailability Reduction of ADMA Upregulation of eNOS activity Decrease of Inflammation	[25,42,75,111]
Vitamins	Improvement of eNOS activity Increase of NO bioavailability Scavenging of ROS generation Antioxidant function	[159,160,162]
Flavonoids	Increase of NO bioavailability Prevention of oxidative stress Improvement of antioxidant enzymes	[15,166,168]
Nuclear receptors	Increase of NO bioavailability Improvement of DDAH Reduction of ADMA Amelioration of hepatic vascular tone	[33,50,187]
Ammonia lowering agents	Detoxification of ammonia levels Increase of NO bioavailability Reduction of ADMA Upregulation DDAH expression	[27,189,190,192,201]
Statins	Decrease of total cholesterol Improvement of Akt-dependent eNOS phosphorylation Promoting NO biosynthesis Reduction of Ox-LDL Attenuation of inflammatory indices	[147,170,172,202,203]
Beta blockers	Amelioration of oxidative stress Attenuation of Inflammation Restoration of antioxidant enzymes	[194,196]
Angiotensin-receptor antagonists	Increase of NO Decrease of Ang-II mediated inflammation Decrease of TIMP-1, MMP-2 mediated fibrosis	[200,204]

NO: Nitric oxide; ADMA: Asymmetric dimethylarginine; eNOS: Endothelial nitric oxide synthase; DDAH: Dimethyl arginine diaminohydrolase; Ox-LDL: Oxidized low-density lipoprotein; Ang Ⅱ: Angiotensin Ⅱ; TIMP-1: Tissue inhibitor of metalloproteinase 1; MMP-2: Matrix metalloproteinase-2.

eicosapentaenoic acid (EPA), ω-3 polyunsaturated fatty acid (PUFA) is abundant in fish oil has shown to enhance the production of NO, *via* activating eNOS and improve normal vascular endothelium[153]. Very recently Lee *et al*[154] have demonstrated that treatment with EPA protects against palmitic acid induced ED through activation of the AMPK-eNOS mediated pathway. Highly purified EPA also shown to prevent the development of inflammation and hepatic fibrosis in rats[155,156]. In addition, peroxisome proliferator-activated receptor (PPAR)-α, a member of the nuclear receptor superfamily and a key regulator of fatty acid homeostasis[157], has been shown to improve endothelial dysfunction and portal pressure in cirrhotic rats[158]. The above indices, therefore, provide a rationale for novel insights into the pathophysiology of ED and the potential for the development of novel biomarkers and therapeutic approaches in patients with endothelial dysfunction and advanced liver disease.

EMERGING THERAPY FOR REVERSAL OF HEPATIC ED IN CIRRHOSIS

ED is an early event in the pathogenesis of cirrhosis with PHT and can be reversible with certain therapies (Table 2). Restoration of ED appears to be a crucial therapeutic target, since ED predicts most of the liver related problems in alcoholic liver disease (ALD), hepatorenal syndrome (HRS), hepatic encephalopathy (HE) and sepsis.

Antioxidant strategy (Vitamins and flavonoids)

Ascorbic acid (vitamin C) has been shown to improve the NO-dependent vasodilatation in vascular beds of patients with conditions characterized by marked ED in cirrhosis[159]. The other antioxidant α-tocopherol (vitamin E) has also shown to improvement of hepatic ED by suppressed hepatic ADMA and oxidative stress and improved hepatic NO in cirrhotic rats[160]. In addition, folic acid, a superoxide scavenging vitamin B9 and its active metabolite 5-methyltetrahydrofolate (5-MTHF) has been shown to restore ED in patients with many cardiovascular diseases[161]. Folic acid mainly involved in downregulating eNOS derived superoxide and eNOS uncoupling thereby improving regeneration of BH_4 from BH_2, by preventing BH4 oxidation, which results in increased NO[161]. The beneficial effects of 5-MTHF have shown in decompensated cirrhotic patients recently[162]. Superoxide dismutase (SOD) gene transfer also has shown to reduce portal pressure in CCl_4 cirrhotic rats with portal hypertension through reducing oxidative stress and increased NO bioavailability[61]. Tempol, a SOD mimetic reduces superoxide, increases nitric oxide, and reduces portal pressure in sinusoidal endothelial cells of cirrhotic livers[163]. Furthermore, flavonoids, an integral part of the human diet have been shown to confer protective effects on vascular endothelial function in humans[164], and its protective effects are chiefly ascribed to their antioxidant and vasodilatory actions[165]. Very recently, Hsu *et al*[15] found that green tea polyphenol decreases the severity of portosystemic collaterals and mesenteric angiogenesis in rats with liver cirrhosis. Furthermore, De Gottardi *et al*[166] observed in cirrhotic patients with portal hypertension that dark chocolate blunted the postprandial increase in hepatic venous pressure gradient (HVPG) by improving flow-mediated hepatic vasorelaxation and ameliorated systemic hypotension. In addition, Lin *et al*[167] showed quercetin supplementation has associated with multifactorial potential as well as down-regulation of NF-κB and TGF-β/Smad signalling, probably *via* interference with TLR signalling. Resveratrol, a natural polyphenolic flavonoid present higher amount in grapes has shown

to reduce portal pressure by attenuating ED. Moreover, resveratrol supplementation also results in reducing oxidative stress and upregulating eNOS expression without affecting systemic hemodynamics in cirrhotic rats[168].

Statins

Statins (HMG-CoA reductase inhibitors) lower serum cholesterol concentrations and exhibits beneficial therapeutic effects in cirrhotic patients, as evidenced by various clinical trials[169-171]. Abraldes *et al*[169] demonstrated that simvastatin improve hepatic NO generation and endothelial function and lowers portal pressure in patients with cirrhosis. Moreover, atorvastatin has been shown to prevent liver inflammation and HSC activation induced by Ang-II infusion[172]. Schwabl *et al*[172] found that pioglitazone, an insulin sensitiser decreases portosystemic shunting by modulating inflammation and angiogenesis in cirrhotic and non-cirrhotic portal hypertensive rats. Additionally, Sorafenib, a tyrosine kinase inhibitor approved in the treatment of hepatocellular carcinoma, has shown to have beneficial effects in reducing portal pressure in cirrhosis[173]. The other multitarget receptor tyrosine kinase inhibitors such as Sunitinib and Imatinib were also shown to use for the treatment of portal hypertension[174] and may have a potential role in regulating ED in cirrhosis through NO mediated mechanisms. However, further encouraging clinical studies of statins strategy to ED in cirrhosis needs to be explored.

Anti-inflammatory agents

Human serum albumin (HSA) is one of the most frequent treatments in patients with decompensated cirrhosis[175]. It also reduced the severity of other chronic liver diseases such as HE and HRS and improved survival of patients with spontaneous bacterial peritonitis (SBP)[175-177]. In addition, albumin has been demonstrated to have a clinically significant beneficial effect on ED and survival during experimental endotoxemia[178]. It also reduced sequential organ failure assessment (SOFA) score in critically ill patients with hypoalbuminemia[179]. Furthermore, pentoxifylline and N-acetylcysteine, the other known anti-inflammatory agents have shown to associated with reduced the risk of inflammation and ED in cirrhosis[180-182]. Antibiotics such as quinolones and rifaximin and high-density lipoprotein (HDL) treatment have shown to associate with the reduction of inflammation and portal pressure by neutralising portal bacterial endotoxin load[20,101,183]. Thus, anti-inflammatory agents would improve NO bioavailability and reduce ED, considered a potential therapeutic approach for the management of portal hypertension in cirrhosis.

Nuclear receptors

Obeticholic acid, a synthetic farnesoid X receptor (FXR) ligand belongs to a nuclear receptor superfamily of transcription factor, which plays an important role in bile acid and lipid metabolism[184,185] has also been the subject of considerable attention over recent years[50]. FXR agonists have numerous target genes including DDAH1[186]. Our previous study has shown evidence that obeticholic acid significantly increases hepatic DDAH-1 and eNOS activity and improved NO bioavailability in cirrhotic rats, leading to improvement in endothelial function and associated drop in portal pressure[33]. Similarly, a multi-centre phase 2a trial of obeticholic acid in decompensated cirrhotic patients show a trend towards a drop in portal pressure[187]. Another promising approach of transfection of cirrhotic liver with DDAH-1 decreased ED and portal hypertension in BDL rats[188]. Furthermore, other member of the nuclear receptor superfamily, PPAR- α also has shown to improve endothelial dysfunction and portal pressure in cirrhosis[158].

Ammonia lowering agents

AST-120, an oral adsorbent carbon microspheres and ammonia-lowering agent[189] has shown to reduce ED in adenine-induced uremic rats[190]. AST-120 treatment was also shown to prevent the progression of HE in cirrhotic rats[189] and chronic kidney disease (CKD) in a clinical setting[191], which may be used for the treatment of ED in cirrhosis. Indeed, further studies would be needed for describing the potential role of AST-120 on NO mediated ED in cirrhosis. Furthermore, we established a new promising therapy such as OCR-002 (ornithine-phenylacetate) for the treatment of HE[27,192]. OCR-002 is currently being advanced in the clinic and also effective in reducing PHT by lowering ammonia mediated inflammation and improving NO bioavailability[193] and may consider for the future therapeutic approach for the management of ED and associated PHT in patient with cirrhosis.

Non-selective β blockers

Carvedilol is a non-selective β blocker with alpha-1 adrenergic blocker activity has been shown to amelioration of oxidative stress and restoration of antioxidant enzyme activities, and attenuation of NF-κB mediated inflammation in chronic liver disease[194]. Interestingly, Reiberger *et al*[195] observed in BDL cirrhotic rat that nebivolol, a third generation beta-blocker increased splanchnic blood flow and portal pressure *via* NO mediated signalling. In this context, Ma *et al*[196] demonstrated in myocardial infraction that targeting NO with a nebivolol treatment improves diastolic dysfunction through reducing myocardial oxidative stress by enhancing 5'-AMP-activated protein kinase and Akt activation of NO biosynthesis. Moreover, long-term nebivolol administration reduces renal fibrosis and prevents endothelial dysfunction in a rat hypertensive model[197]. In this context, Mookerjee *et al*[11] have pointed out that specific controlled studies are addressing the use of β-blockers in patients with severe decompensation of cirrhosis with high risk of

sepsis and renal dysfunction are inadequate. Hence, further clinical studies on the effect of β-blockers through NO mediated pathway are challenging in liver cirrhosis.

Angiotensin-receptor antagonists

Additionally, Candesartan cilextil (CC), a selective angiotensin Ⅱ type Ⅰ (AT1) receptor antagonist widely used as an antihypertensive in clinical practice has shown to improve ED[198,199]. In addition, recent clinical study has shown evidence that CC administration was safe and well tolerated to compensated cirrhotic patients, without an underlying cause of renal failure or hepatic decompensation[200]. Given the substantial experimental evidence that CC has the potential beneficial effect in distinct human diseases by blocking Ang-Ⅱ mediated AT1 receptor and may improve ED and NO bioavailability and associated mechanism in cirrhosis.

CONCLUSION

In conclusion, this review has been discussed the involvement of various inflammatory and oxidative stress markers on the regulation of NO biosynthesis and associated ED. The therapeutic interventions, which including antioxidants, anti-inflammatory and ammonia lowering agents, bile acid receptors, statins, insulin sensitisers, beta blockers and ARBs have been shown to increasingly recognised to attenuate liver cirrhosis by decreasing inflammation, oxidative stress and promoting NO biosynthesis. Subsequently, the development of an ideal therapy based on the increase of hepatic NO synthesis through ADMA-DDAH pathway may improve endothelial function and reduce inflammation, subsequent portal pressure reduction and without compromising systemic arterial pressure in patients with advanced liver disease. Remarkably, DDAH-1 gene strategy to cirrhotic liver would advance future therapeutic attention in the context of improvement of NO synthesis and reduce inflammation and associated ED and portal pressure reduction in-patient with cirrhosis.

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P- Reviewer: Pan WS, Rajeshwari K **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wu HL

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