

von Willebrand factor antigen as a therapeutic target of portal hypertension in cirrhosis

Georgios N Kalambokis, Gerasimos Baltayiannis, Dimitrios Christodoulou

Georgios N Kalambokis, 1st Division of Internal Medicine, Medical School, University of Ioannina, 45110 Ioannina, Greece

Gerasimos Baltayiannis, Dimitrios Christodoulou, Division of Gastroenterology, Medical School, University of Ioannina, 45110 Ioannina, Greece

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Correspondence to: Georgios N Kalambokis, MD, Assistant Professor of Internal Medicine, 1st Division of Internal Medicine, Medical School, University of Ioannina, 45110 Ioannina, Greece. gkalambo@cc.uoi.gr
Telephone: +30-2651-099735
Fax: +30-2651-007883

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Abstract

Increased thrombotic potential within the liver sinusoids due to local endothelial production of von Willebrand factor antigen macromolecules could represent an

additional therapeutic target of portal hypertension in patients with cirrhosis. In this case, anti-inflammatory and antithrombotic drugs could modulate portal pressure by preventing the formation of intrahepatic platelet-induced microthrombi.

Key words: von Willebrand factor antigen; Endothelial dysfunction; Treatment; Portal hypertension

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Core tip: The purpose of this letter to the Editor is to comment on the potential contribution of increased intrahepatic levels of von Willebrand factor as an additional mechanism that could be related to increased portal pressure in patients with cirrhosis and propose drugs which could decrease portal pressure on the basis of von Willebrand factor's production or effects.

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TO THE EDITOR

We read with great interest the article by Garbuzenko^[1] on the pharmacotherapy of cirrhosis associated portal hypertension (PH) on the basis of its pathogenetic mechanisms. We fully agree that the major advances that have been made the recent years in our understanding of the pathophysiology of PH need to be translated into novel therapeutic strategies for the reversal of increased portal pressure. In his review, the author highlighted intrahepatic endothelial dysfunction

(ED) and endotoxemia associated with bacterial translocation (BT) as important targets of future treatment of cirrhosis associated PH. Indeed, a large body of evidence suggests that sinusoidal ED is a key mediator of the pathogenesis of increased intrahepatic vascular resistance *via* a number of mechanisms which synergistically result in decreased hepatic nitric oxide (NO) production^[2,3]. On the other hand, BT-related exposure to bacterial products and activation of cytokine cascade, which increase along with the severity of cirrhosis, are thought to play a dual causal role in PH by inducing downstream effects on intrahepatic NO synthesis^[3,4] while, in contrast, stimulate NO production in the splanchnic arterial bed with a subsequent increase in portal venous inflow^[5].

Apart from NO, the platelet adhesive protein von Willebrand factor antigen (vWF-Ag) has been proposed as a valuable indicator of ED in patients with cirrhosis^[6,7]. vWF-Ag is produced and released as ultralarge multimers by activated endothelial cells in several vascular ED disorders^[8,9], including inflammatory states^[10]. Interestingly, vWF immunostaining is usually positive in large vessels but negative in the sinusoidal endothelial cells in the normal state^[11]. On the occurrence of cirrhosis the sinusoidal endothelial cell becomes positive for vWF^[12,13], presumably in association with the capillarization of hepatic sinusoids^[14]. Based on accumulating data, it can be suggested that vWF-Ag may be a factor which initially links BT-related inflammation and intrahepatic ED, and subsequently predisposes to portal microthrombosis with possible clinical implications in future therapeutic approaches to PH.

Circulating vWF-Ag levels have been found to be markedly elevated in patients with cirrhosis. Similarly to BT-related inflammation, plasma levels of vWF-Ag are significantly correlated with the severity of liver disease and PH^[7,13,15]. A previous report by Ferro *et al.*^[7] demonstrated that endotoxemia is strongly correlated with plasma levels of vWF-Ag in the setting cirrhosis. It is also known that on the occurrence of superimposed systemic inflammation in patients with cirrhosis, plasma levels of vWF-Ag increase according to the degree of inflammatory response^[16]. In this regard, endotoxin in a dose-dependent manner^[7], and inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin (IL)-1 and IL-8, have been shown to stimulate the release of vWF-Ag from activated endothelial cells^[17,18]. Further, the administration of nonabsorbable antibiotics in patients with cirrhosis caused a significant decrease of vWF-Ag plasma levels concomitantly with the decrease of endotoxemia^[7]. vWF-Ag is cleaved by the protease ADAMTS13, which is mainly synthesized in the liver^[19], into smaller forms which are less potent than the macromolecules in mediating platelet adhesion and aggregation^[20]. The inflammatory cytokines TNF- α , IL-4, and IL-8 have been found to suppress ADAMTS13 synthesis in hepatic stellate cells and endothelial cells^[18,21], which may

contribute to the reduced levels of ADAMTS13 reported in cirrhosis^[22].

It can therefore be suggested that increasing BT-mediated inflammatory responses as liver disease progresses predispose to accumulation of vWF-Ag multimers within the liver microcirculation thus enhancing platelet adhesion and aggregation to the sinusoidal endothelium despite the thrombocytopenic conditions of cirrhosis. This could lead to intrahepatic formation of platelet-induced microthrombi, progressive occlusion of portal microvasculature, and intensification of PH. BT-related release of inflammatory cytokines, such as TNF- α and IL-1, could potentiate the prothrombotic state produced by vWF-Ag macromolecules within the cirrhotic liver by downregulating hepatic synthesis of protein C^[23]. Intrahepatic microthrombi have been demonstrated in patients with cirrhosis and have been associated with accelerated liver fibrogenesis^[24], which could further increase portal pressure. Microvascular occlusion of portal vein branches by platelet-rich thrombi due to inflammation stimulated elevation of vWF-Ag levels and decrease in ADAMTS13 activity has also been implicated in the pathogenesis of non-cirrhotic intrahepatic PH^[25].

From a clinical point of view, higher concentrations of vWF-Ag levels in plasma^[7,13,15] and in liver tissue^[13] have been related to more severe PH and increased incidence of decompensation in patients with cirrhosis. Further, we have recently demonstrated in these patients that high levels of thrombin-antithrombin complexes, as a marker of hypercoagulability, was independently associated with major PH-related events, such as new-onset ascites and variceal bleeding, which could be related to the presence of thrombogenic mechanisms operative within the cirrhotic liver^[26].

Consequently, available data suggest that increased thrombotic potential within the liver sinusoids due to high concentrations of vWF-Ag macromolecules could represent an additional therapeutic target of PH in patients with cirrhosis. In this case, anti-inflammatory and antithrombotic drugs could modulate portal pressure by preventing the formation of intrahepatic platelet-induced microthrombi.

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