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Review

The Connection between Hypercoagulability and Fibrogenesis in Chronic Liver Diseases

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Abstract

Not much time has passed since it was established that the coagulation balance is changed towards hypercoagulability in patients with chronic liver disease. The relationship between hypercoagulability and fibrogenesis in these patients can also be surprising, but it is a clinical reality. Microthrombi produced into intrahepatic vascular tree lead to ischemic lesions, followed by parenchymal extinction or hepatocytes collapse and hepatic stellate cells activation through a direct thrombin-mediated pathway or preceded by an inflammatory response. *Hepatic stellate cells* are the main effector cells involved in liver fibrogenesis, although they are also central regulators of liver immunology. Subsequently, a fibrous tissue remodeling occurs. *Hepatitis C virus* can produce direct endothelial lesions involved in tissue factor activation, alteration of fibrinolysis and augmented platelet activity and aggregability. The patients with chronic *hepatitis C* and detectable tissue factor microparticles activity had a higher mean liver stiffness score measured by transient elastography. Liver fibrosis progresses more rapidly in patients with chronic liver diseases who are carriers of some thrombophilic markers. Some of cryptogenic cirrhosis may be due to the presence of thrombophilic factors or their association with the *blood group type non-O*. The relationship between hypercoagulability and fibrogenesis provide new potential therapeutic targets.

Keywords Coagulation disorder, fibrogenesis, liver fibrosis, thrombin generation, thrombophilia.

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Introduction

The Rotterdam Study, that included 1055 subjects, analysed the relationship between the presence of prothrombin G20210A gene variant or factor V Leiden (FVL) mutation and the liver stiffness evaluated by transient elastography. The authors found that the presence of one of those two thrombophilic factors is associated with an increased risk of liver fibrosis – observation which is an argument for hypercoagulability involvement in hepatic fibrogenesis (E.P. PLOMPEN & al [1]). This means that some of cryptogenic cirrhosis may be due to the presence of thrombophilic factors or their association with the blood group type non-O. This combination increases the risk of liver fibrosis (E.P. PLOMPEN & al [1]). But thrombophilia is not the only prothrombotic factor. Such an increased thrombotic risk can be found in patients infected with hepatitis C virus, which can produce direct endothelial damage (followed by tissue factor activation), alter fibrinolysis, and raise platelet aggregation and activation (E. GONZÁLEZ-REIMERS & al [2]). Progression of chronic hepatitis C to liver cirrhosis is favored not only by the presence of factor V Leiden, but also by an increased expression of factor VIII and a protein C deficiency. How hypercoagulability influence the progression to liver cirrhosis? By tissue ischaemia followed by parenchymal extinction and direct stellate cell activation through PAR-1 cleavage – a thrombin-mediated process (Q.M. ANSTEE & al [3]). Hepatic stellate cells (HSC) are the main effector cells involved in liver fibrogenesis, as they have the capacity to transdifferentiate into collagen-producing myofibroblasts. But, their fundamental role is that of central regulators of liver immunology, as it was recently established. They are a source of some cytokines, chemokines, can act as an antigen presenting cell, and have autophagic capacity. HSC respond to different immunological triggers and transduce signals involved in inflammation (R. WEISKIRCHEN & al [4]). The direct activation of the coagulation in the early phases of sepsis is well known and is due to macrophages, monocytes, and neutrophils, which contain tissue factor (K. OKAMOTO & al [5]). But inflammation can also activate HSC and contribute to liver fibrogenesis. This link between hypercoagulability and liver fibrosis offers a therapeutic target to prevent the formation or progression of hepatic fibrosis: the anticoagulant treatment.

I performed a literature review studying the articles published in the last 5 years and available in PubMed, using the following search terms: “coagulation”, “coagulability” or “hypercoagulable state” AND “liver fibrosis” or “fibrogenesis”, “thrombi” AND “liver fibrosis”, “virus C” or “virus B” AND “liver fibrosis”, and “thrombin generation” AND “liver”, to synthesize the new knowledge in this field.

Coagulation dysfunction in chronic liver diseases (Table 1)

Table 1. Coagulation dysfunctions in chronic liver diseases

Factor	Mechanism	Ref
von Willebrand factor	increased levels of von Willebrand factor	[6]
tissue factor	increased tissue factor activity in circulating microparticles	[7]
endothelial lesions	endothelial lesions produced by HCV involved in tissue factor activation	[36]
thrombin-antithrombin complexes	increase of thrombin-antithrombin complexes	[7]
leucocyte	high leucocyte count	[7]
platelet indices	high plateletcrit, platelet distribution width, and mean platelet volume	[8]
platelet activity and aggregability	augmented platelet activity and aggregability	[36]
fibrinogen molecule	oxidation and hypersialylation of fibrinogen molecule involved in a defective conversion of fibrinogen into fibrin	[10]
fibrinolysis	alteration of fibrinolysis	[36]
exposed phosphatidylserine	exposed phosphatidylserine present on activated or injured blood and endothelial cells favors increased levels of factor Xa and thrombin, and higher fibrin formation	[12]
acquired or inherited thrombophilia	increased levels of factor VIII, MTHFR 677TT and or PAI-1 4G-4G or MTHFR TT polymorphism, the presence of FII 20210 G/A, factor XIII Val34Leu mutation, factor V Leiden or reduced protein C, protein S and antithrombin III levels	[13, 14, 15, 23, 24, 30, 54, 56, 59]
thrombomodulin	thrombomodulin resistance was shown in patients with liver cirrhosis	[17]
protein Z	the anticoagulant role of protein Z is inadequate in severe cirrhosis	[18]
thrombin	a higher thrombin generation present in liver cirrhosis is a predictor for portal vein thrombosis	[19]
the ratio between pro- and anti-coagulants factors	the ratio between pro- and anti-coagulant factors is most often changed in favor of the former	[32]
portal microcirculation disorders	portal microcirculation disorders can determine thrombin activation	[36]

Legend: HCV: Hepatitis C virus.

The patients with chronic liver diseases have increased levels of von Willebrand factor that counteract defects in primary hemostasis (J.L. KUJOVICH [6]).

The role of tissue factor

The role of tissue factor in inducing hipercoagulant status in liver diseases was underlined in a wild-type mice model with bile duct ligation for 12 days. In this experimental model, tissue factor activity in circulating microparticles, thrombin-antithrombin complexes and the number of leucocytes were increased (P.E. RAUTOU & al [7]).

The role of platelet indices

Increased platelet indices are other factors involved in hypercoagulable state present in liver cirrhosis, although the patients are frequently thrombocytopenic. It was shown that plateletcrit, platelet distribution width, and mean platelet volume are higer in patients with portal vein thrombosis (I. GÎRLEANU & al [8]). Thrombocytopenia of cirrhotic patients is the result of the disrupted balance between platelet production and their splenic sequestration and destruction and consumption during thrombotic complications (Y. IKURA & al [9]). It was found a correlation between platelet count and number of megakaryocytes, spleen weight, and thrombotic events in patients with chronic liver disease (Y. IKURA & al [9]).

The clot formation

Oxidation and hypersialylation of fibrinogen molecule are described in patients with chronic liver diseases. In addition, permeability assays shown a thrombogenic nature of thrombus in these patients, which is due to hypersialylation of the fibrinogen molecule, that explains the defective conversion of fibrinogen into fibrin (T. LISMAN & al [10]). Despite this, clot formation in plasma from 31 cirrhotic patients was found to be preserved, using the thrombodynamics assay, that evaluated the spatial clot growth, in agreement with data obtained with thrombin generation assay (W. POTZE & al [11]). Exposed phosphatidylserine present on activated or injured blood and endothelial cells is an important factor involved in hypercoagulability of cirrhotic patients. It favors increased levels of factor Xa and thrombin, and higher fibrin formation. The higher exposed phosphatidylserine on blood cells of patients with liver cirrhosis, the higher Child-Pugh class of the disease (X. WU & al [12]).

The role of thrombophilia

Genetic thrombophilia markers were found in 54% of patients with liver cirrhosis, 66% of those with hepatocellular carcinoma, and 36% of healthy controls. The most frequently found thrombophilia markers in post-hepatic splanchnic vein thrombosis were MTHFR 677TT and PAI-1 4G-4G (L. PASTA & al [13]). Between 100 liver cirrhotic patients, those with portal vein thrombosis had also more frequently hepatocellular carcinoma, MTHFR TT status, and hyperhomocysteinemia. The presence of mild hyperhomocysteinemia in liver cirrhotic patients may be involved in portal vein thrombosis occurrence. MTHFR TT polymorphism may be implicated in the connection between hepatocellular carcinoma and portal vein thrombosis (P. VENTURA & al [14]). Factor V Leiden is the second most frequently found thrombotic risc factor, after primary myeloproliferative neoplasms, in patients diagnosed with Budd-Chiari syndrome. They can also have more thrombotic risk factors, including some thrombophilic ones, as a reduced protein C level (S. KARLETI [15]).

How to explore the coagulation dysfunction?

The classical coagulation tests do not entirely reflect the hemostatic disorder present in these patients and can not accurately estimate the risk of bleeding or thrombosis (J.L. KUJOVICH [6]). The study of plasma samples from 40 cirrhotic patients by rotational thromboelastometry shown hypocoagulability which was correlated with hepatic dysfunction, but the plasma samples from the same patients examined with thrombin generation test indicated a potential for hypercoagulability. Therefore, rotational thromboelastometry may not be adequate for haemostasis estimation in cirrhotic patients (C. LENTSCHENER & al [16]). The study of thrombin generation provides the most accurate assessment of global coagulation cascade, considering the action of procoagulant and anticoagulant factors, in the same extent, and that of platelets and fibrinolytic system (J.L. KUJOVICH [6]).

The study of thrombin generation in chronic liver diseases

The patients with liver cirrhosis generated a higher thrombin quantity after thrombomodulin addition and presented thrombomodulin resistance compared to those with non-cirrhotic portal vein thrombosis and healthy controls. Between hypercoagulability and splanchnic vein thrombosis was no correlation (R. CHAIRETI & al [17]). Indeed, other authors have also found that the ratio between endogenous thrombin potential with thrombomodulin and endogenous thrombin potential without thrombomodulin was significantly higher compared to control in a study made on 158 cirrhotic patients and 59 healthy controls. In addition, this ratio was not correlated with liver cirrhosis severity. At thrombin generation assays, the ratio between the lag time with protein Z and the lag time without protein Z and the ratio between peak thrombin with protein Z and peak thrombin without protein Z were associated with thrombotic complications (S.Y. KIM & al [18]). The anticoagulant role of protein Z, that physiologically accelerates the inhibitory effect of protein Z-dependent protease inhibitor on factor Xa is inadequate in severe cirrhosis (S.Y. KIM & al [18]). The augmented thrombin generation, explored through its marker – thrombin-antithrombin complexes, was associated with higher cirrhosis severity and was a predictor for portal vein thrombosis, in a study made on 81 patients (G.N. KALAMBOKIS & al [19]).

The study of thrombin generation is the most useful method for the study of balance between pro- and anticoagulant factors. The endogenous thrombin potential is the most useful parameter and it measures the net amount of thrombin that can be generate by the tested plasma (A. TRIPODI [20]). Thrombin generation assay with

thrombomodulin addition can highlight the presence of hypercoagulability in patients with liver cirrhosis, even when prothrombin time is long (N. YOUNGWON & al [21]). In other words, if International Normalized Ratio in patients with liver dysfunction is prolonged, they are not "autoanticoagulated", but rather prone to thrombotic events, du to their hypercoagulability (E. SCHADEN & al [22]).

Changes during chronic liver disease progression

It is known that thrombosis is favored by hemodynamic changes (and especially the decrease of portal venous flow velocity), endothelial injury and hypercoagulable state of patients with chronic liver disease. Hypercoagulability of these patients increases during the progression of liver cirrhosis from the class A to C Child-Pugh. This increase is a consequence of the decrease of protein C (W. TANG & al [23] and A. TRIPODI & al [24]), protein S and antithrombin III levels, while that of factor VIII does not change. Thus, the ratio between the pro- and anti-coagulants factors changes in favor of the former. It is interesting that this coagulation balance disorder is not associated with the presence of portal hypertension, but with liver cirrhosis progression (C W. TANG & al [23]). It follows that hypercoagulability is mainly the consequence of hepatocytes failure.

Protein S is not only a cofactor for protein C, but also of tissue factor pathway inhibitor. Despite an aquired lower level of protein S in cirrhotic patients, their levels of tissue factor pathway inhibitor were comparable to those of healthy controls (W. POTZE & al [25]). This functionally impaired mechansim is an other explanation for hypercoagulability of cirrhotic patients.

Soluble fibrin complexes are a more significant diagnostic and prognostic factor of disseminated intravascular coagulation in cirrhotic patients, compared to fibrin degradation product or D-dimer, and can help differentiate this condition from coagulation dysfunction present in liver cirrhosis (S.Y. KIM & al [26]).

Liver fibrosis and fibrogenesis

Today, liver biopsy is more often replaced with noninvasive techniques for liver fibrosis assessing, as it is an invasive procedure which offer a nondynamic evaluation of the hystopatological aspect, with differences of interpretation depending on the observer, and, sometimes, with sampling errors (A. COPPOLA & al [27]). It has also contraindications, as in the case of hemophilic patients or of those with other congenital bleeding. More and more studies use methods as transient elastography, magnetic resonance elastography, or acoustic radiation force impulse imaging elastography (A. COPPOLA & al [27]) to noninvasively quantify the hepatic fibrosis.

Liver fibrogenesis supposes a dynamic action, with possible evolutions towards recovery and remodeling. Various stimuli can cause repeated hepatocyte injury, followed by inflammatory response and hepatic stelate cells (HSC) (also known as Ito cells) activation (R.J. CHEN & al [28]). They are the main cell type involved in liver fibrogenesis by extracellular matrix components production and transdifferentiation in myofibroblasts. New pathways involved in hepatic fibrogenesis were recognized: epigenetic regulation of Ito cells, peroxisome proliferator-activated receptor gamma and leptin mechanisms, autophagy (R.J. CHEN & al [28]) and hypercoagulability (R.J. CHEN & al [28] and A. AGGARWAL & al [29]).

Thromboses in the portal venous system

The patients with chronic liver diseases can frequently have recurrence of thrombosis in the portal venous system, a serious complication that can endanger patients' lives (J. TREBICKA & al [30]), or non-portal thrombosis due to their hypercoagulable state (A. AGGARWAL & al [29]). But microthrombi can appear more often, with consequences on the evolution of chronic liver disease, through their relationship with liver fibrogenesis.

The thrombotic occlusion of portal vein is frequently found in chronic liver disease; its prevalence varies between 1% and 16% of population (C.R. DEBNATH & al [31]). The main risk factor for portal vein thrombosis is the presence of progressive chronic liver diseases (J. TREBICKA & al [30]) and especially liver cirrhosis (C.R. DEBNATH & al [31]), which involves a change of the ratio between pro- and anti-coagulant factors, most often in favor of the former, and a decrease of portal venous blood velocity (M. SCHULTHEIß & al [32]). Other risk factors can be: acquired or inherited thrombophilia, processes localized to the epigastrium (J. TREBICKA & al [30]) and malignant liver or choledocus diseases. But idiopathic forms of thrombosis can also be found (M. SCHULTHEIß & al [32]). Increased liver resistance in cirrhosis is the cause of the deterioration in portal vein outflow present in portal vein thrombosis, which is the overt manifestation of liver fibrogenesis process, but a link between portal vein thrombosis appearance and the progression of chronic liver disease was not proved yet (F.R. PONZIANI & al [33]).

Portal vein thrombosis was found in 16.3% of those 380 consecutive patients subsequently subjected to primary orthotopic liver transplantation. Only obesity was found to be an independent risk factor for this pretransplant complication, which had no influence in the overall survival of patients (R. AYALA & al [34]).

Hypercoagulability and liver fibrogenesis

The hipercoagulable state of patients with chronic liver diseases may increase hepatic fibrosis progression (F. ABERG & al [35]).

What is the mechanism by which coagulation is involved in liver fibrogenesis? The most often formulated hypothesis is the following: microthrombi into the intrahepatic vascular tree lead to ischemic changes which favor the loss of hepatic tissue (F.R. PONZIANI & al [33]) or parenchymal extinction (J. TREBICKA & al [30] and E. GONZÁLEZ-REIMERS & al [36]), followed by collapse

of hepatocytes (E. GONZÁLEZ-REIMERS & al [36]) and fibrotic tissue remodeling [30, (F.R. PONZIANI & al [33]), G. PIERI & al [37], I.R. WANLESS & al [38] and I.R. WANLESS & al [39]). According to this hypothesis, there is a link between coagulation activity and liver fibrogenesis (J. TREBICKA & al [30] and F.R. PONZIANI & al [33]). What are the consequences of a thrombotic obstruction of the portal venous system? Studies show that these patients have a higher mortality rate than their MELD score and a decreased posttransplant survival (J. TREBICKA & al [30], M.J. ENGLESBE & al [40] and A. DOENECKE & al [41]), which depends on the extent of the thrombosis (J. TREBICKA & al [30] and A. DOENECKE & al [41]).

A higher thrombotic risk was shown in hepatitis C virus (HCV) infected patients. HCV can produce direct endothelial lesions, which are involved in tissue factor activation, alteration of fibrinolysis and augmented platelet activity and aggregability. When the disease caused by HCV attains the stage of liver cirrhosis, the portal micro-circulation disorders can determine thrombin activation, increase the platelet aggregability, and thrombi formation, which have a high prevalence in intrahepatic portal vein system. The high quantity of new-formed thrombin may be involved in HSC activation - the main cells responsible for liver fibrogenesis (E. GONZÁLEZ-REIMERS & al [36]) (Fig. 1). HCV liver cirrhosis has the faster evolution to end-stage hepatic disease (E. GONZÁLEZ-REIMERS & al [36]).

Among 865 Caucasian liver cirrhotic patients, 243 developed portal vein thrombosis during 5 years and 8 months. But we have to note that 339 from 865 patients presented at least one thrombophilic genetic factor; the most frequently found factors were PAI-1 4G-4G and MTHFR 677TT. Statistical analysis showed that these factors could be involved in liver cirrhosis development, especially in patients without HCV and HBV, and portal vein thrombosis (M. D'AMICO & al [42]). The presence of prothrombin 20210 mutation in hepatitis C virus-infected patients is able to increase the rate of hepatic fibrosis in these patients (N. MAHARSHAK & al [43]).

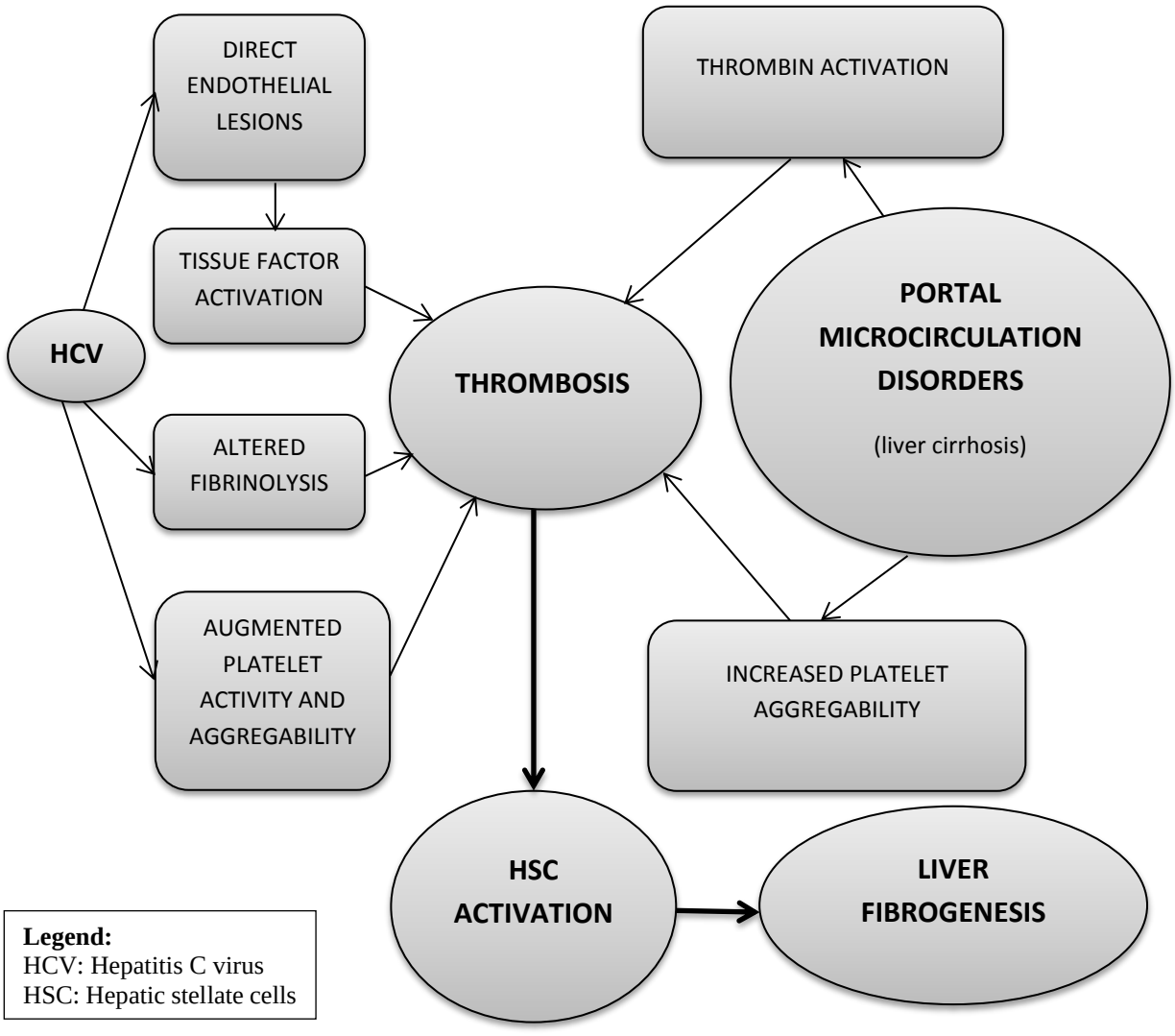

Figure 1. Liver fibrogenesis in HCV infected patients

In a nonhomogeneous group of patients with chronic noncirrhotic nontumoral portal vein thrombosis (but 32% of them had thrombophilic disorder, 32% presented a local factor, and 36% had no evident etiological factor) had higher endogenous thrombin potential with thrombomodulin, increased levels of some coagulant factors (as factor VIIa), and fibrinolysis markers (S. RAFFA & al [44]). Further studies are needed to clarify the pathogenetic mechanism of thrombosis, if this hypercoagulability was also present in the subgroup of patients with idiopathic portal vein thrombosis.

Protease-activated receptor (PAR-2) is present including in HSCs, liver macrophages, and endothelial cells and is involved in the connection between coagulation – inflammation – liver fibrogenesis. The progression of experimental hepatic fibrosis induced by CCl(4) in PAR-2 knockout mice decreased, as liver collagen gene expression, and hepatic hydroxyproline quantity. In human beings PAR-2 also has profibrogenic actions on HSC: it augments the production of collagen and some profibrogenic cytokines (as transforming growth factor beta) *in vitro* and *in vivo* (V. KNIGHT & al [45]).

Protein C is not only the strongest anticoagulant factor, involved in activated factor VIII and V inhibition, but it is able to regulate tight junction molecules and promote intestinal mucosa healing. Thus, protein C system is implicate in intestinal permeability control (S. D'ALESSIO & al [46]). If the level of protein C decreases, as in thrombophilic patients, intestinal permeability may increase. As it is known that endotoxaemia is frequently found in cirrhotic patients and is relevant within the pathogenesis of their disease (H. LIEHR & al [47]), we can speculate that endotoxins might be absorbed in larger amount from the intestinal lumen and may contribute to fibrogenesis in patients with chronic liver diseases – another possible fibrogenetic pathway related to protein C.

Liver sinusoids and fibrogenesis

Sinusoidal fenestration disappear, vasoconstriction and angiogenesis can be found and some molecular changes are reported to be induced by hepatic injury. It is well known the communication relationship between sinusoidal endothelial cells and HSC. Thus, the reduced endothelial nitric oxide synthase activity or augmented PDGF and TGF-β production is involved in HSC activation and migration. Sinusoidal dilatation and liver fibrogenesis can also be produced by noninflammatory pathways and be associated with the presence of sinusoidal thrombi, as in congestive liver disease (T. GREUTER & al [48]).

Coagulation peculiarities in some fibrotic liver diseases

Viral hepatits may be invloved in venous thromboembolism development and especially in portal vein thrombosis (A. SQUIZZATO & al [49]).

Chronic hepatitis C

The role of hepatitis C virus in the blood clotting is underlined by the presence of tissue factor microparticles activity in 40% of patients with chronic hepatitis C, compared to only 7% of those infected with HIV and HCV cleared or 14% in those with HIV / HCV coinfection. The patients with detectable tissue factor microparticles activity had a higher mean liver stiffness score measured by transient elastography (and therefore a more advanced liver fibrosis) compared to those without this detectable activity (A.C. HODOWANEC & al [50]). This catagory of patients had also CD4 + HLADR+ immune activation (A.C. HODOWANEC & al [50]), which argue for a pathogenetic link between coagulation – immunity – liver fibrogenesis.

Protein C activity was decreased in early liver fibrosis stage in patients with chronic hepatitis C. The more severe protein C deficiency the more severe liver fibrosis. It is believed that protein C can have an imporatnt role in the connection between the hypercoagulable state and liver fibrogenesis. Not only protein C activity but also antithrombin III was associated with advanced hepatic fibrosis in these patients (A. SARAY & al [51]).

The fibrinolytic pathway is also involved in liver fibrogenesis. In a group of 146 patients with chronic hepatitis C, mean fibrinolysis-associated soluble urokinase plasminogen activator receptor levels were significantly higher in F3 and F4 stages of hepatic fibrosis. Thus, this marker can differentiate mild/moderate from severe fibrosis, and noncirrhotic from cirrhotic disease. Moreover, this serum fibrinolysis marker correlated to transient elastography, and aspartate aminotranspherase to platelets ratio – a noninvasive marker of hepatic fibrosis (M.L. BERRES & al [52]).

Liver fibrosis progresses more rapidly in chronic hepatitis C patients who are carriers of the following thrombophilic markers: PAI-I -675 5G/4G (mainly the 4G allele), FII 20210 G/A (in particular the polymorphic marker GA), and FV 1691 G/A (especially the A allele). The presence of more of these genes in a patient, the faster fibrosis progression rate (E.F. STAROSTINA & al [53]). Liver stiffness was measured in 17 patients with chronic hepatitis C virus infection and inherited bleeding disorders before antiviral treatment and after a median time of 2.5 years since this treatment. It significantly decreased in 82% of patients, from a median value of 10.3 to that of 6.1 kPa. This means that eradication of hepatitis C virus would result in a significant decrease in liver fibrosis, even if the period of viral infection was long (D.E. FRANSEN VAN DE PUTTE & al [54]).

The presence of factor XIII Val34Leu mutation with or without PAI-1 4G/5G mutation was proved to be a risk factor for a higher rate of hepatic fibrosis development in chronic hepatitis C or B patients (K. DIK & al [55]).

Patients coinfected with HCV and HIV and with higher median levels of proinflammatory markers (IL-6 and CD14) also had increades hyaluronic acid values – a hepatic fibrosis marker, but their coagulation profile was not influenced (L. PETERS & al [56]).

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) patients have an augmented risk of thrombotic events (W. POTZE & al [57]). Plasma levels of factor VIII increased while those of protein C decreased from the stage of steatosis to

that of cirrhosis in patients with NAFLD. This imbalance in coagulation state towards hypercoagulation might be involved in liver fibrogenesis (A. TRIPODI & al [58]). However, there are researchers who found a comparable overall hemostatic profile of non-cirrhotic NAFLD patients with that of controls. They observed only a decreased clot permeability and hypofibrinolysis in NAFLD patients, probably due to obesity, which means that their hemostasis is hyperactive (W. POTZE & al [57]). Indeed, the presence of obesity and metabolic syndrome is involved in the change of thrombogenic properties of the fibrin clot in NAFLD patients (T. LISMAN & al [10]).

Thrombophilia in chronic liver diseases

MTHFR 677TT and PAI-1 4G-4G polymorphisms were more frequently found in patients with no viral liver cirrhosis, compared to those with viral liver cirrhosis, and could be regarded as thrombotic risk factors invloved in the rise of inflammatory response and liver fibrogenesis (L. PASTA & al [59]).

Experimental fibrosis model

In a mice model of fibrin-mediated fibrosis, inducible nitric oxide synthase, induced by IFN-gamma, produced bile duct hyperplasia and hepatic fibrosis. It was proved that fibrin(ogen)-αMβ2 interaction was able to inhibit inducible nitric oxide synthase and reduce biliary fibrosis (N. JOSHI & al [60]).

Liver resection or transplant

Intraoperative practiced thromboelastography shown high net clot strength values and short reaction times in liver transplant recipients. These two parameters were correlated with thrombotic events, but the link between them is unclear. The hypercoagulable state was higher especially in patients with cholestatic diseases, as primary biliary cirrhosis or primary sclerosing cholangitis, but also in nonalcoholic steatohepatitis or fulminant liver failure (D. KRZANICKI & al [61]). Other authors have also found a hypercoagulable condition after liver resections, using thrombin generation assay with thrombomodulin addition, that may be explained by lower levels of antithrombin, protein C, and S, and by higher levels of factor VIII (W. POTZE & al [62]).

Conclusions and practical consequences

The identification of all individual risk factors involved in the progression of chronic liver disease is required for a personalized treatment aimed to stopp its progression and induce its regression, including that of liver fibrosis. It is accepted that liver cirrhosis would regress if the cause of liver damage was removed. This regression would be more likely to be realized if liver cirrhosis occurred recently, the regeneration capacity did not disappear and vascular thromboses were not present. There are no validated markers or scoring sistem to evaluate the possibility of this process, at the moment (P. BEDOSSA [63]).

Regression of liver fibrosis, and of their hypercoagulable state to, can be achieved in patients with chronic hepatitis C with an antiviral treatment able to eradicate the virus.

The study of thrombophilic profile of the patient with chronic liver disease of known or unknowed etiology can contribute to better understand the fibrogenetic pathways and choose a more appropriate treatment. If thrombophilic profiling is too expensive, it can be replaced by the study of thrombin generation, which would also quantify the thrombotic risk of each patient, in the future.

According to the recommendations formulated by the Japanese Society of Gastroenterology which revised the guidelines for liver cirrhosis in 2015, anticoagulant drugs are proposed only for patients with recently appeared or progressive portal vein thromboses and for those who will be subjected to liver transplant (evidence level C, strength 2) (H. FUKUI & al [64]). This attitude is justified as the presence of portal vein thrombosis in a cirrhotic patient favors liver disease decompensation and worses its prognosis (F. ABERG & al [35]). Indeed, anticoagulant therapy is indicated in acute portal vein thrombosis and in chronic portal vein thrombosis if the patient has a concurrent thrombotic risk factor. Several experimental and human clinical studies shown that anticoagulant therapy was able to decrease the fibrogenesis rate and the disease progression (F.R. PONZIANI & al [33] and E.P. PLOMPEN & al [65]). Thus, some cirrhotic patients could benefit from anticoagulant therapy, but there is no guide recommendation or contraindicatation for chronic anticoagulant treatment in chronic liver diseases, as each recommendation should be cautiously made and will account for the risk / benefit ratio in each patient.

Treatment with low molecular weight heparins should be done with caution in cirrhotic patients, as they have an increased response to these drugs. It was shown that endogenous thrombin potential ratio at enoxaparin 0.35 U anti-Xa mL was significantly reduced in these patients than in controls and the lowering was higher as the disease was more advanced, despite their antithrombin and anti-Xa diminished activity (M. SENZOLO & al [66]). They also require a drug-specific dose adjustments as the anticoagulant potency of various drugs differs. It has been proven that rivaroxaban and fondaparinux had a lower anticoagulant effect in cirrhotic patients compared to dabigatran, heparin and low molecular weight heparin (W. POTZE & al [67]).

The relationship between hypercoagulability and fibrogenesis in chronic liver diseases is a fascinating area of research, which is focusing on HSC, with their multiple functions (immune regulator, involved in synthesis of collagen and extracellular matrix elements and capacity of transdifferentiation into myofibroblasts). As the research in this area will progress, they will provide new therapeutic targets for the scientific world, which could substantially improve the results of antifibrotic therapy. The research in this field will serve as a model for other diseases in which the relationship inflammation – fibrogenesis, or thrombosis – inflammation – fibrogenesis is present.

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References

1. E.P. PLOMPEN, S. DARWISH MURAD, B.E. HANSEN, D.W. LOTH, J.N. SCHOUTEN, P. TAIMR, A. HOFMAN, A.G. UITTERLINDEN, B.H. STRICKER, H.L. JANSSEN, F.W. LEEBEEK. Prothrombotic genetic risk factors are associated with an increased risk of liver fibrosis in the general population: The Rotterdam Study. *J. Hepatol*, 63, 1459-1465 (2015).
2. E. GONZÁLEZ-REIMERS, G. QUINTERO-PLATT, C. MERTIN-GONZÁLEZ, O. PÉREZ-HERNÁNDEZ, L. ROMERO-ACEVEDO, F. SANTOLARIA-FERNÁNDEZ. Thrombin activation and liver inflammation in advanced hepatitis C virus infection. *World J. Gastroenterol*, 22, 4427-4437 (2016).
3. Q.M. ANSTEE, A. DHAR, M.R. THURSZ. The role of hypercoagulability in liver fibrogenesis. *Clin. Res. Hepatol. Gastroenterol*, 35, 526-533 (2011).
4. R. WEISKIRCHEN, F. TACKE. Cellular and molecular functions of hepatic stellate cells in inflammatory responses and liver immunology. *Hepatobiliary Surg. Nutr*, 3, 344-363 (2014).
5. K. OKAMOTO, T. TAMURA, Y. SAWATSUBASHI. Sepsis and disseminated intravascular coagulation. *J. Intensive Care*, 4, 23 (2016).
6. J.L. KUJOVICH. Coagulopathy in liver disease: a balancing act. *Hematology Am. Soc. Hematol. Educ. Program*, 2015, 243-249 (2015).
7. P.E. RAUTOU, K. TATSUMI, S. ANTONIAK, A.P. OWENS, E. SPARKENBAUGH, L.A. HOLLE, A.S. WOLBERG, A.K. KOPEC, R. PAWLINSKI, J.P. LUYENDYK, N. MACKMAN. Hepatocyte tissue factor contributes to the hypercoagulable state in a mouse model of chronic liver injury. *J. Hepatol*, 64, 53-59 (2016).
8. I. GÎRLEANU, A. TRIFAN, C. COJOCARIU, M. DIMACHE, A.M. SÎNGEAP, O. STOICA, C. SAFARI, C. STANCIU. Platelet indices in patients with de novo portal vein thrombosis and liver cirrhosis. *Rev. Med. Chir. Soc. Med. Nat. Iasi*, 117, 641-647 (2013).
9. Y. IKURA, M. OHSAWA, M. OKADA, Y. IWAI, K. WAKASA. The significance of platelet consumption in the development of thrombocytopenia in patients with cirrhosis. *Am. J. Med. Sci*, 346, 199-203 (2013).
10. T. LISMAN, R.A. ARIËNS. Alterations in Fibrin Structure in Patients with Liver Diseases. *Semin. Thromb. Hemost*, 42, 389-396 (2016).
11. W. POTZE, J. ADELMEIJER, R.J. PORTE, T. LISMAN. Preserved clot formation detected by the Thrombodynamics analyzer in patients with cirrhosis. *Thromb. Res*, 135, 1012-1016 (2015).
12. X. WU, Z. YAO, L. ZHAO, Y. ZHANG, M. CAO, T. LI, W. DING, Y. LIU, R. DENG, Z. DONG, H. CHEN, V.A. NOVAKOVIC, Y. BI, J. KOU, Y. TIAN, J. ZHOU, J. SHI. Phosphatidylserine on blood cells and endothelial cells contributes to the hypercoagulable state in liver cirrhosis. *Liver Int*, 36, 1800-1810 (2016).
13. L. PASTA, F. PASTA, M. D'AMICO. PAI-1 4G-4G, MTHFR 677TT, V Leiden 506Q, and Prothrombin 20210A in Splanchnic Vein Thrombosis: Analysis of Individual Patient Data From Three Prospective Studies. *J. Clin. Exp. Hepatol*, 6, 10-14 (2016).
14. P. VENTURA, G. VENTURELLI, M. MARCACCI, M. FIORINI, S. MARCHINI, C. CUOGHI, A. PIETRANGELO. Hyperhomocysteinemia and MTHFR C677T polymorphism in patients with portal vein thrombosis complicating liver cirrhosis. *Thromb. Res*, 141, 189-195 (2016).
15. S. KARLETI. Budd-Chiari Syndrome in a patient with Multiple Hypercoagulopathies. *J. Ark. Med. Soc*, 112, 90-91 (2015).
16. C. LENTSCHENER, C. FLAUJAC, F. IBRAHIM, I. GOUIN-THIBAULT, M. BAZIN, P. SOGNI, C.M. SAMAMA. Assessment of haemostasis in patients with cirrhosis: Relevance of the ROTEM tests?: A prospective, cross-sectional study. *Eur. J. Anaesthesiol*, 33, 126-133 (2016).
17. R. CHAIRETI, R. RAJANI, A. BERGQUIST, T. MELIN, I.L. FRIIS-LIBY, M. KAPRAALI, S. KECHAGIAS, T.L. LINDAHL, S. ALMER. Increased thrombin generation in splanchnic vein thrombosis is related to the presence of liver cirrhosis and not to the thrombotic event. *Thromb. Res*, 134, 455-461 (2014).
18. S.Y. KIM, J.E. KIM, Y.J. KIM, K.S.HAN, H.S. KIM. Prominent protein Z-induced thrombin inhibition in cirrhosis: a new functional assay for hypercoagulability assessment. *J. Gastroenterol. Hepatol*, 30, 784-793 (2015).
19. G.N. KALAMBOKIS, A. OIKONOMOU, G. BALTAYIANNIS, L. CHRISTOU, N.I. KOLAITIS, E.V. TSIANOS. Thrombin generation measured as thrombin-antithrombin complexes predicts clinical outcomes in patients with cirrhosis. *Hepatol. Res*, 46, E36-44 (2016).
20. A. TRIPODI. Thrombin Generation Assay and Its Application in the Clinical Laboratory. *Clin. Chem*, 62, 699-707 (2016).
21. N. YOUNGWON, J.E. KIM, H.S. LIM, K.S. HAN, H.K. KIM. Coagulation proteins influencing global coagulation assays in cirrhosis: hypercoagulability in cirrhosis assessed by thrombomodulin-induced thrombin generation assay. *Biomed. Res. Int*, 2013, 856754 (2013).
22. E. SCHADEN, F.H. SANER, K. GOERLINGER. Coagulation pattern in critical liver dysfunction. *Curr. Opin. Crit. Care*, 19, 142-148 (2013).
23. W. TANG, Y. WANG, X. ZHAO, X WANG, T. ZHANG, X. OU, W. SHOU, H. YOU, J. JIA. Procoagulant imbalance aggravated with falling liver function reserve, but not associated with the presence

of portal vein thrombosis in cirrhosis. *Eur. J. Gastroenterol. Hepatol*, 27, 672-678 (2015).
24. A. TRIPODI, M. PRIMIGNANI, L. LEMMA, V. CHANTARANGKUL, P.M. MANNUCCI. Evidence that low protein C contributes to the procoagulant imbalance in cirrhosis. *J. Hepatol*, 59, 265-270 (2013).
25. W. POTZE, F. ARSHAD, J. ADELMEIJER, H. BLOKZIJL, A.P. VAN DEN BERG, J.C. MEIJERS, R.J. PORTE, T. LISMAN. Decreased tissue factor pathway inhibitor (TFPI)-dependent anticoagulant capacity in patients with cirrhosis who have decreased protein S but normal TFPI plasma levels. *Br. J. Haematol*, 162, 819-826 (2013).
26. S.Y. KIM, J.E. KIM, H.K. KIM, I. KIM, S.S. YOON, S. PARK. Higher prognostic value of soluble fibrin complexes than D-dimer and fibrin degradation product for disseminated intravascular coagulation in patients with liver cirrhosis. *Blood Coagul. Fibrinolysis*, 24, 150-156 (2013).
27. A. COPPOLA, M. DI CAPUA, P. CONCA, E. CIMINO, A. TUFANO, A.M. CERBONE, G. DI MINNO, G. TARANTINO. Noninvasive assessment of liver fibrosis in patients with chronic hepatitis C (and congenital bleeding disorders): where do we stand? *Semin. Thromb. Hemost*, 39, 803-815 (2013).
28. R.J. CHEN, H.H. WU, Y.J. WANG. Strategies to prevent and reverse liver fibrosis in humans and laboratory animals. *Arch. Toxicol*, 89, 1727-1750 (2015).
29. A. AGGARWAL, K. PURI, S. LIANGPUNSAKUL. Deep vein thrombosis and pulmonary embolism in cirrhotic patients: systematic review. *World J. Gastroenterol*, 20, 5737-5745 (2014).
30. J. TREBICKA, C.P. STRASSBURG. Etiology and Complications of Portal Vein Thrombosis. *Viszeralmedizin*, 30, 375-380 (2014).
31. C.R. DEBNATH, M.R. DEBNATH, M.M. ALAM, M.M. MOSHWAN, M.J. ALAM, M.S. RANA, D. BISWAS, M. MAHMUDUZZAMAN, A.J. TARAFDER. Cirrhosis of liver and portal vein thrombosis – a review article. *Mymensingh Med*. J, 23, 606-608 (2014).
32. M. SCHULTHEIß, D. BETTINGER, R. THIMME. Nonsurgical Therapeutic Options in Portal Vein Thrombosis. *Viszeralmedizin*, 30, 388-392 (2014).
33. F.R. PONZIANI, M.A. ZOCCO, M. GARCOVICH, F.D'AVERSA, D. ROCCARINA, A. GASBARRINI. What we should know about portal vein thrombosis in cirrhotic patients: a changing perspective. *World J. Gastroenterol*, 18, 5014-5020 (2012).
34. R. AYALA, S. GRANDE, R. BUSTELOS, C. RIBERA, A. GARCIA-SESMA, C. JIMENEZ, E. MORENO, J. MARTINEZ-LÓPEZ. Obesity is an independent risk factor for pre-transplant portal vein thrombosis in liver recipients. *B.M.C. Gastroenterol*, 12, 114 (2012).
35. F. ABERG, R. LASSILA, M. ILMAKUNNAS, K. JOKELAINEN, K. NUMMINEN, H. MÄKISALO. Chronic liver disease and thrombosis risk. *Duodecim*, 131, 321-330 (2015).
36. E. GONZÁLEZ-REIMERS, G. QUINTERO-PLATT, C. MARTIN-GONZÁLEZ, O. PÉREZ-HERNÁNDEZ, L. ROMERO-ACEVEDO, F. SANTOLARIA-FERNÁNDEZ. Thrombin activation and liver inflammation in advanced hepatitis C virus infection. *World J. Gastroenterol*, 22, 4427-4437 (2016).
37. G. PIERI, E. THEOCHARIDOU, A.K. BURROUGHS. Liver in haematological disorders. Best. *Pract. Res. Clin. Gastroenterol*, 27, 513-530 (2013).
38. I.R. WANLESS, J.J. LIU, J. BUTANY. Role of thrombosis in the pathogenesis of congestive hepatic fibrosis (cardiac cirrhosis) *Hepatology*, 21, 1232-1237 (1995).
39. I.R. WANLESS, F. WONG, L.M. BLENDIS, P. GREIG, E.J. HEATHCOTE, G. LEVY. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. *Hepatology*, 21, 1238-1247 (1995).
40. M.J. ENGLESBE, D.E. SCHAUBEL, S. CAI, M.K. GUIDINGER, R.M. MERION. Portal vein thrombosis and liver transplant survival benefit. *Liver Transpl*, 16, 999-1005 (2010).
41. A. DOENECKE, T.Y. TSUI, C. ZUELKE, M.N. SCHERER, A.A. SCHNITZBAUER, H.J. SCHLITT, A. OBED. Pre-existent portal vein thrombosis in liver transplantation: influence of pre-operative disease severity. *Clin. Transplant*, 24, 48-55 (2010).
42. M. D'AMICO, F. PASTA, L. PASTA. Thrombophilic genetic factors PAI-1 4G-4G and MTHFR 677TT as risk factors of alcohol, cryptogenic liver cirrhosis and portal vein thrombosis, in a Caucasian population. *Gene*, 568, 85-88 (2015).
43. N. MAHARSHAK, P. HALFON, V. DEUTSCH, H. PERETZ, S. BERLINER, S. FISHMAN, S. ZELBER-SAGI, U. ROZOVSKI, M. LESHNO, R. OREN. Increased fibrosis progression rates in hepatitis C patients carrying the prothrombin G20210A mutation. *World J. Gastroenterol*, 17, 5007-5013 (2011).
44. S. RAFFA, J.C. REVERTER, S. SEIJO, D. TASSIES, J.G. ABRALDES, J. BOSCH, J.C. GARCIA-PAGÁN. Hypercoagulability in patients with chronic noncirrhotic portal vein thrombosis. *Clin. Gastroenterol. Hepatol*, 10, 72-78 (2012).
45. V. KNIGHT, J. TCHONGUE, D. LOURENSZ, P. TIPPING, W. SIEVERT. Protease-activated receptor 2 promotes experimental liver fibrosis in mice and activates human hepatic stellate cells. *Hepatology*, 55, 879-887 (2012).
46. S. D'ALESSIO, M. GENUA, S. VETRANO. The protein C pathway in intestinal barrier function: challenging the hemostasis paradigm. *Ann. N. Y. Acad. Sci*, 1258, 78-85 (2012).
47. H. LIEHR, M. GRÜN, D. BRUNSWIG, T. SAUTTER. Endotoxinemia in liver cirrhosis. *Z. Gastroenterol*, 14, 14-23 (1976).
48. T. GREUTER, V.H. SHAH. Hepatic sinusoids in liver injury, inflammation, and fibrosis: new pathophysiological insights. *J. Gastroenterol*, 51, 511-519 (2016).

49. A. SQUIZZATO, V.E. GERDES. Viral hepatitis and thrombosis: a narrative review. *Semin. Thromb. Hemost*, 38, 530-534 (2012).
50. A.C. HODOWANEC, R.D. LEE, K.E. BRADY, W. GAO, S. KINCAID, J. PLANTS, M. BAHK, N. MACKMAN, A.L. LANDAY, G.D. HUHN. A matched cross-sectional study of the association between circulating tissue factor activity, immune activation and advanced liver fibrosis in hepatitis C infection. *B.M.C. Infect. Dis*, 15, 190, (2015).
51. A. SARAY, R. MESIHOVIC, N. VANIS, M. AMILA. Protein C Deficiency in Chronic Hepatitis C: Correlation With Histological Extent of Liver Fibrosis. *Clin. Appl. Thromb. Hemost*, 23, 72-77 (2017).
52. M.L. BERRES, B. SCHLOSSER, T. BERG, C. TRAUTWEIN, H.E. WASMUTH. Soluble urokinase plasminogen activator receptor is associated with progressive liver fibrosis in hepatitis C infection. *J. Clin. Gastroenterol*, 46, 334-338 (2012).
53. E.F. STAROSTINA, L.M. SAMOKHODSKAYA, T.P. ROZINA, T.N. KRASNOVA, E.B. YAROVAYA, N.A. MUKHIN. Role of polymorphic markers for the genes of hemostasis and platelet receptors in liver fibrosis progression in patients with chronic hepatitis C. *Ter. Arkh*, 88, 93-98 (2016).
54. D.E. FRANSEN VAN DE PUTTE, K. FISCHER, R.J. DE KNEGT, D. POSTHOUWER, K.J. VAN ERPECUM, D.H. BIESMA, E.P. MAUSER-BUNSCHOTEN. Beneficial effect of successful HCV treatment in patients with inherited bleeding disorders, assessed by liver stiffness measurements. *Haemophilia*, 18, e266-272 (2012).
55. K. DIK, J. DE BRUIJNE, R.B. TAKKENBERG, J.J. ROELOFS, M.J. TEMPELMANS, M.G. DIJKGRAAF, H.C. GELDERBLOM, H.W. REESINK, J.C. MEIJERS, P.L. JANSEN, M. LEVI. Factor XIII Val34Leu mutation accelerates the development of fibrosis in patients with chronic hepatitis B and C. *Hepatol. Res*, 42, 668-676 (2012).
56. L. PETERS, J. NEUHAUS, D. DUPREZ, J.D. NEATON, R. TRACY, M.B. KLEIN, A. MOCROFT, J. ROCKSTROH, G. DORE, J.D. LUNDGREN; INSIGHT SMART STUDY GROUP. Biomarkers of inflammation, coagulation and microbial translocation in HIV/HCV co-infected patients in the SMART study. *J. Clin. Virol*, 60, 295-300 (2014).
57. W. POTZE, M.S. SIDDIQUI, S.L. BOYETT, J. ADELMEIJER, K. DAITA, A.J. SANYAL, T. LISMAN. Preserved hemostatic status in patients with non-alcoholic fatty liver disease. *J. Hepatol*, 65, 980-987 (2016).
58. A. TRIPODI, A.L. FRACANZANI, M. PRIMIGNANI, V. CHANTARANGKUL, M. CLERICI, P.M. MANNUCCI, F. PEYVANDI, C. BERTELLI, L. VALENTI, S. FARGION. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. *J. Hepatol*, 61, 148-154 (2014).
59. L. PASTA, F. PASTA. PAI-1 4G-4G and MTHFR 677TT in non-hepatitis C virus/hepatitis B virus-related liver cirrhosis. *World J. Hepatol*, 7, 2920-2926 (2015).
60. N. JOSHI, A.K. KOPEC, J.L. RAY, H. CLINE-FEDEWA, A. NAWABI, T. SCHMITT, R. NAULT, T.R. ZACHAREWSKI, C.E. ROCKWELL, M.J. FLICK, J.P. LUYENDYK. Fibrin deposition following bile duct injury limits fibrosis through an αMβ2-dependent mechanism. *Blood*, 127, 2751-2762 (2016).
61. D. KRZANICKI, A. SUGAVANAM, S. MALLETT. Intraoperative hypercoagulability during liver transplantation as demonstrated by thromboelastography. *Liver Transpl*, 19, 852-861 (2013).
62. W. POTZE, E.M. ALKOZAI, J. ADELMEIJER, R.J. PORTE, T. LISMAN. Hypercoagulability following major partial liver resection – detected by thrombomodulin-modified thrombin generation testing. *Aliment. Pharmacol. Ther*, 41, 189-198 (2015).
63. P. BEDOSSA. Reversibility of hepatitis B virus cirrhosis after therapy: who and why? *Liver Int*, 35 Suppl 1, 78-81, (2015).
64. H. FUKUI, H. SAITO, Y. UENAO, H. UTO, K. OBARA, I. SAKAIDA, A. SHIBUYA, M. SEIKE, S. NAGOSHI, M. SEGAWA, H. TSUBOUCHI, H. MORIWAKI, A. KATO, E. HASHIMOTO, K. MICHITAKA, T. MURAWAKI, K. SUGANO, M. WATANABE, T. SHIMOSEGAWA. Evidence-based clinical practice guidelines for liver cirrhosis 2015. *J. Gastroenterol*, 51, 629-650 (2016).
65. E.P. PLOMPEN, J.N. SCHOUTEN, H.L. JANSSEN. Role of anticoagulant therapy in liver disease. *Hepatol. Int*, 7, 369-376 (2013).
66. M. SENZOLO, K.I. RODRIGUEZ-CASTRO, V. ROSSETTO, C. RADU, S. GAVASSO, P. CARRARO, P. ZERBINATI, M.T. SARTORI, P. SIMIONI. Increased anticoagulant response to low-molecular-weight heparin in plasma from patients with advanced cirrhosis. *J. Thromb. Haemost*, 10, 1823-1829 (2012).
67. W. POTZE, F ARSHAD, J. ADELMEIJER, H. BLOKZIJL, A.P. VAN DEN BERG, J.C. MEIJERS, R.J. PORTE, T. LISMAN. Differential *in vitro* inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. *PLoS One*, 9, e88390 (2014).