Preface

Hemostatic Dysfunction in Liver Diseases

Ton Lisman, PhD¹ Hau C. Kwaan, MD, FRCP²¹ Section of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands² Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois

Semin Thromb Hemost 2015;41:445–446.

The liver plays a central role in hemostasis, as it is the site of synthesis of most procoagulant and anticoagulant factors. It also synthesizes many fibrinolytic proteins, and is an important source of thrombopoietin. Furthermore, it is involved in clearance of many hemostatic and fibrinolytic components. Consequently, patients with a decreased synthetic capacity of the liver acquire a complex coagulopathy, with decreased plasma levels of hepatocyte-derived hemostatic proteins and a decreased platelet count.¹ In addition, chronic and acute liver diseases are characterized by chronic endothelial cell activation resulting in additional hemostatic changes such as substantially elevated plasma levels of von Willebrand factor (VWF).^{2,3} Finally, systemic or intrahepatic activation of coagulation results in consumption of platelets and hemostatic proteins.^{4,5}

These hemostatic changes accompanying liver diseases are among the most complex acquired hemostatic changes, and the net effects of these changes have, therefore, long been unclear. Historically, patients with liver diseases were considered to have a significant bleeding risk. This belief arose primarily from observations of prolonged coagulation screening test results, especially the prothrombin time/international normalized ratio (PT/INR), the apparent reduction of many liver-derived coagulation factors (e.g., II, V, VII, IX, X, and XI), and reduction in platelet count, leading to a perceived “hypocoagulable” state. Careful clinical observation and extensive laboratory studies, however, have led to the concept of a rebalanced hemostasis.⁶ The notion that the hemostatic balance in liver disease is reset because of a concomitant decline in both prohemostatic (as noted earlier) and anti-hemostatic (e.g., proteins C and S) components and consequent processes is therefore rapidly gaining acceptance.^{7,8} Furthermore, it is increasingly recognized that the hemostatic status of patients with liver disease comprises hypercoagulable components (e.g., increases in VWF, factor VIII, and decreases in anticoagulant proteins).^{9–12} These hypercoagulable features explain, at least partly, why systemic and local

thrombotic events in patients with liver diseases are common.^{13,14}

In total, the hemostatic balance in liver disease appears more fragile compared with that of healthy individuals, and this explains why both bleeding and thrombotic complications can occur in these patients. The current clinical challenges include the prediction and management of bleeding and thrombotic events in patients with both chronic and acute liver diseases. Thus, we have assembled in this issue of *Seminars in Thrombosis and Hemostasis* several articles on the pathophysiology and clinical management of the coagulopathy of liver diseases by prominent investigators in this field, and thus providing our readers with updated information on this important clinical field.

To begin, Hoffman outlines the central role of the liver in hemostasis, citing the concept of the cell-based hemostasis model to show the limited value of common tests such as the PT.¹⁵ Next, Giannini and Peck-Radosavljevic discuss how thrombopoietin with thrombocytopenia may be affected in the different liver diseases.¹⁶ This is followed by an article by Tripodi and Mannucci who describe the imbalance between the procoagulant and anticoagulant effects in the chronic liver diseases.¹⁷ Lisman and Stravitz then discuss hemostatic changes in patients with acute liver failure, which are similar, but not identical to the changes in patients with cirrhosis, and provide evidence for hemostatic rebalance in this particular type of liver disease.¹⁸ Excessive fibrinolysis, another major abnormality in liver dysfunction, is then reviewed by Leebeek and Rijken, who present findings of hyperfibrinolysis in various liver diseases and provide critical analysis of different laboratory tests for fibrinolytic activity.¹⁹ Barrera et al then show the link between hemostatic alterations and the risk for variceal bleeding in patients with cirrhosis.²⁰

The increased risk for cardiovascular events in patients with diabetes, obesity, and the metabolic syndrome have been well established, and the increased risk has been partly ascribed to prohemostatic changes. However, less is known

Address for correspondence Hau C. Kwaan, MD, FRCP, Division of Hematology/Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611 (e-mail: h-kwaan@northwestern.edu).

Issue Theme Hemostatic Dysfunction in Liver Diseases; **Guest Editors:** Ton Lisman, PhD, and Hau C. Kwaan, MD, FRCP.

Copyright © 2015 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0035-1550441>.
ISSN 0094-6176.

on the hemostatic changes in patients with nonalcoholic fatty liver disease (NAFLD), particularly, when it has advanced to cirrhosis. Potte et al discuss the incidence and risk factors for vascular disease in NAFLD and explore the potential role of hemostatic changes therein.²¹ Valla then outlines risk factors, diagnosis, and treatment of splanchnic vein thrombosis,²² after which Derman and Kwaan provide additional data from their single institutional findings.²³ Intagliata and Northup then discuss opportunities and pitfalls for prevention and treatment of thrombotic disease in patients with liver diseases using anticoagulant therapy.²⁴ A pragmatic approach to prevention and treatment of bleeding and thrombosis in critically ill patients with liver disease is then provided by Roberts and Bernal,²⁵ and Mallett subsequently outlines how viscoelastic tests of coagulation help in management decisions on bleeding and thrombosis in patients with liver disease and during liver transplantation.²⁶ Finally, Massicotte et al present data from their institution which uses state-of-the-art approaches to prevention of blood loss during liver transplantation.²⁷

In total, the contributions to this issue of *Seminars in Thrombosis and Hemostasis* amply illustrate that the field of coagulopathy in liver diseases has been rapidly evolving over the last decade, with novel concepts that truly impact on our understanding of this disorder and on the clinical consequences that are changing the way we are managing patients with liver disease. We trust that our readers will be as excited to be updated with this remarkable progress as we are.

References

- 1 Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. *J Hepatol* 2002;37(2):280–287
- 2 Ferro D, Quintarelli C, Lattuada A, et al. High plasma levels of von Willebrand factor as a marker of endothelial perturbation in cirrhosis: relationship to endotoxemia. *Hepatology* 1996;23(6):1377–1383
- 3 Hugenholtz GC, Adelmeijer J, Meijers JC, Porte RJ, Stravitz RT, Lisman T. An unbalance between von Willebrand factor and ADAMTS13 in acute liver failure: implications for hemostasis and clinical outcome. *Hepatology* 2013;58(2):752–761
- 4 Bakker CM, Knot EA, Stibbe J, Wilson JH. Disseminated intravascular coagulation in liver cirrhosis. *J Hepatol* 1992;15(3):330–335
- 5 Anstee QM, Wright M, Goldin R, Thursz MR. Parenchymal extinction: coagulation and hepatic fibrogenesis. *Clin Liver Dis* 2009;13(1):117–126
- 6 Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood* 2010;116(6):878–885
- 7 Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2011;365(2):147–156
- 8 Northup PG, Caldwell SH. Coagulation in liver disease: a guide for the clinician. *Clin Gastroenterol Hepatol* 2013;11(9):1064–1074
- 9 Tripodi A, Primignani M, Mannucci PM. Abnormalities of hemostasis and bleeding in chronic liver disease: the paradigm is challenged. *Intern Emerg Med* 2010;5(1):7–12
- 10 Groeneweld D, Porte RJ, Lisman T. Thrombomodulin-modified thrombin generation testing detects a hypercoagulable state in patients with cirrhosis regardless of the exact experimental conditions. *Thromb Res* 2014;134(3):753–756
- 11 Gatt A, Riddell A, Calvaruso V, Tuddenham EG, Makris M, Burroughs AK. Enhanced thrombin generation in patients with cirrhosis-induced coagulopathy. *J Thromb Haemost* 2010;8(9):1994–2000
- 12 Kleinegris MC, Bos MH, Roest M, et al. Cirrhosis patients have a coagulopathy that is associated with decreased clot formation capacity. *J Thromb Haemost* 2014;12(10):1647–1657
- 13 Tripodi A, Anstee QM, Sogaard KK, Primignani M, Valla DC. Hypercoagulability in cirrhosis: causes and consequences. *J Thromb Haemost* 2011;9(9):1713–1723
- 14 Congly SE, Lee SS. Portal vein thrombosis: should anticoagulation be used? *Curr Gastroenterol Rep* 2013;15(2):306
- 15 Hoffman M. Coagulation in liver disease. *Semin Thromb Hemost* 2015;41(5):447–454
- 16 Giannini EG, Peck-Radosavljevic M. Platelet dysfunction: status of thrombopoietin in thrombocytopenia associated with chronic liver failure. *Semin Thromb Hemost* 2015;41(5):455–461
- 17 Tripodi A. Liver disease and hemostatic (dys)function. *Semin Thromb Hemost* 2015;41(5):462–467
- 18 Lisman T, Stravitz RT. Rebalanced hemostasis in patients with acute liver failure. *Semin Thromb Hemost* 2015;41(5):468–473
- 19 Leebeek FW, Rijken DC. The fibrinolytic status in liver diseases. *Semin Thromb Hemost* 2015;41(5):474–480
- 20 Barrera F, Zúñiga P, Arrese M. Prediction of esophageal variceal bleeding in liver cirrhosis: is there a role for hemostatic factors? *Semin Thromb Hemost* 2015;41(5):481–487
- 21 Potte W, Siddiqui MS, Sanyal AJ. Vascular disease in patients with nonalcoholic liver disease. *Semin Thromb Hemost* 2015;41(5):488–493
- 22 Valla D. Splanchnic vein thrombosis. *Semin Thromb Hemost* 2015;41(5):494–502
- 23 Derman BA, Kwaan HC. Risk Factors, Diagnosis, Management, and Outcome of Splanchnic Vein Thrombosis: A Retrospective Analysis. *Semin Thromb Hemost* 2015;41(5):503–513
- 24 Intagliata NM, Northup PG. Risk factors, diagnosis, management, and outcome of splanchnic vein thrombosis: a retrospective analysis. *Semin Thromb Hemost* 2015;41(5):514–519
- 25 Roberts LN, Bernal W. Management of bleeding and thrombosis in critically ill patients with liver diseases. *Semin Thromb Hemost* 2015;41(5):520–526
- 26 Mallett S. Clinical utility of viscoelastic tests of coagulation (TEG®/ROTEM®) in patients with liver disease and during liver transplantation. *Semin Thromb Hemost* 2015;41(5):527–537
- 27 Massicotte L, Thibeault L, Roy A. Classical notion of coagulation revisited in relation with blood losses, transfusion rate for 700 consecutive liver transplantation. *Semin Thromb Hemost* 2015;41(5):538–546