

Is non-alcoholic fatty liver disease a prothrombotic risk factor?

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The prevalence of non-alcoholic fatty liver disease (NAFLD) in the general population (regardless of ethnicity) across the world is steadily increasing, along with the global epidemics of such metabolic diseases as obesity and diabetes. Recently, in a prospective study of a cohort of diabetic patients, NAFLD was observed in 65% of the investigated patients, with 14% having advanced liver fibrosis and 6% cirrhosis.¹ NAFLD represents the hepatic manifestation of a systemic condition associated with the metabolic syndrome, liver-related morbidity and mortality and, to a greater extent, cardiovascular disease.²

Whether NAFLD acts as an innocent bystander or actively supports a prothrombotic milieu in different stages of the disease is likely but still debated. Indeed, numerous clinical and preclinical observations have associated the presence of NAFLD with endothelial dysfunction, atherosclerosis, and arterial/venous ischemic events.² Moreover, cirrhosis, often observed in patients with nonalcoholic steatohepatitis, is associated with a higher incidence of portal vein thrombosis than in other etiologies.³ In 2014, thrombin generation (TG) was measured in 113 patients with biopsy-proven metabolic liver disease, ranging from NAFLD to metabolic cirrhosis.⁴ The ratio of endogenous thrombin potential (ETP) assessed in the presence and absence of thrombomodulin (TM) (*i.e.* ETP-TM-ratio), taken as an index of procoagulant imbalance, was increased even in the non-cirrhotic stages of the disease. ETP-TM-ratio was further increased in cirrhotic patients, and was comparable with that of patients with cirrhosis of viral etiology.⁴ Consistent with TG results, there was evidence of a progressive procoagulant imbalance as indicated by increased factor VIII (FVIII), one of the main procoagulants, and decreased protein C (PC), one of the main anticoagulants. The ratio FVIII/PC is considered one of the determinants of the increased TG and the resistance to the anticoagulant action of TM.⁵ A subsequent study on smaller numbers of patients did not replicate the data on TG.⁶ However, results of the two studies were poorly comparable due to differences in experimental TG procedures and the unusually high levels of FVIII in the control group in one of the two studies.⁶ Furthermore, a novel investigation confirmed plasma hypercoagulability in patients with NAFLD with a TM-modified TG procedure.⁷ Recently, Valenti *et al.* evaluated a group of 581 apparently healthy blood-donors with metabolic risk factors for the presence of NAFLD and its potential impact on hemostasis.⁸ Markers of fibrosis were also investigated as indexes of procoagulant imbalance. NAFLD was diagnosed in 296 of the investigated patients (50%). Elevated von Willebrand factor (VWF) and FVIII correlated with liver fibrosis but not with fat accumulation in the liver. The latter finding is unsurprising, as in previous studies of patients with NAFLD, the prothrombotic status was associated with body mass index and peripheral, rather than hepatic fat accumulation.⁴ Furthermore, predisposition to higher VWF and FVIII/PC ratio were independently associated with Pro-C3, a specific marker of fibrosis in this population.⁸ This evidence suggests that liver fibrosis in NAFLD can be the result of a procoagulant imbalance that could act synergistically to other known mechanisms such as mitochondrial dysfunction, hepatic stellate cells activations and chronic inflammation.⁹ Moreover, a diffuse perturbation of the endothelium characterizes patients with metabolic comorbidities and the liver seems no exception.¹⁰ Therefore, the development of fibrosis in

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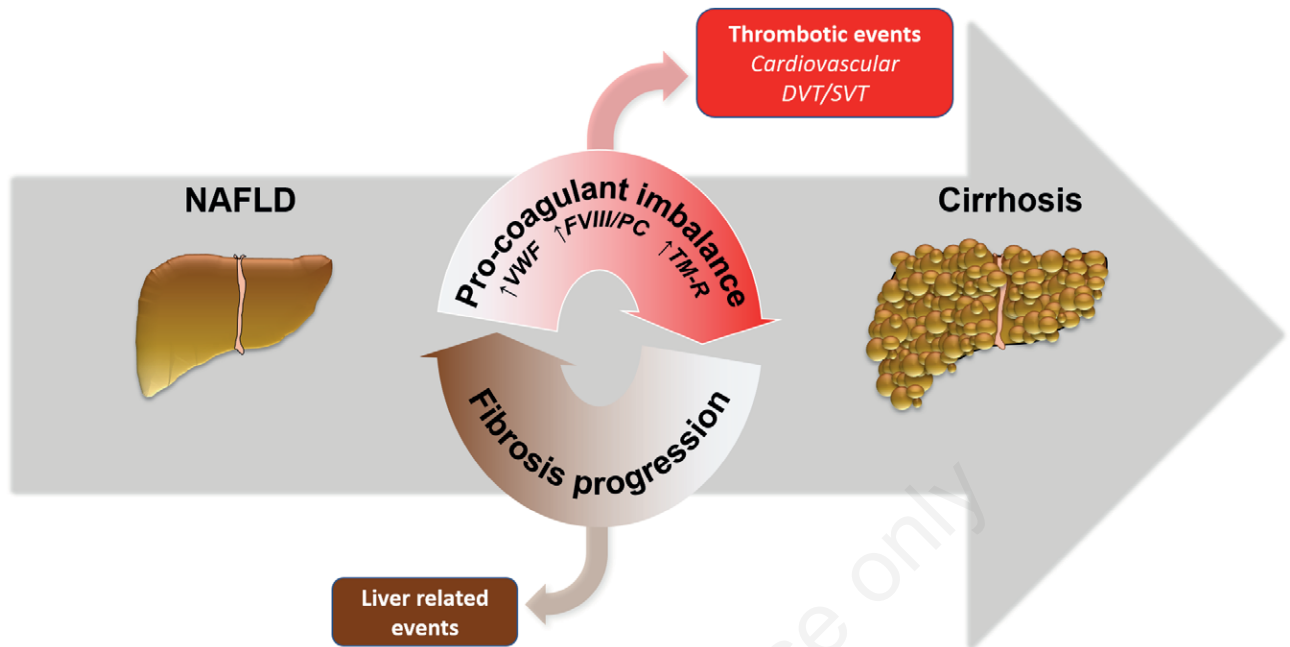
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NAFLD, nonalcoholic fatty-liver disease; DVT, deep vein thrombosis; SVT, splanchnic vein thrombosis; VWF, von Willebrand factor; FVIII, factor VIII; PC, protein C; TM-R, thrombomodulin resistance.

Figure 1. The vicious circle between procoagulant imbalance and fibrosis development in the evolution from nonalcoholic fatty-liver disease to cirrhosis, impacting cardiovascular and liver related events.

NAFLD, in addition to hypercoagulability, endothelial perturbation, and reduced blood flow (collectively known as the Virchow's triad), may contribute to an increased risk of thrombosis.¹¹ This notwithstanding, NAFLD is probably undiagnosed in the absence of an active search policy, because it can be asymptomatic unless decompensated cirrhosis develops. Although the need for NAFLD screening in the general population is debated, diagnosis of this condition in high-risk patients could enable to early detect subjects at risk of both vascular prothrombotic events and life-threatening complications associated with the liver disease (e.g., hepato-cellular carcinoma and acute variceal bleeding) (Figure 1). For the same reason, we believe that the efficacy of a hepatological screening in the setting of patients with metabolic disease, arterial or venous thrombotic events, should be advisable. All the above observations deserve a potential practical consequence since the prothrombotic imbalance observed in NAFLD could be the premise to undertake anticoagulation as a potential preventive strategy. Notably, in 2014 Kopec *et al.* showed that fibrin deposition inside the liver precedes the increase of aminotransferases, hepatic steatosis and inflammation together with an increase of thrombin-antithrombin complex levels in C57BL/6J mice fed with a high-fat diet (HFD).¹² Importantly, thrombin inhibition by dabigatran prevented all these HFD-induced changes suggesting a cause-effect relation between the procoagulant imbalance and the systemic features associated with the metabolic disease.¹² Consequently, these observations support new studies exploring the potential value of hemostasis as target of therapy in NAFLD. In conclusion, the relevance of NAFLD in determining hypercoagulability

and thrombotic tendency is steadily growing, particularly when fibrosis is present. This represents a starting point for a research agenda sought to fill the gap from experimental evidence of the noxious hypercoagulability/metabolic axis to bedside interventions aimed at reducing the cardiovascular, thrombotic and liver-related burden associated to this mounting pandemic.

References

1. Ajmera V, Cepin S, Tesfai K, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. *J Hepatol* 2022;78:471-8.
2. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Amp Hepatol* 2013;10:330-45.
3. Stine JG, Argo CK, Pelletier SJ, et al. Advanced non-alcoholic steatohepatitis cirrhosis: A high-risk population for pre-liver transplant portal vein thrombosis. *World J Hepatol* 2017;9:139-46.
4. Tripodi A, Fracanzani AL, Primignani M, et al. Procoagulant imbalance in patients with non-alcoholic fatty liver disease. *J Hepatol* 2014;61:148-54.
5. Tripodi A. Detection of procoagulant imbalance. Modified endogenous thrombin potential with results expressed as ratio of values with-to-without thrombomodulin. *Thromb Haemost* 2017;117:830-6.
6. Potze W, Siddiqui MS, Boyett SL, et al. Preserved hemosta-

- tic status in patients with non-alcoholic fatty liver disease. *J Hepatol* 2016;65:980-7.
7. Cerletti C, Colucci M, Storto M, et al. Randomised trial of chronic supplementation with a nutraceutical mixture in subjects with non-alcoholic fatty liver disease. *Br J Nutr* 2020;123:190-7.
 8. Valenti L, Tripodi A, La Mura V, et al. Clinical and genetic determinants of the fatty liver-coagulation balance interplay in individuals with metabolic dysfunction. *JHEP Rep* 2022;4:100598.
 9. Paolini E, Longo M, Corsini A, Dongiovanni P. The non-invasive assessment of circulating D-Loop and mt-ccf levels opens an intriguing spyhole into novel approaches for the tricky diagnosis of NASH. *Int J Mol Sci* 2023;24:23-31.
 10. Pasarin M, La Mura V, Gracia-Sancho J, et al. Sinusoidal endothelial dysfunction precedes inflammation and fibrosis in a model of NAFLD. *PLoS One* 2012;7:e32785.
 11. Tripodi A, Lombardi R, Primignani M, et al. Hypercoagulability in patients with non-alcoholic fatty liver disease (NAFLD): causes and consequences. *Biomedicines* 2022; 10:249.
 12. Kopec AK, Joshi N, Towery KL, et al. Thrombin inhibition with dabigatran protects against high-fat diet-induced fatty liver disease in mice. *J Pharmacol Exp Ther* 2014;351:288-97.

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