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Nonalcoholic Fatty Liver Disease-Evidence for a Thrombophilic State?

Margaret Spinosa[1], **Jonathan G. Stine**[2,3]

[1]Department of Medicine, Pennsylvania State University Milton S. Hershey Medical Center;

[2]Division of Gastroenterology & Hepatology, Department of Medicine, Pennsylvania State University Milton S. Hershey Medical Center;

[3]Department of Public Health Sciences, Pennsylvania State University Milton S. Hershey Medical Center

Abstract

Nonalcoholic fatty liver disease is the leading cause of liver disease worldwide. It has expansive extrahepatic morbidity and mortality including increased rates of both cardiovascular disease and venous thromboembolism. Derangements in primary, secondary and tertiary hemostasis are found in nonalcoholic fatty liver disease independent of those ascribed to end-stage liver disease. The abnormalities across all stages of hemostasis explain the increased rates of clinically relevant thrombotic events, including pulmonary embolism, deep vein thrombosis and portal vein thrombosis, which on an epidemiologic basis appears to be independent of obesity and other traditional venous thromboembolic risk factors. However, given the complex interaction between obesity, body composition and nonalcoholic fatty liver disease and the potential for exercise to benefit all three, more research is needed to further define the role of each in contributing to the prohemostatic state of nonalcoholic fatty liver disease in order to improve patient oriented outcomes.

Keywords

Thrombosis; nonalcoholic steatohepatitis; liver transplantation; hypercoagulable; exercise

1. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide with prevalence rates exceeding 25 percent. [1] NAFLD is also the leading etiology of liver disease in the United States (US), where prevalence rates are even greater. [2] Often comorbid with obesity and metabolic syndrome, more than 70% of US adults are overweight or obese.[3] As a result, the healthcare burden of NAFLD is considerable with more than one hundred billion dollars in direct costs annually attributable to NAFLD.[7]

*Address correspondence to this author at the Division of Gastroenterology and Hepatology, Milton S. Hershey Medical Center, 200 Campus Drive, Hershey, PA 17033; Tel: 717-531-1710; jstine@pennstatehealth.psu.edu.

CONFLICT OF INTEREST

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According to the American Association for the Study of Liver Diseases guidelines, NAFLD is defined by 1) evidence of hepatic steatosis by imaging and 2) lack of secondary causes of hepatic fat accumulation including significant alcohol consumption (<21 drinks/week for men and <14 drinks/week for women).[115] NAFLD is an umbrella term for a spectrum of disease states that range from simple steatosis or nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH), which is characterized by inflammation and/or fibrosis. If uncorrected, NASH may progress to cirrhosis and end-stage liver disease. Currently, NASH is the second leading etiology for liver transplantation in the US after viral infection with chronic Hepatitis C [4,5]. In parallel with the worsening obesity epidemic, NASH cirrhosis is expected to become the most common reason for liver transplantation by 2025; it is already the leading indication for liver transplantation in women [6].

However, the impact of NAFLD is seen beyond that of chronic liver disease and progression to cirrhosis. Extrahepatic manifestations are common and include colorectal cancer, cardiovascular disease (CVD), endocrinopathies (*e.g.*, diabetes, hypothyroidism, osteoporosis, polycystic ovarian syndrome iron overload, obstructive sleep apnea, psoriasis and venous thromboembolism (VTE). Hemostatic alterations in NAFLD affect lead to both CVD and VTE. In fact, CVD is the leading cause of death in patients with NAFLD, largely attributable to arterial thrombosis (*e.g.*, myocardial infarction, cerebrovascular accident). Furthermore, multiple epidemiologic studies document increased rates of deep vein thrombosis (DVT), pulmonary embolism (PE) and portal vein thrombosis (PVT) in patients with NASH cirrhosis, independent of traditional risk factors.[15–17] While alterations in hemostasis have been described in advanced liver disease and cirrhosis, the focus of this systematic review is to highlight the abnormalities of hemostasis that are present across all types of NAFLD independent of those found in the presence of end-stage liver disease.

2. HEMOSTASIS AND CHRONIC LIVER DISEASE

Hemostasis involves a series of steps leading to the formation of a blood clot intended to avert hemorrhage following vascular injury. Hemostasis is divided into three phases (Fig. 1). Primary hemostasis is characterized by rapid formation of a platelet plug at the site of vascular injury [18]. Platelet activation and aggregation are mediated by von Willebrand factor (vWF)[19]. Secondary hemostasis refers to the generation and deposition of fibrin *via* the coagulation cascade. Secondary hemostasis is driven by the complex interaction of coagulation proteins or clotting factors that circulate in their inactive forms until activated by tissue factor [19]. Tertiary hemostasis or fibrinolysis, is critical for the dissolution of the fibrin clot and relies on plasminogen activation. Plasminogen, a proenzyme, generates plasmin by the action of the serine proteases tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) on the surface of the fibrin clot or in the presence of the uPA receptor, respectively [20]. Dysregulation of fibrinolysis can lead to an increased risk of thrombosis or bleeding [21, 22].

In patients with cirrhosis, abnormalities exist within each phase of hemostasis that are both pro and antihemostatic. Thus, the hemostatic environment in cirrhosis is complicated and can often be tipped towards either bleeding or clotting. In order to discuss the abnormalities

in hemostasis in less advanced forms of NAFLD, prohemostatic abnormalities that have been established in cirrhosis will be described as a model for comparison.

In patients with cirrhosis, prohemostatic alterations in primary hemostasis involve vWF, ADAMTS13 (A Disintegrin and Metalloproteinase with a ThromboSpondin type 1 motif, member 13), as well as platelet count and function. The changes which promote hemostasis are elevated levels of vWF and low levels of ADAMTS13. The hepatic stellate cells generate ADAMTS13 which cleaves vWF. In chronic liver disease, hepatic stellate cells are damaged resulting in lower levels of ADAMTS13. Decreased plasma ADAMTS13 activity may serve as a prognostic indicator for patients with liver cirrhosis. The severity of deficiency of ADAMTS13 activity (ADAMTS13:AC) has been used to estimate survival rates in patients with liver cirrhosis. Diminishing survival rates correlated with the degree of ADAMTS13:AC deficiency and may be a useful adjunct alongside well-established predictors including the Child Turcotte-Pugh Score and Model for End-Stage Liver Disease score [25]. While alterations in levels of vWF and ADAMTS13 promote hemostasis, thrombocytopenia acts as a driving factor in direct opposition.

In secondary hemostasis, dysregulation of the coagulation cascade is a consequence of the liver failing to synthesize coagulation factors [26]. While the synthesis of most clotting factors is reduced, an elevation in plasma Factor VIII is seen in chronic liver disease. This is in part due to increased levels of vWF as together, vWF and Factor VIII circulate as a noncovalent complex [27,28].· Both procoagulant and anticoagulant factors are affected in cirrhosis and while a new equilibrium may be established, a delicate balance exists between pro and anticoagulant factors. Drivers that promote secondary hemostasis include low levels of anticoagulant protein C, protein S, and antithrombin [29–31].·In contrast, low levels of procoagulants fibrinogen and Factors II, V, VII, IX, X, XI are found in cirrhosis. Low levels of these procoagulant factors oppose the effects of hemostasis. Furthermore, not only are the quantity of factors affected, but there are also qualitative defects in these coagulation factors, especially with vitamin K dependent factors [32].

In the last stage of liver disease, alterations in tertiary hemostasis or fibrinolysis are also common. As seen in secondary hemostasis, the major components of tertiary hemostasis involved in fibrinolysis are a product of liver synthesis [33]. Fibrinolysis occurs along the fibrin surface and is mediated by tPA and uPA, serine proteases found on endothelial cells. tPA and uPA bind to plasminogen, a zymogen that is then activated into plasmin, the major driver of the breakdown of fibrin into fibrin degradation products. Regulation of these activators is mediated by plasmin inhibitor as well as plasminogen activator inhibitors. The principal inhibitor at the level of endothelial cell is plasminogen activator inhibitor (PAI)-1, which is produced by several sources including endothelial cells and adipose tissue [21]. The prohemostatic imbalance in cirrhosis is partially steered by low plasminogen levels and elevated levels of PAI-1 [35–37] While the antihemostatic balance is propelled by elevated levels of tPA, low levels of thrombin activatable fibrinolysis inhibitor and plasmin inhibitor also contribute to the imbalance [38–41]. Plasma levels of tPA are elevated due to both increased secretion from endothelial cells and also reduced clearance by the diseased liver [42].

3. THE PROCOAGULANT IMBALANCE IN NAFLD

Independent of the hemostatic imbalance of cirrhosis, there is a growing body of literature stating that NAFLD is a prohemostatic state (Fig. 2). Over time, hepatic steatosis leads to chronic inflammation which causes changes in normal hemostasis [36]. In fact, there is a step-wise progression in hemostatic abnormality with the lowest aberration seen in NAFL and the greatest in NASH cirrhosis. Similar to the alterations found in cirrhosis, there are changes in all three stages of hemostasis in NAFLD.

4. PRIMARY HEMOSTASIS

Patients with NAFLD have abnormal primary hemostasis due to aberrations in both platelet recruitment and function. Mean platelet volume (MPV), a marker of platelet function, is associated with platelet dysfunction. In patients with increased MPV, greater amounts of platelet activation and aggregation are observed [47–52]. MPV is greater in patients with NAFLD in response to chronic inflammatory mediators and worsening insulin resistance [53]. Moreover, increased MPV is associated with the development of CVD, such as coronary artery disease. MPV is also a marker for unprovoked VTE. Collectively, these findings suggest a role for platelet dysfunction in thrombosis generation [54, 56]. Further investigation to elucidate the role of platelets in the NAFLD state would be of significant clinical importance, especially given the widespread use of aspirin for comorbid CVD. While the role of antiplatelet agents, such as aspirin, is well established both for primary prevention and treatment of CVD in patients with NAFLD, whether or not antiplatelet agents reduce the risk of VTE remains unknown and offers an intriguing avenue for future study as the fibrin rich venous clot still requires activated platelets for thrombosis formation.

Increased levels of vWF are also found in NAFLD [36]. However, its' clinical significance remains unclear as alterations in vWF correlate more strongly with characteristics of metabolic syndrome including increased body mass index (BMI) and visceral adipose tissue rather than histologic features of NAFLD [36] Additionally, low levels of ADAMTS13 have also been reported in NASH and may play a role in abnormal primary hemostasis [57]. More studies focusing on the role of both vWF and ADAMTS13 in NAFLDare presently needed to further clarify the role of each in the thrombophilic state of NAFLD.

5. SECONDARY HEMOSTASIS

In NAFLD, there are multiple abnormalities in secondary hemostasis, namely involving increased activity of Factors VII, VIII, IX, XI, and XII [58, 62]. In their cohort of 98 subjects, Kotronen *et al.* demonstrated the activity of circulating Factors VIII, IX, XI, and XII that were consistently higher independent of age, gender and BMI in subjects with NAFLD compared to those without NAFLD [58]. Similarly, increased factor VII activity has also been reported in otherwise healthy men with hepatic steatosis compared to healthy men without liver steatosis [62] Utilizing endogenous thrombin potential (ETP) measurement, Tripodi *et al.* demonstrated further evidence that NAFLD is a thrombophilic state [45]. ETP is a measurement of thrombus formation utilizing area under the thrombin generation curve to quantify the capacity of thrombin generation in plasma after stimulation of the clotting

cascade [23]. Thus, ETP is a tool that is useful in assessing the forces of pro- and anti-coagulation in plasma [24]. In patients with NAFLD, Tripodi *et al.* found increasing ETP ratios with worsening severity of NAFLD; the greatest ETP ratio wasobserved for patients with NASH cirrhosis. Additionally, low levels of anticoagulants antithrombin, protein C and protein S have been found in similar dose-dependent fashion with the lowest levels in the most advanced stages of NAFLD [45, 58, 61]. These findings suggest that the procoagulant imbalance worsens as NAFLD progresses [45].

6. TERTIARY HEMOSTASIS

Alterations in tertiary hemostasis are also present in NAFLD independent of cirrhosis. PAI-1, which plays a featured role in tertiary hemostasis, and is a strong procoagulant driver in NAFLD [34]. Levels of PAI-1 are elevated in patients with NAFLD and increase with the severity of steatosis [36]. In their series of 273 subjects, Verrijken *et al.* found levels of PAI-1 increased with the NASH Activity Score as well as with fibrosis stage in subjects with biopsy-proven NASH [36]. Elevation of PAI-1 levels, in addition to decreases in tissue activating factor antigen and tPA, lead to a state of chronic hypofibrinolysis and prothrombotic potential [44, 62, 63]. Elevated PAI-1 levels lead to longer clot lysis times by inhibiting breakdown of fibrin based clots through physiologic inhibition of plasminogen activators [65].

One major source of PAI-1 is adipose tissue. PAI-1 functions as an adipocytokine, a secretory protein derived from visceral fat, and modulates inflammation [44]. As elevated PAI-1 levels lead to the alteration of normal regulation of the fibrinolytic system, this results in increased CVD risk [60]. Weight loss and dietary restriction lowers PAI-1 level as do certain anti-diabetic agents (*e.g.*, thiazolidinediones and metformin) [60]. Additionally, elevated PAI-1 may accelerate liver disease progression due to local tissue ischemia stemming from intrahepatic thrombi, known as parenchymal extinction, however, further study confirm the requirement at this time [36].

7. CLINICAL IMPLICATIONS- ARTERIAL THROMBOSIS AND CARDIOVASCULAR DISEASE

Many NAFLD risk factors overlap with those that predispose to CVD. Natural history studies have shown patients with NAFLD and NASH have an overall lower survival, [67, 73] largely due to increased rates of CVD [67, 74, 75]. While the majority of NAFLD and NASH patients will die from CVD, only 1% of patients with NASH will die from a liver-related event [75]. The longest longitudinal experience of 33years by Ekstedt *et al.* demonstrated that patients with NAFLD had a 55% increased risk of CVD [68]. This confirmed their earlier interim analysis at 13.7 years where 43% of deaths were due to CVD, followed by non-hepatic malignancy (15%), and liver-related causes including hepatocellular carcinoma (8%) [67]. Multiple studies have shown that NAFLD is independently associated with non-fatal CVD events [10, 76, 77]. When compared to traditional CVD risk factors, NASH is the strongest adjusted independent predictor of CVD in liver transplant candidates with over a three-fold increased risk. Liver transplant recipients

with NASH have significantly greater post-transplant fatal and non-fatal CV events when compared to recipients without NASH [78–80].

Proposed mechanisms for the development of CVD in patients with NAFLD include a genetic predisposition, chronic inflammation, endothelial dysfunction, oxidative stress, as well as hemostatic alterations in the balance between procoagulant and anticoagulant factors [14]. Of all these mechanistic factors, endothelial dysfunction is perhaps the best characterized. Endothelial dysfunction leads to abnormal blood flow and development of an arterial plaque with a fibrous cap, lipid core, and *de novo* atherosclerosis. Over time, this stable plaque progresses, leading to intimal narrowing. If uncorrected, this progresses to an unstable plaque at risk of rupture and arterial thrombosis [81, 82]. Flow-mediated dilation of the brachial artery is an effective, non-invasive measure of endothelial function [83, 84]. A recent meta-analysis of 5,547 subjects found that after adjusting for confounding factors, for each 1% decrease in brachial flow-mediated dilation, there was a 13% increased risk of adverse CV events [85].

Independent of traditional CVD risk factors (*e.g.*, obesity, insulin resistance, visceral adiposity), endothelial dysfunction is found globally in NAFLD in both systemic and portal venous systems [86–90]. While the exact mechanism in which NAFLD results in endothelial dysfunction is unknown, what is known is that this strongly contributes to increased CVD risk. It is hypothesized that overwhelmed lipid processing and trafficking lead to production of pro-inflammatory cytokines (Interleukin-6, Tumor necrosis factor alpha) and resultant continuous low-grade inflammation. This culminates in inefficient endothelial vasodilation and may accelerate liver fibrosis through local tissue hypoxemia (hypoperfusion), apoptosis, and fibrogenesis [91–93].

8. CLINICAL IMPLICATIONS- VENOUS THROMBOSIS

The prohemostatic environment in patients with NAFLD leads to an increased risk of clinically significant thrombotic events in both the portal venous as well as the systemic circulation. Consequently, liver transplant recipients with NASH have a greater risk of PVT, DVT and PE [15, 17, 94, 95]. Independent of metabolic comorbidities, liver transplant recipients with NASH have a 55% greater risk of PVT. The odds of PVT increase exponentially for candidates who have high-risk NASH (age >60 years with diabetes, hypertension and obesity) [OR 2.1 (95% CI 1.6–2.8)]. Furthermore, the thrombotic state of NASH is not only localized to the portal venous system, but also includes the systemic circulation given the risk of PE and/or DVT is nearly two and a half-fold greater when comparing hospitalized patients with NASH cirrhosis to all other etiologies of liver disease.[16] Additionally, in their case-control study of 414 subjects with PE or DVT, DiMinno *et al.* found that 81% of VTE cases had NAFLD compared to 30% in age, sex and BMI matched controls without VTE (RR 2.7, 95% CI 2.2–3.2, p<0.001).[96] When adjusting for inherited thrombophilia, NAFLD was still associated with increased rates of VTE (OR 1.8, 95% CI 1.2–2.7, p<0.001). The importance of this cannot be overstated as patients with cirrhosis have a higher 30-day mortality following DVT, PE, or PVT [116].

Elevated levels of PAI-1 also pose risk for the development of VTE due to decreased fibrinolytic activity [64, 65, 66] Multiple studies have documented PAI-1 to be an independent predictor of VTE when adjusting extensively for prothrombotic confounders [65, 66, 97]. In fact, PAI-1 is one of the strongest independent risk factors for PVT [OR 6.4 (95% CI 2.5–16.1) [97]. Papatheodorois *et al.* found that patients with NASH have higher levels of IgG anti-cardiolipin antibodies compared to patients with NAFL. In 56% of NASH patients, one or more thrombotic risk factors was isolated compared to only 8% in patient with NAFL [67]. Furthermore, the authors demonstrate that the presence of at least one thrombotic risk factor was associated with a nearly two-fold fibrosis stage increase in NASH, confirming earlier observational reports correlating thrombotic risk factors to the extent of hepatic fibrosis [61].

9. ROLE OF OBESITY AND THROMBOSIS

Across the medical and surgical literature, obesity is a well-established VTE risk factor [98, 99]. Despite multiple basic science, translational, epidemiologic and clinical studies suggesting a hypercoagulable state existing in patients with NAFLD independent of obesity, a recent report by Potze *et al.* challenges this paradigm [59]. In this study, the authors found very similar hemostatic profiles when comparing subjects with non-cirrhotic biopsy proven NAFLD to controls without NAFLD with several notable exceptions, such as increased PAI-1 levels, less fibrinolysis and a different fibrin clot infrastructure were present in subjects with NAFLD. However, obese controls also had elevations in PAI-1, impaired fibrinolysis and similar fibrin clot changes, leading the authors to conclude that obesity, not NAFLD, was the main driver of prothrombotic risk [59]. Given the conflicting evidence, further studies are necessary to better define the complex interaction between obesity, NAFLD and thrombosis risk. As BMI is a poor marker in patients with end-stage liver disease, it is suggested that measurement of body composition may be a more direct approach to determine the role of adiposity and the production of prothrombotic adipokines, especially given the role of fat mass and adipose tissue in VTE development in populations without NAFLD [100].

10. ROLE OF EXERCISE IN THROMBOSIS

Exercise has a favorable effect on the coagulation system across all three phases of hemostasis [101–103]. Habitual exercise improves primary hemostasis *via* endothelial-dependent vasodilation and nitric oxide production leading to less platelet activation and aggregation [104]. Moderate intensity exercise improves hemostasis efficiency by activating fibrinolysis in concert with improving coagulation [101, 102]. Specifically, chronic aerobic based training leads to improved fibrinolytic activity in both healthy subjects and those with CVD [101, 102, 105–108]. Reductions in PAI-1 following aerobic exercise programs lasting 3–8 months range from 23–37% [105, 107–109]. When comparing subjects who are aerobically trained to those who are not, further benefit has been observed in fibrinolytic activity *via* skeletal muscle tPA efficiency [106]. Patients with higher baseline PAI-1 experience the greatest benefit from exercise through both weight and fat loss [105, 108, 110]. Resistance training also appears to improve the efficiency of the fibrinolytic system in the immediate post-exercise period following short-term strength-training routines (<2

weeks) [104, 111]. However, the effect of chronic resistance training on coagulation and fibrinolysis remains unknown. Furthermore, while the current standard of care for NAFLD is lifestyle changes through diet and exercise where guidelines recommend ≥30 minutes of moderateintensity physical activity 3–5 times/week, the benefit of exercise in modulating coagulation and improving the prothrombotic state of NAFLD also remains unknown [112, 113].

CONCLUSION

In conclusion, NAFLD is the leading cause of liver disease worldwide and has expansive extrahepatic morbidity and mortality including increased rates of both CVD and VTE. Derangements in primary, secondary and tertiary hemostasis are found in NAFLD independent of those ascribed to end-stage liver disease. These hemostatic abnormalities explain the increased rates of clinically relevant thrombotic events including PE, DVT and PVT, which on an epidemiologic basis appear to be independent of obesity and other traditional VTE risk factors. However, given the complex interaction between obesity, body composition and NAFLD and the potential for exercise to improve all three, more research is needed to further define the role of each in the prothrombotic state of NAFLD.

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LIST OF ABBREVIATIONS

ADAMTS13	A Disintegrin and Metalloproteinase with a ThromboSpondin type 1 motif, member 13
BMI	body mass index
CVD	cardiovascular disease
DVT	deep vein thrombosis
ETP	endogenous thrombin potential
MPV	mean platelet volume
NAFL	nonalcoholic fatty liver
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
PAI	plasminogen activator inhibitor
PE	pulmonary embolus
PVT	portal vein thrombosis

tPA	tissue plasminogen activator
uPA	urokinase-type plasminogen activator
US	United States
VTE	venous thromboembolism
vWF	vonWillebrand factor

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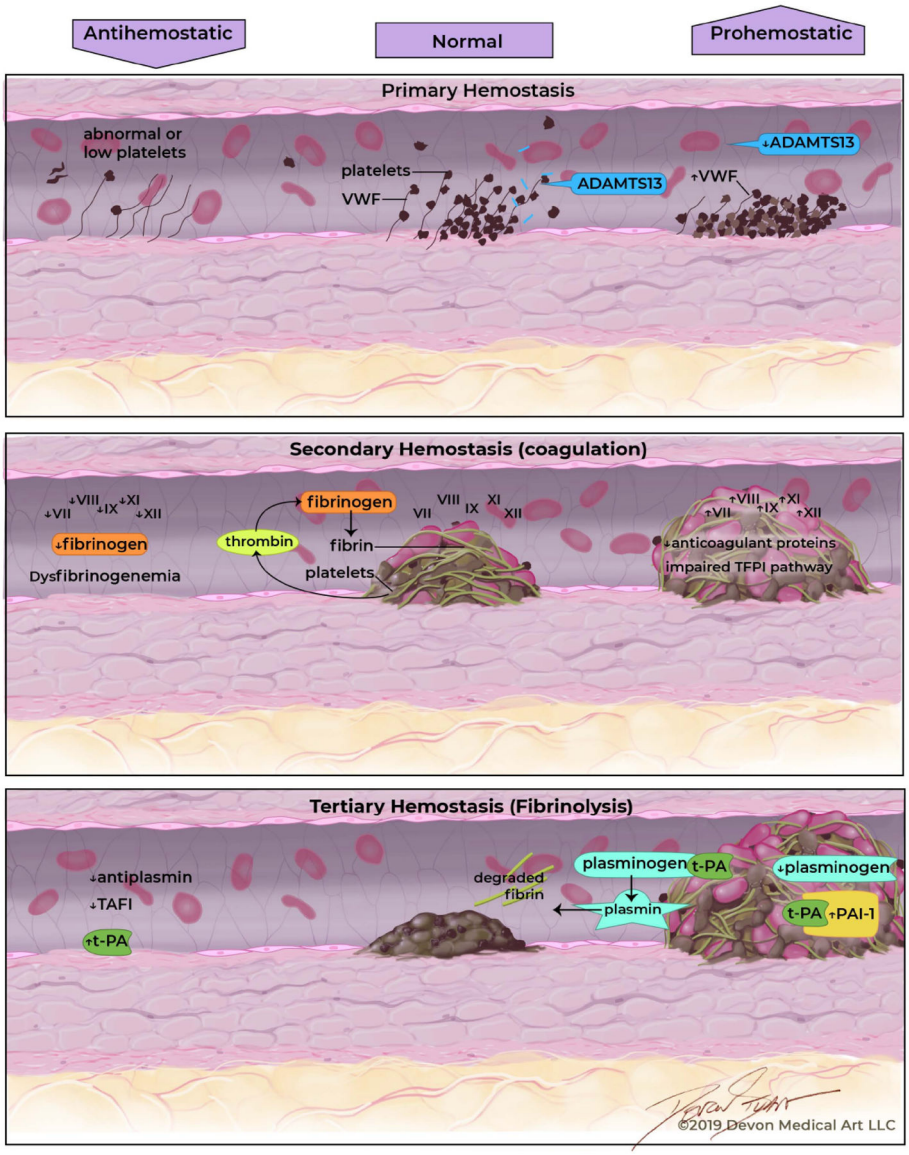

Fig. (1).
The precarious balance of hemostasis in patients with chronic liver disease.

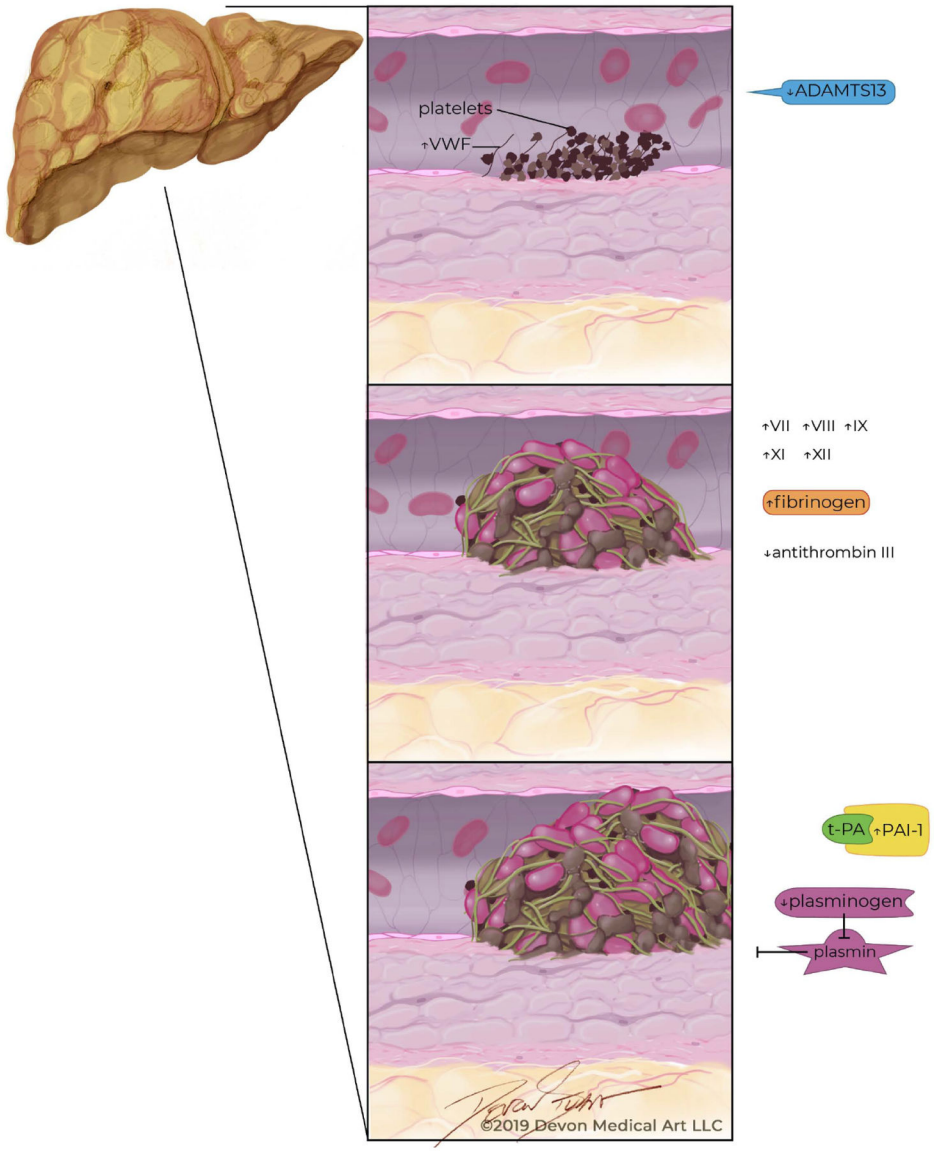

Fig. (2).

Abnormalities across all three phases of hemostasis in patients with nonalcoholic fatty liver disease.