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Connecting impaired fibrinolysis and dyslipidemia

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Abstract

A State of the Art lecture entitled "Connecting Fibrinolysis and Dyslipidemia" was presented at the International Society on Thrombosis and Haemostasis Congress 2023. Hemostasis balances the consequences of blood clotting and bleeding. This balance relies on the proper formation of blood clots, as well as the breakdown of blood clots. The primary mechanism that breaks down blood clots is fibrinolysis, where the fibrin net becomes lysed and the blood clot dissolves. Dyslipidemia is a condition where blood lipid and lipoprotein levels are abnormal. Here, we review studies that observed connections between impaired fibrinolysis and dyslipidemia. We also summarize the different correlations between thrombosis and dyslipidemia in different racial and ethnic groups. Finally, we summarize relevant and new findings on this topic presented during the 2023 International Society on Thrombosis and Haemostasis Congress. More studies are needed to investigate the mechanistic connections between impaired fibrinolysis and dyslipidemia and whether these mechanisms differ in racially and ethnically diverse populations.

KEYWORDS
dyslipidemia, hypercholesterolemia, hypertriglyceridemia, impaired fibrinolysis, lipoproteins, HDL, lipoproteins, LDL, plasminogen activator inhibitor 1, tissue plasminogen activator

Essentials

- Impaired fibrinolysis is the breakdown of fibrin clots.
- Dyslipidemia is characterized by abnormal levels of lipids and lipoproteins in the blood.
- A State of the Art lecture, "Connecting Fibrinolysis and Dyslipidemia," was presented at International Society on Thrombosis and Haemostasis 2023.
- Impaired fibrinolysis and dyslipidemia are associated with one another in cardiovascular disease.

1 | INTRODUCTION

Blood clotting is a pillar of hemostasis, as the body depends on the ability to prevent the loss of blood. Thrombin catalyzes the activation of fibrinogen to fibrin [1], which is then polymerized and cross-linked to become an insoluble and stable fibrin clot. Fibrin polymerization and covalent linkage are a result of the common pathway of the coagulation cascade, which develops a net around the growing blood clot to stabilize it [2]. Fibrin is also cross-linked by covalent ε-(γ-glutamyl)-lysine, which stabilizes the polymerized structure to prevent unintended bleeding [3]. Excessive blood clotting can cause obstruction in blood flow, leading to tissue ischemia and damage. The fibrin clot needs to be properly removed by a mechanism called fibrinolysis, allowing blood to reflow.

Accumulated evidence showed that dyslipidemia is associated with impaired fibrinolysis. Dyslipidemia is characterized by abnormal levels of lipids or lipoproteins. Lipoproteins are water-soluble micellar particles that primarily transport hydrophobic lipids throughout the bloodstream [4]. Lipoproteins can be distinguished by their densities, size, and other unique features, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), intermediate-density lipoproteins, very LDL (VLDL), chylomicrons, chylomicron remnants, and lipoprotein (a) (Lp[a]) [4]. Lp(a) is assembled when apolipoprotein a (apo [a]) forms a disulfide bond with apolipoprotein B (apoB) on an LDL-like particle [5]. Lipoproteins transport lipids and other cargo from the liver or small intestine to peripheral tissues and back to the liver through circulation [6–8]. Except for HDL, all other lipoproteins contain apoB and are atherogenic.

2 | OVERVIEW OF FIBRINOLYSIS

Fibrinolysis is the primary mechanism that removes fibrin accumulated in blood clots or on the cell surface (Figure). The key drivers of fibrinolysis are tissue-type plasminogen activator (tPA), urokinase plasminogen activator (uPA), and plasmin, all of which are serine proteases. Fibrinolysis is initiated by tPA [9], which catalyzes the conversion of zymogen plasminogen to its active enzyme form, plasmin [9]. Both plasminogen and tPA have lysine-binding sites on their Kringle domains, allowing them to interact with the lysine residues on the fibrin molecules [10,11]. The localization of tPA and plasminogen on fibrin makes plasminogen activation efficient. uPA, however, differs from tPA in that uPA lacks a lysine-binding site on the Kringle domain, thereby lacking binding affinity to fibrin [12]. A uPA receptor is needed to localize uPA on the cell surface, allowing its interaction with plasminogen [13]. Another key difference between tPA and uPA is that tPA is made as an active enzyme, whereas uPA is made as a zymogen and requires activation by a protease, such as plasmin, to feed forward the activation of more plasminogen to plasmin. uPA also serves other biological roles, such as promoting cell apoptosis [14], tumor progression [15], and cell migration [16]. Therefore, plasminogen activation by tPA is more efficient than by uPA.

Plasminogen contains 5 Kringle domains and a serine protease domain [17]. When plasminogen is in its open conformation, the activation loop is exposed for cleavage by tPA or uPA. Upon activation, plasmin degrades fibrin by breaking down the insoluble cross-linked fibrin into the soluble fibrin degradation products. Specifically, fibrin's α-chain becomes cleaved, resulting in a separate fragment X. This fragment X is then further cleaved in the α-, β-, and γ-chains. These cleavages result in fragments Y and D, which are cleaved into fragments E and D. Fragments E and D then become the E and D regions of a new fibrinogen molecule [18].

Plasminogen activator inhibitor-1 (PAI-1) is the main inhibitor for plasminogen activation by inactivating tPA and uPA [19]. Elevated levels of PAI-1 are associated with cardiovascular disease risk and thrombotic events such as venous thromboembolism and coronary arterial thrombosis [20,21]. PAI-1 forms a complex with tPA through tPA's finger and Kringle 2 (K2) domains, leading to conformational change and inactivation of tPA [19]. tPA binds to fibrin through the finger and K2 domains [22,23]. Thus, the tPA-PAI-1 complex formation also inhibits tPA's ability to bind to fibrin. tPA activity is mostly determined by the net balance of tPA and PAI-1 concentration. Higher PAI-1 than tPA levels may result in hypofibrinolysis, leading to deficient fibrinolytic response [24]. Fibrinolysis is also inhibited by Lp(a), which contains an inactive protease domain and inhibits plasminogen-to-plasmin conversion [25,26].

Thrombin activatable fibrinolysis inhibitor (TAFI) also attenuates fibrinolysis. TAFI is a carboxypeptidase B-like proenzyme that is synthesized in the liver [27]. After being activated by thrombin, TAFI removes carboxy-terminal lysine residues on fibrin [28,29]. When this occurs, tPA is unable to interact with fibrin to activate plasminogen to plasmin [28]. As such, increased levels of TAFI are associated with increased risk of thrombosis [30]. α2-Antiplasmin (α_2AP) perturbs fibrinolysis by inhibiting plasmin by forming a complex and cross-linking to fibrin by coagulation factor XIIIa. This cross-linking interferes with the binding between plasminogen and fibrin [31]. Therefore, α_2AP proactively inhibits the activation of plasminogen and thus reduces fibrinolysis [32].

Fibrin polymerization is essential for the stability of a blood clot, as a polymerized fibrin net with covalent linkages stabilizes the clot to stop bleeding [33]. Resistance to tPA-mediated clot lysis was observed in trauma patients with denser fibrin clots. Within 1 hour of trauma, tPA sensitivity was determined by thromboelastography in blood samples, and fibrin polymerization, integrity, and porosity were measured using confocal microscopy in plasma samples. Patients with tPA resistance developed densely packed clots, whereas tPA-sensitive trauma patients had loose clots. These observations describe denser fibrin polymerization that is associated with resistance to fibrinolysis and more stabilized clots [34].

In cases of hypofibrinolysis, the mechanism to break down blood clots becomes inadequate. Impaired fibrinolysis increases risk of both arterial and venous blood clots that can cause severe tissue ischemia [35]. Genetic disorders with impaired fibrinolysis have been reported, including deficiency in plasminogen [36]. Deficiency in plasminogen activity is marked by recurrent fibrin deposition and inflamed mucous membranes, specifically ligneous conjunctivitis [36,37]. Genetic disorders that cause excess fibrinolysis are extremely severe but do exist [38], including α_2AP deficiency (Miyasato disease), PAI-1 deficiency, and gain of function in uPA (Quebec platelet disorder [QPD]) in humans [38]. Miyasato disease is a rare autosomal recessive disorder that causes a deficiency in α_2AP. Symptoms of this disease are delayed traumatic bleeding and spontaneous rebleeding, often in the form of hematomas [39,40]. These symptoms are typical clinical presentations due to normal clot formation yet with hyperfibrinolysis. QPD is an autosomal dominant, rare disorder that causes increased expression of uPA in megakaryocytes and higher uPA levels in platelets [41]. This gain of function in uPA leads to hyperfibrinolysis upon platelet activation. Patients with QPD also have higher platelet counts but display delayed-onset bleeding after trauma [41]. Complete PAI-1 deficiency is an autosomal recessive disorder that causes mild to moderate

FIGURE Schematic of fibrinolysis mechanisms. Red arrows depict interactions that contribute to impaired fibrinolysis, and green arrows represent the fibrinolysis pathway. Tissue-type plasminogen activator (tPA) interacts with plasminogen on fibrin to convert plasminogen into plasmin. Plasmin leads to the cleavage of the fibrin net, which allows the degradation of fibrin. Plasminogen activator inhibitor-1 (PAI-1) directly interacts with and inactivates tPA. α2-Antiplasmin (α_2AP) mediates the binding and cross-linking between fibrin and coagulation factor XIIIa, interfering with the interaction of plasminogen and fibrin. Thrombin activatable fibrinolysis inhibitor (TAFI) attenuates fibrinolysis by removing the carboxy-terminal lysine residues on fibrin, which inhibits the localization of plasminogen on fibrin.
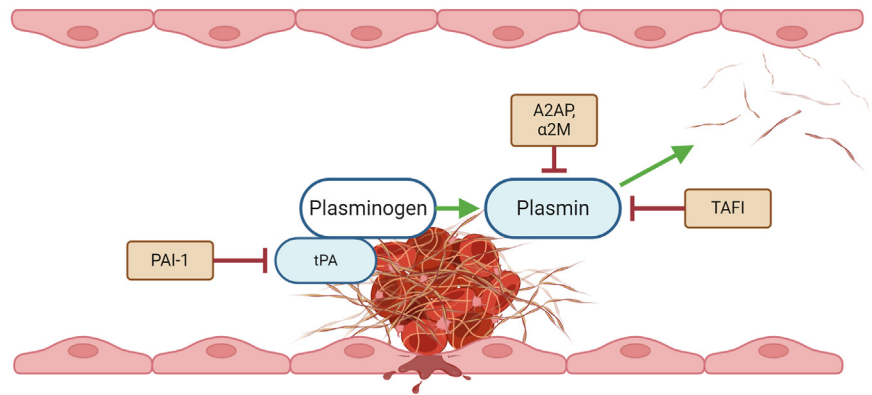
bleeding in humans [42]. PAI-1 deficiency in humans was reported to lower plasma proprotein convertase subtilisin/kexin 9 (PCSK9) levels [43]. PCSK9 inhibition causes lower cholesterol levels by promoting the recycling of low density lipoprotein-receptor (LDLR) onto the cell surface. In our recent study [44], we observed that in plasma samples from patients deficient in PAI-1, there were lower concentrations of plasma apoB and apoB-lipoprotein cholesterol compared with unaffected controls. No abnormal lipid levels have been reported in plasminogen deficiency, Miyasato disease, and QPD, which require further investigation.

3 | OVERVIEW OF DYSLIPIDEMIA

Dyslipidemia is defined as the abnormal levels of lipids, which is typically a chronic condition that can occur due to genetic, lifestyle, or acquired medical conditions [45,46]. Hypercholesterolemia is defined as blood LDL cholesterol greater than 190 mg/dL, greater than 160 mg/dL with 1 risk factor, or greater than 130 mg/dL with 2 risk factors [47]. Risk factors for hypercholesterolemia include male age greater than 45 years, female age greater than 55 years, family history of atherosclerosis, hypertension, diabetes, smoking, and HDL cholesterol levels lower than 40 mg/dL in males and 55 mg/dL in females [47]. Hypertriglyceridemia is defined as triglyceride levels greater than 150 mg/dL [48]. Other abnormal levels of lipids exist, including low HDL cholesterol and hyperchylomicronemia. High levels of apoB-containing lipoproteins significantly contribute to the progression of atherosclerosis [49]. Oxidation modifications in LDL result in oxidized LDL, which accumulates in foam cells and builds an atherosclerotic lesion [50].

Several proteins facilitate the uptake of lipoproteins, such as LDLR and LDL receptor–related protein 1 (LRP1). LDLR is an extracellular surface receptor that binds to circulating LDL. This interaction stimulates the uptake of LDL by vesicular endocytosis into the cell

[51]. The vesicle fuses with a lysosome, where LDL can be degraded. LDLR, when bound to PCSK9, is degraded in the lysosome as well, however, the receptor, if unbound to PCSK9, is recycled to the surface of the cell to continue uptaking more LDL [52]. These interactions describe the use of PCSK9 inhibitors as a therapy to treat high cholesterol. LRP1, which is a transmembrane receptor, is expressed by many cell types, including hepatocytes, epithelial cells, fibroblasts, monocytes, macrophages, and adipocytes [53]. LRP1 promotes lipoprotein lipase (LPL) to hydrolyze the chylomicron remnants [54]. LRP1 and LDLR then work to clear chylomicron remnants and VLDL in the hepatocyte [55,56]. LRP1 contains cysteine-rich complement-type repeats and is chaperoned by receptor-associated protein, which supports diverse ligand binding [56–58]. Decrease in lipoprotein uptake in patients with severe obesity by reduced LRP1 expression in visceral and subcutaneous adipose tissues has been observed [59]. Accordingly, obesity is correlated with increased risk of dyslipidemia, specifically hypercholesterolemia, hypertriglyceridemia, and low HDL cholesterol [60–62].

4 | IMPAIRED FIBRINOLYSIS IN DYSLIPIDEMIA

Dyslipidemia promotes the progression of atherosclerosis, whereas impaired fibrinolysis can contribute to thrombosis upon atherosclerotic plaque rupture. Atherosclerotic plaque forms as lipids build up in the intima layer of the subendothelial matrix. Lipoproteins ionically bind to the negatively charged proteoglycans of the extracellular matrix on the arterial wall [63]. When this occurs, lipoproteins may become oxidized [64,65] and then engulfed by macrophages, which then become lipid-laden foam cells that exacerbate atherogenesis [64]. When the plaque becomes overloaded with lipids, it becomes more vulnerable to rupture. When the rupture occurs, the exposed

subendothelium triggers platelet activation and aggregation [66,67], and coagulation follows, which leads to a thrombus formation. When the fibrinolytic mechanism is impaired, the undissolved thrombus worsens the narrowed atherosclerotic artery to occlude, resulting in tissue ischemia. The coupling of dyslipidemia and impaired fibrinolysis contributes to atherosclerosis and severe thrombotic cardiovascular outcomes.

Clinical observational studies have communicated correlations between tPA activity, PAI-1 antigen levels, atherogenic apoB-containing lipoproteins, and serum or plasma lipid levels [68,69]. The findings from these studies are summarized in Table 1. A study investigated tPA activity and antigen levels in 111 healthy patients and found that patients with low tPA activity had the highest levels of serum cholesterol and triglyceride [70]. In a separate study, 30 patients with hypertriglyceridemia showed a positive correlation between serum triglyceride and PAI-1 antigen levels [71]. In another study of 71 patients under the age of 45 who had survived a heart attack, PAI-1 levels were positively correlated with serum triglyceride levels. This study also observed that patients with low tPA activity also had high triglyceride levels [72].

Lp(a), which is assembled by an LDL-like particle with apo(a), is antifibrinolytic. Apo(a) on Lp(a) can bind to fibrin through its lysine-binding site on its Kringle 4 domain [75–77]. The interaction between apo(a) and fibrin becomes competitive for plasminogen/fibrin binding, which halts the conversion of plasminogen to plasmin, thus impairing the fibrinolysis mechanism that follows this reaction [78,79]. Lp(a) also inhibits fibrinolysis by inhibiting the conversion from glutamine–plasminogen to lysine–plasminogen [80], which is a better substrate for tPA [81]. A study investigating Lp(a) in 60 patients with a history of stroke measured serum levels of Lp(a). They found that Lp(a) levels had a positive correlation with PAI-1 activity, but Lp(a) levels alone did not differ between control and experimental groups [73]. The authors suggest that Lp(a)'s inhibition of fibrinolysis is less dependent on Lp(a) concentration but more dependent on the interaction of apo(a) with fibrin.

Obesity, which is often associated with dyslipidemia, is linked with impaired fibrinolysis. Specifically, in obesity, both PAI-1 and tPA are increased [82,83]. Increased PAI-1 causes a compensatory response of increased tPA synthesis in the hepatocytes [84,85]. However, the PAI1 increase is greater than tPA, causing a net inhibition of tPA [85]. Thus, in obesity, larger increase in PAI-1 and the smaller compensatory increase in tPA leads to an overall net reduction in fibrinolytic potentials. This is one mechanism that offers insight into this relationship; however, it is worthwhile investigating lipoprotein metabolism in obesity that could drive impaired fibrinolysis.

Other fibrinolytic protein concentrations and activity have also been investigated in dyslipidemia. Fibrinolytic inhibitors α_2AP and TAFI are higher in patients with hypertriglyceridemia compared with controls with normal triglyceride levels [74,86,87]. Patients with hypertriglyceridemia also displayed prolonged dilute blood clot lysis time, which is consistent with the findings that fibrinolysis may have been attenuated in the patients with dyslipidemia [74].

5 | REGULATION OF LIPID METABOLISM BY FIBRINOLYTIC PROTEINS

In our recent study, we showed that tPA can interact with apoB in the hepatocyte. This interaction is possible through the binding of the apoB N-terminus to the lysine-binding site on the K2 domain of tPA. When this interaction occurs, the microsomal transport protein and apoB interaction is interrupted. The transfer of cholesterol and triglycerides to the growing VLDL molecule becomes limited, causing decreased VLDL assembly, size, and secretion. When lipids are loaded to hepatocytes, PAI-1 and tPA form a complex, and tPA becomes sequestered from interacting with apoB. This allows microsomal transport protein to incorporate lipids onto nascent apoB, leading to increased VLDL assembly and larger particle size [44]. This study revealed a novel relationship between lipoprotein and fibrinolysis by tPA-reducing VLDL assembly and secretion that eventually leads to lower atherogenic apoB-lipoprotein cholesterol in circulation.

LPL activity is inhibited by angiopoietin-like protein 4 (ANGPTL4) by preventing translocation to the luminal surface of adipose capillary endothelium [88]. This inhibition is interrupted when ANGPTL4 is bound with ANGPLT8. Although ANGPTL8 inhibits the inhibition of LPL activity by ANGPTL4, ANGPLT4/8 complex is still able to inhibit LPL activity [89]. ANGPTL4 has a fibrinogen-like domain. As such, a recent study showed that ANGPTL4/8 binds plasminogen and tPA, which promotes plasmin generation. Plasmin can then cleave the ANGPTL4/8 complex and promote LPL activity [90]. ANGPTL3, which inhibits LPL activity, also has a fibrinogen-like domain and can form a complex with ANGPTL8 [89]. In the presence of ANGPTL4/8, tPA, and plasminogen, ANGPTL3/8 inhibition of LPL is also reduced [91]. These findings suggest that the fibrinogen-like domains of ANGPTL 4 and 3 are cleaved by plasmin and support a mechanism of promoting postprandial LPL activity.

Reduced plasma PAI-1 activity is associated with decreased plasma PCSK9 levels in mice with lower total and LDL cholesterol levels [43]. In our study, we found that hepatocyte-specific PAI-1 knockout mouse plasma has lower apoB and lower cholesterol levels in VLDL and LDL compared with controls [44]. $\alpha M\beta_2$ is a leukocyte receptor that mediates inflammation during host defense from bacterial infections. Mice with a fibrinogen mutation in the binding motif for $\alpha M\beta_2$ were protected from high plasma total cholesterol and HDL cholesterol levels when given a high-fat diet [92]. Mice with plasminogen deficiency have higher LDL cholesterol concentrations but lower triglyceride concentrations compared with controls. Plasminogen-deficient mice also had decreased plaque formation compared with controls [93]. These findings suggest that tPA, PAI-1, and fibrinogen have causal roles in regulating lipoprotein metabolism.

6 | IMPAIRED FIBRINOLYSIS AND DYSLIPIDEMIA DURING INFECTION

The link between impaired fibrinolysis and dyslipidemia can also be seen in COVID-19, acquired immunodeficiency syndrome, and viral

TABLE 1 Clinical studies that describe relationships between dyslipidemia and fibrinolytic outcomes.

Study groups	Relationship between lipids and fibrinolytic proteins	Article
Patients with both hypertension and elevated serum cholesterol levels vs healthy controls	↑tPA activity is associated with ↓ triglyceride levels.	Jansson et al. (1991) [68]
Male patients with hyperlipidemia	↑tPA activity is associated with ↓ apoB-containing lipoprotein levels.	Glueck et al. (1993) [69]
Routine patients seeking regular health examinations	Patients with low tPA activity had the highest levels of serum cholesterol and triglyceride.	Yamada et al. (1990) [70]
Patients with type IV hyperlipoproteinemia before vs after TG-reducing treatment	↑Serum triglyceride levels are associated with ↑PAI-1 antigen levels.	Mussoni et al. (1992) [71]
Patients who survived myocardial infarction vs healthy controls	↑Serum triglyceride levels are associated with ↑PAI-1 antigen levels. ↑tPA activity is associated with ↓ triglyceride levels.	Hamsten et al. (1985) [72]
Patients who had an ischemic stroke vs healthy controls	↑Lp(a) levels are associated with ↑PAI-1 activity. Inhibition by Lp(a) is dependent on the interaction of apo(a) with fibrin.	Vuckovic et al. (2010) [73]
Patients with hypertriglyceridemia vs healthy controls	Patients with hypertriglyceridemia displayed prolonged dilute blood clot lysis time.	Cucuianu et al. (1991) [74]

apo(a), apolipoprotein (a); apoB, apolipoprotein B; Lp(a), lipoprotein (a); PAI-1, plasminogen activator inhibitor-1; TG, triglyceride; tPA, tissue-type plasminogen activator; ↑, increase; ↓, decrease.

hepatitis. Changes in fibrinolytic proteins and apoB-containing lipoprotein levels are observed in these infections, but the underlying mechanism requires detailed investigation in future studies.

In viral infections, viruses utilize the host's lipid metabolism to sustain an infection. At the same time, during an infection, cytokines and other inflammatory mediators are released, including interleukins and interferons. The release of cytokines, tumor necrosis factor, and prostaglandin causes a decrease in LPL levels and decreases lipolysis in adipocytes [94]. This result is paradoxical and requires further investigation, as a decrease in LPL levels should lower lipolysis activity. This response causes reductions in cholesterol levels [94–98]. In other words, during an acute viral infection, overall cellular and lipid metabolism is hijacked by viral infection, which may promote the progression of viral infections.

SARS-CoV-2 infection is an example of a viral infection causing disturbances in both lipid metabolism and impaired fibrinolysis. Sterol regulatory element–binding protein-2 (SREBP2) is a transcription factor responsible for regulating cholesterol synthesis using the MAPK activation pathway [99]. A study observed that SREBP2 was increased in the peripheral blood mononuclear cells of patients with pneumonia or septic shock during SARS-CoV2 infection [100]. In patients with COVID-19, SREBP2 is activated by the release of cytokines and disturbs the biosynthesis of cholesterol [100]. This study proposes a potential mechanism that links COVID-19 infection and lipid metabolism.

In our retrospective study, the link between hypertriglyceridemia and COVID-19 was investigated during the early wave of the pandemic between March 1, 2020, and December 21, 2020. In this study, triglyceride levels of 600 deidentified patients were investigated, along with other health parameters. We found that patients positive for COVID-19 who developed hypertriglyceridemia during a

hospital stay correlated with mortality [101]. In a separate study, we investigated tPA and Lp(a) in patients with COVID-19. Lp(a) binds to fibrin and competes with plasminogen activators, causing an overall decrease in fibrinolysis. We found that in patients with COVID-19, tPA activity decreased, and Lp(a) levels increased in plasma. Interestingly, Lp(a) levels and tPA activity were decreased and increased after recovery, respectively [102]. These findings are consistent with the previous studies discussed, where it is possible that a viral infection may leverage the host cell's metabolic mechanisms or apoB-containing lipoproteins, which could exacerbate triglyceride and cholesterol levels and impair fibrinolysis.

7 | IMPAIRED FIBRINOLYSIS AND DYSLIPIDEMIA IN DIVERSE POPULATIONS

Prospective studies with an ethnically and racially diverse study population are needed to investigate the link between impaired fibrinolysis and dyslipidemia. Studies of this nature may provide data that describe how this relationship may or may not impact different communities. For example, a study has shown that people from ethnic minority groups have a high association with dyslipidemia. In this study, 169,430 patients in primary care in Northern California were included. Compared with non-Hispanic White patients, ethnic minorities, not including African Americans, are associated with high triglyceride and LDL cholesterol and low HDL cholesterol concentrations [103].

In a separate study, we investigated the relationship between inpatient mortality and COVID-19 in 904 deidentified patients. We were also able to evaluate triglyceride levels and incidences of thrombosis in a racial and ethnically diverse population. Interestingly,

TABLE 2 Clinical studies that analyze infection, dyslipidemia, and thrombotic outcomes with diverse populations.

Impact on lipid metabolism	Impact on fibrinolysis	Race/ethnicity or country	Sex	Article
SREBP2 was increased in the peripheral blood mononuclear cells of patients with pneumonia or septic shock	N/A	South Korea	Male = 43 Female = 47	Lee et al. (2020) [100]
Patients positive for COVID-19 who developed hypertriglyceridemia during a hospital stay correlated with mortality	N/A	United States	Male = 307 Female = 293	Dai et al. (2021) [101]
Plasma Lp(a) levels increased	tPA activity decreased	United States	Male = 153 Female = 203	Zhang et al. (2023) [102]
Ethnic minorities, not including African Americans, are associated with high triglyceride and LDL cholesterol and low HDL cholesterol concentrations	N/A	United States Non-Hispanic White (n = 58,117) Asian Indian (n = 6808) Chinese (n = 12,895) Filipino (n = 3300) Japanese (n = 2284) Korean (n = 1114) Vietnamese (n = 1401) Mexican (n = 2795) African American (n = 1571)	Male = 79,145 Female = 90,285	Frank et al. (2014) [103]
Non-White Hispanics had the highest incidence of hypertriglyceridemia but the lowest incidence of thrombosis. Non-White Hispanics and Asians with hypertriglyceridemia during hospitalization were associated with mortality	N/A	United States Non-White Hispanic (n = 52) Asian (n = 27) Black (n = 301) White (n = 524)	Male = 456 Female = 448	Rodriguez et al. (2022) [104]
N/A	Racial and ethnic groups differ in average PAI-1 levels	United States Non-Hispanic White (n = N/A) Black (n = N/A) Hispanic (n = N/A)	Male = N/A Female = N/A	Festa et al. (2003) [105]

COVID-19, coronavirus disease-19; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); N/A, not available; PAI-1, plasminogen activator inhibitor-1; SREBP2, sterol regulatory element–binding protein 2; tPA, tissue-type plasminogen activator.

we found that in patients who were hospitalized with COVID-19, the non-White Hispanics had the highest incidence of hypertriglyceridemia but the lowest incidence of thrombosis [104]. This is contrary to the hypothesis that dyslipidemia and impaired fibrinolysis may occur because of one another. Future prospective studies may be able to address the different risk factors and potential different mechanisms among racial and ethnic groups.

Documentation of impaired fibrinolysis in different races and ethnicities is understudied. Insulin resistance has shown different effects on PAI-1 levels. As shown in Table 2, racial and ethnic groups differ in average PAI-1 levels, which is associated with changes in insulin resistance and diabetes [105]. This finding is important; however, these studies did not specify and compare the differences among racial and ethnic groups. Future studies are required to investigate whether impaired fibrinolysis and dyslipidemia are different in diverse patient populations.

8 | CONCLUSION AND FUTURE DIRECTIONS

This review outlines the connections between impaired fibrinolysis and dyslipidemia. Fibrinolysis is the mechanism that breaks down a blood clot and is essential for normal hemostasis. Dyslipidemia occurs when there is an abnormal level of blood lipids and lipoproteins. Data suggest that impaired fibrinolysis and dyslipidemia may occur together or because of one another. During infections, certain pathogenic agents may utilize lipids to sustain their infection, while thrombosis is a frequent severe outcome in infections. Thus, investigation of the mechanisms leading to impaired fibrinolysis and dyslipidemia is needed. Furthermore, studies that investigate this relationship in different ethnic and racial populations are needed.

AUTHOR CONTRIBUTIONS
M.R. and Z.Z. conceptualized the review and wrote and edited the manuscript. All authors read and approved the manuscript.

RELATIONSHIP DISCLOSURE
The authors declare no competing interests.

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