

Venous Thromboembolism in Kidney Diseases and Genetic Predisposition

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Keywords

Kidney diseases · Venous thrombosis · Risk factors · Hereditary influencing factors

Abstract

Background: Many renal diseases have been associated with profound clinical effects on thrombosis. To our knowledge, patients with nephrotic syndrome (NS) and chronic kidney disease (CKD) display an elevated risk of vein thrombosis, which is among the common causes of mortality in patients with renal diseases. In addition, venous thrombosis, as a complication, has also been reported in a variety of other renal diseases such as glomerulonephritis without the NS, hypertensive nephropathy, and polycystic kidney disease. With the increasing incidence of kidney diseases and the deeper understanding of the disease, clinicians are becoming more and more aware of the complications of thrombus formation in kidney disease. **Summary:** We reviewed recent publications of vein thrombosis in kidney diseases, including primary and secondary glomerular diseases, CKD, hereditary kidney disease, renal transplantation, and hemodialysis-induced, catheter-related thrombus, focusing mainly on the main clinical manifestations, possible mechanisms, related

risk factors as well as hereditary influencing factors. **Key Messages:** Vein thrombosis is a complicated complication of a wide spectrum of kidney diseases due to different possible underlying mechanisms.

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Introduction

The kidney plays an important physiological role in maintaining the homeostasis of the internal milieu via its sophisticated function, including excretion, metabolism, and endocrine. Kidney disease is a kind of broad-spectrum disease caused by diverse etiologies, which has been regarded as a major global health burden. From 1999 to 2016, the global toll of chronic kidney disease (CKD) has increased significantly and was not evenly distributed [1]. Cardiovascular complications in patients with kidney disease, for example, myocardial infarction, stroke, and atrial fibrillation, are associated with high mortality and poor outcomes [2]. Additionally, impaired renal function may

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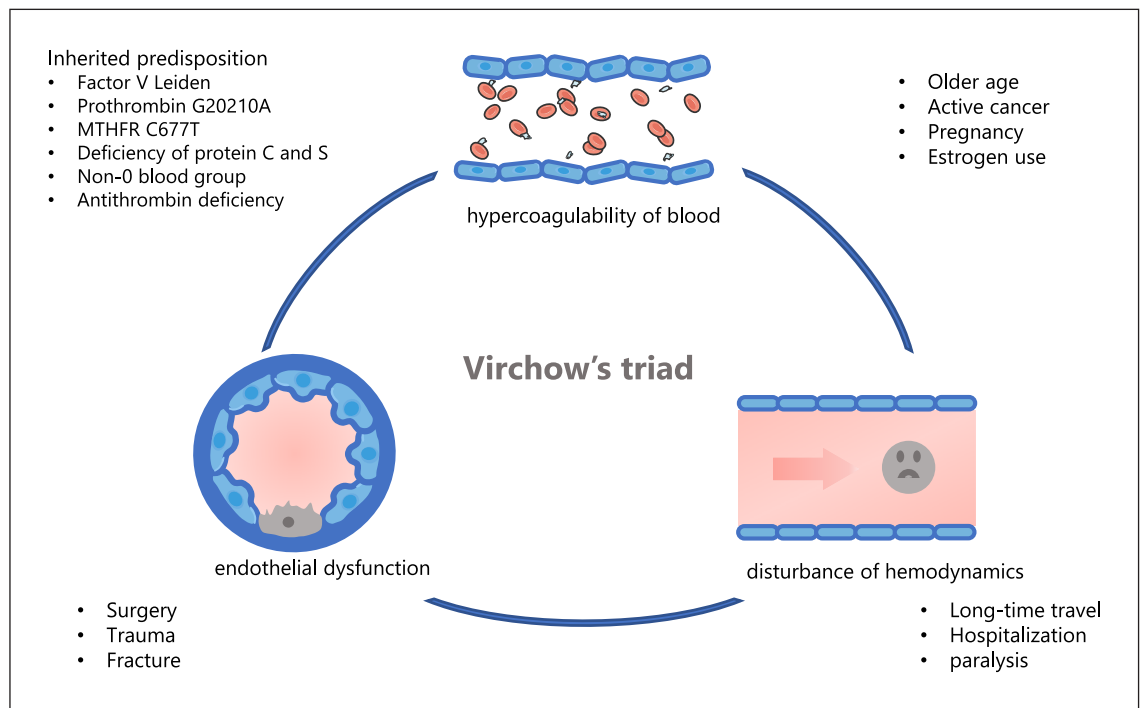


Fig. 1. Virchow's triad and risk factors for VTE. Virchow's triad contains three elements that contribute to venous thrombosis, including endothelial dysfunction, hypercoagulability of blood, and disturbance of hemodynamics. Risk factors for VTE are shown above, and inherited risk factors are mainly associated with hypercoagulability of blood.

cause abnormal thrombosis and hemostasis status, leading to the abnormal venous thrombus. In a pooled analysis using the data of five prospective general population cohorts, decreased estimated glomerular filtration rate (eGFR) is associated with venous thrombosis, and the risk increases as eGFR decreases [3]. Patients with CKD who suffered venous thromboembolism (VTE) had higher mortality, and the overall mean healthcare expenditures were 13-fold greater than the group without VTE in children [4].

VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE), represents one of the major global disease burdens, with annual incidences ranging from 0.75 to 2.69 per 1,000 individuals [5]. In Virchow's triad (shown in Fig. 1), endothelial dysfunction, hypercoagulability of blood, and disturbance of hemodynamics contribute to thrombosis in the veins. VTE is a disease affected by multiple risk factors, both acquired and inherited; acquired factors involve older age, active cancer, surgery, and others causing hypercoagulability, vascular damage, or venous blood stasis, and hereditary factors include factor V Leiden mutation, mutations in prothrombin gene, deficiency of protein C (PC) and protein S (PS), and antithrombin (AT) deficiency [6].

Here, we reviewed recent publications of vein thrombosis in kidney diseases, including nephrotic syndrome (NS), CKD, renal transplantation, hemodialysis-associated thrombosis, and other kidney diseases. We focus on possible mechanisms, related risk factors, and inherited thrombophilia factors.

Inherited Thrombophilia Factors

Normal blood coagulation relies on multiple mechanisms, and the balance of procoagulant and anticoagulant components, once compromised, may lead to thrombogenesis. Numerous genetic mutations affecting the process have been demonstrated. Factor V Leiden and prothrombin G20210A are predominantly prevalent in Caucasians, whereas the prevalence of inherited natural anticoagulant defects including PC, PS, and AT is higher in Asians [7].

Factor V Gene Mutation

Factor V gene mutation is a known predisposition for thrombosis. PC is a serine protease, and the activated PC

(APC) can inactivate factor Va and factor VIIIa, thus playing an anticoagulant role. The inhibition of FVa relies on three active PC cleavage sites, including Arg306, Arg506, and Arg679. The point mutation in the factor V gene, G1691A, which means the arginine is replaced by glutamine at the position of 506, leads to APC resistance resulting in an inherited thrombophilia state [6]. Patients with heterozygous factor V Leiden and homozygous FVL had 7-fold and 80-fold higher relative risk for developing venous thrombosis, respectively [8].

Prothrombin G20210A Mutation

Prothrombin is the inactive form of thrombin synthesized in the liver and then secreted into the blood circulation. Thrombin promotes hemostasis through the specific binding to substrates, mainly fibrinogen. Prothrombin G20210A mutation, a single-nucleotide substitution in the 3' untranslated region thus does not influence the protein-coding sequence, is responsible for increased plasma prothrombin levels without changes in the structure of the molecule, leading to thrombophilia [6]. Factor V Leiden and prothrombin G20210A have been regarded as predominant genetic risk factors for VTE in Caucasian populations, and the double heterozygosity had a 20-fold increased risk for VTE, while individuals with prothrombin G20210A allele had approximately 4-fold increased thrombosis risk [9].

AT Deficiency

AT deficiency is an inherited thrombophilia factor that can be attributed to mutations in the gene SERPINC1 which encodes AT. AT is an inhibitor for thrombin and also can inhibit all the proteolytic factors participating in the coagulation pathway, and its anticoagulant activity is enhanced when stimulated by heparan sulfate, especially heparin [10]. Hereditary AT deficiency includes two subtypes; type I deficiency is defined as parallelly decreased functional activity and levels of antigens, whereas type II deficiency involves only reduced functional activity.

PC Deficiency

A series of molecules composed of thrombomodulin (TM), endothelial PC receptor (EPCR), thrombin, PC, and PS drive the PC anticoagulant pathway. PC-TM/thrombin complex interplay mediates gain of function of PC, and APC inactivates FVa and FVIIIa, thus controlling the reactions of coagulation [10]. Variants in PROC gene encoding PC and THBD gene encoding TM may increase VTE risk. The p.Arg189Trp and p.Lys192del heterozygous mutations are predominant variants in

PROC, representing approximately 6.4- and 2.8-fold risk of VTE, respectively [7].

PS Deficiency

PS serves as a cofactor to APC and includes two forms; one is free, and the other is bound with the complement regulator C4b-binding protein to present as a complex [11]. Several mutations in PROS1 which encodes PS have been detected. Inherited PS deficiency is classified as types I, II, and III. Type I deficiency is characterized by reduced levels of both free and total PS, and type II involves only impaired PS function, while type III is characterized by normal total PS and decreased free forms.

MTHFR C677T Mutation

The methylenetetrahydrofolate reductase assists the conversion of 5, 10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate. In this procedure, a methyl donor is produced, which participates in the conversion of homocysteine to methionine. The C677T polymorphism of MTHFR contributes to the decreased activity of the enzyme, causing hyperhomocysteinemia. Mechanisms associated with MTHFR C677T mutation and venous thrombosis remain confusing. In a pooled analysis of 24 case-controlled studies in the Chinese population, Zhang et al. [12] demonstrated that the C677T mutation was associated with a significantly increased risk of VTE.

Hypercoagulability in Kidney Diseases: Aspects from Structure and Function of Kidney

The kidney is closely related to the maintaining of homeostasis of the internal milieu with the exquisite regulation system and complex renal function, including filtration, excretion, metabolism, and endocrine. The nephron is the basic unit of renal anatomy and function, and each kidney consists of approximately one million nephrons on average. The glomerular capillary wall (fenestrated and specialized), glomerular basement membrane, the foot processes of podocytes, and their slit diaphragms together constitute the glomerular filtration barrier. The glomerular filtration membrane performs the selectivity of glomerular filtration to limit the filtration of proteins, such as albumin [13]. The failure of selective filtration was caused by damage of the glomerular filtration barrier resulting in protein loss in urine called proteinuria, which is a manifestation of NS. Pathological filtration and excretion of proteins that inhibit thrombosis in the urine, such as AT III, which has the ability to inactivate several en-

zymes in the coagulation system, have been regarded as a possible mechanism of venous thrombosis in NS [14]. Furthermore, the leak of albumin in urine leads to disorders of proteins and subsequently abnormal hepatic synthesis of proteins, for example, the elevated level of fibrinogen, causing prothrombotic state [15]. The defects of the glomerular filtration barrier in kidney diseases resulting in the leak of proteins in urine and imbalance of anticoagulant and procoagulant proteins thus may be partly responsible for complications of thrombosis.

The kidney is a highly vascular organ. The homeostasis in the glomerular milieu involves multiple factors, glomerular capillary endothelial cells, mesangial cells, and podocytes, together contributing to the maintenance of glomerular homeostasis. Under the pathological condition, the glomerular endothelial cells abnormally express and secrete molecules such as platelet endothelial cell adhesion molecule and membrane microparticles which are prothrombotic factors, resulting in the hypercoagulability of blood [16]. Vascular endothelial growth factor produced by podocytes is essential for the function and survival of glomerular endothelial cells, and when compromised, the communication between endothelial cells and podocytes is disturbed thus, thrombosis can occur [16]. Deposition of fibrin in the glomerulus was observed in several kidney diseases, including IgA nephropathy, membranous nephropathy (MN), and lupus nephropathy, suggesting intraglomerular coagulation activation may play a role in venous thrombosis [17]. Furthermore, nephrotic patients presented with higher expression of plasminogen activator inhibitor-1 (PAI-1) [18]. Hence, changes in the hemostasis of the glomerular milieu possibly account for the prothrombotic state in kidney diseases.

Immune-mediated inflammation response and immune complex, both circulating and in situ, potentially play a part in primary glomerular diseases. Circulating immune complexes may be a contributor to the coagulation process in MN, as evidence indicated that the complexes were detected only in patients having MN and renal vein thrombosis comorbidity [19].

One of the unique functions of the kidney is filtration and excretion, which can be measured by the glomerular filtration rate (GFR). The decreased GFR is a major characteristic of CKD, resulting in a series of clinical problems. Accumulation of metabolites, termed uremic toxins, for example, indoxyl sulfate and indoxyl acetate, is considered possible prethrombotic risk factors. Additionally, the abnormal patterns of hemodynamics, including hydrostatic pressure and fluid shear stress due to

disarranged water-electrolyte metabolism, may promote hypercoagulability in patients with CKD [20]. Due to the indispensable role of the kidney in homeostasis maintenance of the internal milieu, damage of the renal structure and insufficiency of renal function may be associated with a hypercoagulable state, thus contributing to venous thrombosis.

Hypercoagulability in Kidney Diseases: Aspects from Components Participating in Coagulation and Anticoagulation

Platelet Abnormalities

Platelets contribute to thrombus formation following vascular injury via a series of processes, including activation, adhesion, and aggregation. The disarrangement of platelets might be associated with hypercoagulability in patients with NS. Platelet hyperaggregability was observed in NS patients when stimulated by collagen, epinephrine, and arachidonic acid, whereas the results remain inconsistent. Surface markers of platelet, CD63, and P-selectin, which represent the functional activity of platelet, were elevated in patients with NS, and the active substances released by platelets such as β -thromboglobulin and platelet-derived growth factor increased, indicating higher activation of platelet in those patients [21]. Furthermore, hypoalbuminemia and subsequently decreased binding of arachidonic acid along with the increased synthesis of thromboxane A₂ and may contribute to hyperaggregability of platelets in NS since thromboxane A₂ is a potent factor for aggregating of platelets [22]. Von Willebrand factor (vWF) mediates platelet-vascular wall adhesion, and the increased level of vWF may contribute to the hypercoagulable state [23].

Coagulation System Abnormalities

Normal blood coagulation consists of a series of cascade reactions and is precisely regulated. The disturbance of anticoagulant and procoagulant substances could result in venous thrombosis. The higher levels of factor V, factor VIII, and vWF have been observed in patients with NS [24]; in addition, individuals with reduced kidney function had significantly increased factor V and vWF levels compared with people whose eGFR was within the normal range [25]. Increased levels of inflammatory biomarkers, including D-dimer and C-reactive protein, are associated with decreased eGFR [26]. The above results indicate that an elevated level of procoagulant factors may be a possible contributor to VTE. Furthermore, the leak

of proteins in the urine capable of preventing thrombosis, such as AT III, is possibly responsible for venous thrombosis in NS [24]. It is hypothesized that the urine loss of proteins triggers abnormal hepatic synthesis, leading to raised procoagulant factors.

Fibrinolytic System Abnormalities

The balance of the fibrinolytic system is maintained by the coordination of various factors, including tissue plasminogen activator, urinary plasminogen activator, plasminogen, fibrinogen, and fibrinolytic inhibitors. PAI-1 inhibits tissue plasminogen activator through specific binding with it. A higher level of PAI-1mRNA was detected in patients with focal segmental glomerulosclerosis and MN [27]. Compared with normal individuals, plasma fibrin in patients with NS was more tight and rigid, thus resulting in hypofibrinolysis status, which was a possible mechanism for thrombogenesis in NS [28].

NS and VTE

The NS, a type of renal disease characterized by hypertension, large amounts of proteinuria, hypoproteinemia, hyperlipidemia, and edema, can be caused by a wide spectrum of primary glomerular diseases and secondary diseases, for instance, diabetes mellitus, systemic lupus erythematosus, drugs, infections, and cancer [29]. VTE is a well-known life-threatening complication of NS, including DVT, PE, and renal vein thrombosis. Rarely, NS-associated cerebral thrombosis, superior mesenteric vein, splenic, and portal vein thrombosis have also been reported. The association between NS and VTE has been established in several studies. The relative risks for the development of deep venous thrombosis and PE were 1.72 and 1.39 in a large study including 925,000 patients with NS, respectively, and the risk for developing deep venous thrombus was higher among young adults aged from 18 to 39 years [30]. It seems that the risk of vein thrombosis, including renal vein thrombosis, is different according to pathological types of NS. The incidence of VTE is the highest in patients with MN and membranoproliferative glomerulonephritis, and the IgA nephropathy group and minimal change disease group had the lowest risk compared to other histological groups; in addition, venous thromboembolic events occurred mainly in the first 6 months during follow-up [31].

The potential mechanisms of thrombogenesis in NS have not been clearly revealed, whereas abnormal activation and accumulation of platelets, activation of the co-

Table 1. Risk factors for the development of VTE in kidney diseases

Risk factors	References
NS and VTE	[33–36]
MN	
FSGS	
Lupus nephritis	
Low albumin levels	
Sepsis	
Intravenous corticosteroid use	
BMI ≥ 30 kg/m ²	
AKI	
Female sex	
CKD and VTE	[43]
Immobilization	
Surgery	
Prothrombin G20210A	
Malignancy	
Factor V Leiden	
Low eGFR	
ESRD and VTE	[46, 47]
Receiving hemodialysis than patients with peritoneal dialysis	
Toxic nephropathy as the cause of ESRD	
Atrial fibrillation	
Female sex	
Kidney transplantation and VTE	[51, 53–54]
Recipient female gender	
eGFR less than 30 mL/min/1.73 m ²	
Right kidneys	
The ADPKD group	

VTE, venous thromboembolism; MN, membranous nephropathy; FSGS, focal segmental glomerular sclerosis; BMI, body mass index; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ADPKD, autosomal dominant polycystic kidney disease.

agulation system, decreased endogenous anticoagulants, and activity of the fibrinolytic system, as well as changes in the glomerular hemostatic system, may play a role in thrombosis as mentioned above. However, the mechanisms associated with NS and VTE in different histological types have not been demonstrated clearly. Huang et al. [32] used thromboelastography to analyze the causes of hypercoagulability in patients with MN and demonstrated that abnormalities in the entire thrombosis process contributed to the hypercoagulable state.

While most studies indicated that the higher proteinuria and lower serum albumin could predict VTE [33, 34], female gender, body mass index over 30, acute kidney injury, nephritis associated with lupus, sepsis, and the use of intravenous corticosteroid may contribute to the risk of

developing VTE according to a recent study [35]. In addition, histopathological subtype was an independent risk factor for occurring VTE, even adjusted for other factors (history of cancers, proteinuria, patient's gender, and serum albumin), with the highest risk in MN groups [36]. The risk factors related to thrombosis in patients with renal diseases are summarized and shown in Table 1. PE is a fatal complication of NS, and a higher level of plasma D-dimer, even within the normal range, may predict PE [37].

Since VTE is a complex disease with multiple factors acting together, genetic susceptibility factors play an important role in the process. Some cases reported genetic abnormalities in NS patients with thrombotic events. Given the correlation between NS and venous thrombosis, there are also several studies on whether genes play a role. Ismail et al. [38] evaluated the gene polymorphisms of factor V, MTHFR, prothrombin, and PAI among patients with primary NS and demonstrated that the association of two mutations was an independent predictor for the development of VTE with the hazard ratio at 8.92. Underlying hereditary thrombophilia may result in thrombotic events in idiopathic NS patients, especially in those the occurrence of venous thrombosis cannot be attributed to other causes [39]. Fabri et al. [40] assessed genes associated with thrombotic disease, including factor V mutation, the prothrombin variant, and MTHFR focusing on pediatric NS patients, but found no significant influence for the risk of nonrecurrent thrombosis. In this case series of NS in children, the compound heterozygous mutations of MTHFR 677 and 1,298, the homozygous mutation in MTHFR 677, and homozygous mutation in MTHFR 1298 were recognized as thrombosis risk factors [41].

CKD and VTE

The diagnosis criteria of CKD include a) $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ and b) markers of kidney damage, if patients fulfill both or one of the two criteria and last for at least 3 months, the diagnosis can be confirmed, and CKD is mainly caused by diabetes, hypertension, or glomerulonephritis [42]. According to international guidelines, CKD can be divided into six stages. The classification is based on GFR, and when the GFR is below $15 \text{ mL/min/1.73 m}^2$, the patient is in the stage termed end-stage renal disease (ESRD) meaning that his residual renal function cannot satisfy his long-term survival [42].

As the GFR decreases, the risk of thrombosis increases in patients with CKD, patients with moderately (eGFR

$30\text{--}60 \text{ mL/min}$) and severely ($\text{eGFR} < 30 \text{ mL/min}$) decreased GFRs were 2.5 times and 5.5 times more likely to develop venous thrombosis than those with normal GFRs, respectively [43]. The risk of developing DVT was significantly higher in patients with ESRD compared with those without and in patients with ESRD; people older than 50 years of age and with abnormal blood lipids are at increased risk of DVT [44]. Rattazzi et al. [45] conducted an ambispective observational investigation on 409 patients and found that patients with a history of recurrent venous thrombosis had higher CKD prevalence. Additionally, compared to individuals whose renal function was within the normal range, the risk of VTE recurrence was higher in CKD patients with an adjusted HR of 5.32 [45].

ESRD-Associated Dialysis and VTE

When the patient is in the CKD stage 5 ($\text{GFR} < 15 \text{ mL/min/1.73 m}^2$) meaning that the residual kidney function cannot meet the patient's physiological needs, thus renal replacement therapy, kidney transplantation, or dialysis is needed. Wang et al. [46] evaluated the risk of VTE focusing on PE in patients with ESRD who received dialysis using the claims data of the National Health Insurance (NHI) Research Database of Taiwan and revealed that when compared with those without kidney disease, patients receiving dialysis were at an approximately 2-fold increased hazard of suffering PE; furthermore, they also showed a greater risk of PE in patients receiving hemodialysis than patients with peritoneal dialysis. According to a large population-based cohort [47], the IR of vascular access thrombosis and VTE were 111.6 events per 1,000 patient-years and 10.9 per 1,000 patient-years on hemodialysis, respectively. Meanwhile, they pointed out that ESRD caused by toxic nephropathy may be an independent risk factor for the development of vascular access thrombosis.

Several studies have investigated the role of genes associated with thromboembolism in dialysis. Grupp et al. [48] assessed some thrombophilic risk factors, including mutations in factor V, MTHFR, and prothrombin in hemodialysis patients, and the results indicated that thrombophilic risk factors were significantly associated with increased shunt thrombosis risk [48]. In 395 patients with stage 5 CKD receiving hemodialysis, there was no significance in the expression of Leiden (FVG1691A Leiden), prothrombin gene mutation, and MTHFR C677T between patients and controls; however, a significant difference was observed in the prevalence of Leiden mutation between patients with CKD caused by unknown etiology and patients with CKD due to other etiologies [49].

Kidney Transplantation and VTE

Venous thrombosis is a well-known complication after kidney transplantation which could result in graft losses, and approximately 34% of failure of kidney transplants can be attributed to venous thrombosis [50]. The incidence of venous thrombosis was 2.9 episodes/1,000 person-years after 1.5–3 years of transplantation in the study using the US Renal Data System database [51]. In another study involving 4,343 transplant recipients, renal transplant recipients had a 7-fold increased risk of VTE compared with the general population [52].

Recipients, female gender, right kidneys, and patients with autosomal dominant polycystic kidney disease (ADPKD) had more thrombotic events after transplantation [53, 54]. Patients with GFR less than 30 mL/min/1.73 m² 1 year after transplantation had an increased risk of subsequent VTE with an adjusted hazard ratio of 2.05 [51].

The study by Wüthrich et al. [55] demonstrated that heterozygosity for the FVL mutation was a possible predisposition for developing VTE in patients who received renal transplantation; furthermore, the mutation also contributed to early transplant loss. Several inherited prothrombotic risk factors, including factor V G1691A, prothrombin G20210A mutations, and MTHFR C677T polymorphisms, were associated with acute rejections, and many of the acute rejections were acute vascular rejections, which may lead to the poor outcome of kidney transplantation [56].

Other Renal Diseases and VTE

Compared with those without kidney diseases, individuals with kidney diseases presented an increased risk of VTE, and the association was established well in NS and CKDs. Furthermore, glomerulonephritis without the NS, polycystic kidney disease, hypertensive nephropathy, and diabetic nephropathy was associated with VTE with the odds ratios ranging from 1.83 (95% CI: 1.52–2.20) to 2.57 (95% CI: 2.26–2.93); additionally, even adjusted for other factors (such as surgery, cancer history, pregnancy, and congestive heart failure) the ORs were still statistically significant [57]. ADPKD is the most common polycystic kidney disease characterized by cysts in the kidney, liver, or pancreas. The kidney transplantation recipients with ADPKD appeared to suffer more thromboembolic complications than those who had no ADPKD [53]. In a nationwide longitudinal cohort study in Taiwan, Kuo et al. [58] demonstrated that when compared to the non-AKI population, patients with acute kidney injury had a

1.44-fold and 1.49-fold higher risk of DVT within 3 and 5 years, respectively. The pandemic caused by SARS-CoV-2 is ongoing, and the infection may affect a wide range of organs, including the kidney. Microthrombi were observed in the kidney of the patients. The analysis of multi-organ proteomic landscape using autopsy samples indicated increased F13A1 (the activation of F13A1 contributes to the stabilization of fibrin clots thus plays an antifibrinolytic role) and vWF in the renal cortex, which might be responsible for the observed thrombosis. In addition, the downregulation of SERPIND1 (heparin cofactor 2, a cofactor for heparin) and the upregulation of SERPINE1 (PAI-1, an inhibitor for plasmin) were also detected [59].

Conclusion

The association between VTE and kidney diseases has been established in a series of studies. A wide spectrum of kidney diseases, including NS, CKD, ESRD-associated dialysis, and kidney transplantation, increase the risk of developing venous thrombosis. In addition, there is also evidence that acute kidney injury is associated with increased VTE risk. Kidney transplantation and dialysis are important replacement therapy for patients with ESRD, and venous thrombosis may increase mortality. VTE is a multifactorial disease with acquired and inherited thrombophilia factors; genetic susceptibility factors include FV G1691A Leiden, prothrombin G20210A, MTHFR C677T, and deficiencies of PC and PS. Whether it is recommended to screen for thrombophilia in children and adults remains with confusion; Bock et al. [60] evaluated the utility of thrombophilia screening in 100 pediatric patients who undergone renal transplantation and demonstrated that preoperative screening is not beneficial for all patients; thus, the strategy may be considered in patients who had a history of VTE. Given the high prevalence of venous thrombosis in NS, prophylactic anticoagulation therapy is not a routine treatment but may be considered in the selected population [61]. The management of VTE in those individuals needs to take multiple factors into consideration, for instance, the underlying etiologies and thrombophilic states. To better identify this selected population, the role of risk factors, including genetic predispositions for venous thrombosis in kidney diseases, needs further investigation.

Patients with kidney diseases represent a high risk to suffer venous thrombosis, and the underlying mechanisms remain unclear and may be different due to vari-

ous etiologies that trigger kidney injury. Abnormal activation and accumulation of platelets, activation of the coagulation system, decreased endogenous anticoagulants, and activity of the fibrinolytic system are possible contributors. In NS, the damage of the glomerular filtration barrier leads to disturbance of proteins, including anticoagulant and procoagulant factors, and the loss of proteins may be associated with the disproportionate hepatic synthesis of proteins, causing hypercoagulability. In addition, abnormal hemodynamics and endothelial dysfunction may play a role. In conclusion, the mechanisms for VTE in kidney diseases require further investigation.

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