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Chronic kidney disease and venous thromboembolism: epidemiology and mechanisms

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Abstract

Purpose of review—An estimated 13% of Americans have kidney disease. We sought to describe the association of kidney disease with risk of venous thromboembolism and discuss possible mechanisms explaining this association.

Recent findings—All severities of kidney disease appear to increase the risk of venous thromboembolism. In the general population the risk associated with mild to moderate kidney disease is 1.3–2-fold increased, and present even for microalbuminuria, although stage 1 chronic kidney disease itself has not been studied. End-stage renal disease is also associated with a 2.3-fold increased risk, compared to the general population. Although data are limited, risk increases after kidney transplant and with nephrotic syndrome as well.

Summary—Rates of kidney disease are increasing rapidly in the population and kidney disease is a risk factor for venous thromboembolism. An improved understanding of mechanisms linking kidney disease with venous thromboembolism will allow further study of best prevention efforts.

Keywords

blood coagulation; kidney disease; risk factor; venous thromboembolism

Introduction

The epidemiology of deep venous thrombosis (DVT) and pulmonary embolism, collectively referred as venous thromboembolism (VTE), has been studied in the general population, although there are many areas needing further work. The annual incidence of VTE is approximately 1 in 1000 adults, with a sharply higher risk in the elderly [1,2]. Proposed nearly 150 years ago, Virchow was the first to suggest that VTE occurs as a result of vascular endothelial injury, alteration in blood flow, and a hyper-coagulable state [3]. When these abnormalities co-occur, the combination of endogenous and acquired risk factors leads to a VTE episode. For example, when reduced blood flow occurs as in the case of immobility, pooling of blood leads to activation of coagulation locally and simultaneous consumption of blood coagulation inhibitors. In other words, the pathogenesis of VTE is multifactorial, often requiring the presence of multiple risk factors to cause a clinical event.

Established VTE risk factors include surgery, cancer, hospitalization, immobilization, obesity, exogenous hormones, pregnancy and the puerperium and inherited thrombophilia. The well known inherited thrombophilias include factor V Leiden, prothrombin 20210A, elevated factor

VIII/von Willebrand factor, and deficiencies of antithrombin, protein C and protein S. Given the high prevalence of chronic kidney disease (CKD), especially with aging, there is recent interest in evaluating the role of CKD as a risk factor for VTE. This is not a surprise given that CKD patients have underlying hemostatic derangements predisposing to a hypercoagulable state. This review summarizes the epidemiology of VTE in the CKD population and focuses on potential mechanisms leading to its development.

Overview of chronic kidney disease

In order to understand the association of CKD with VTE risk it is first important to understand the epidemiology of CKD and trends over time in its prevalence.

Chronic kidney disease is common in the general US population, affecting 13% of adults 20 years and older studied between 1999 and 2004 [4]. The rate of kidney failure requiring dialysis, or end-stage renal disease (ESRD), increased 43% over the 1990s [5], and is felt largely due to increases in diabetes, hypertension and obesity. Determination of CKD status is typically done using creatinine measurement, along with age, sex and race, to calculate estimated glomerular filtration rate (eGFR). A commonly used equation for this is the four-variable modification of diet in renal disease equation:

$$\text{eGFR} = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 1.212(\text{if black}) \times 0.742(\text{if female}).$$

Table 1 shows the classification of the stages of increasing severity of CKD. The eGFR can also be determined in research settings using equations based on cystatin C measurement [6], and by newer creatinine-based equations [7].

Associations of stages of chronic kidney disease with risk of venous thromboembolism

We review here the evidence for associations of CKD with risk of VTE.

End-stage renal disease and venous thromboembolism

Epidemiologic evidence on the VTE risk in the ESRD population is very limited. Initial postmortem examinations suggested that VTE is a rare event in ESRD [8–11]. However, the series by Wiesholzer *et al.* [11] in 1999 was the first to suggest that VTE in dialysis patients was relatively common. In that study, pulmonary embolism was observed in 1753 of 8051 (21.8%) postmortem examinations in nondialysis patients who were hospitalized. This compared to a prevalence of pulmonary embolism of 23 of 185 (12.5%) postmortem examinations in chronic dialysis patients who were hospitalized. Although significantly less than the nondialysis group, the frequency among dialysis patients was higher than anticipated, suggesting that the occurrence of VTE in dialysis patients was more common than previously believed.

Other investigators have used larger databases to further investigate the risk of VTE in patients with ESRD. Tveit *et al.* [12] combined the US Renal Data System records from 1996 and data from the National Center for Health Statistics to compare the incidence of pulmonary embolism occurring within 1 year after initiating dialysis treatment with the expected rate in the US population. The incidence was 149.9 events per 100 000 dialysis patients compared with an expected rate of 24.6 per 100 000 people in the US population. This led to an age-adjusted incidence rate ratio of 2.34. Because this utilized administrative data, errors in coding and sampling are possible.

Chronic kidney disease and venous thromboembolism

To date, the Longitudinal Investigation of Thromboembolism Etiology (LITE) study is the only population-based study we are aware of that evaluated VTE risk in the nondialysis, nontransplant CKD population [13•]. In that study, 19 073 middle-aged and elderly adults were followed for an average of 12 years. Kidney disease was associated with increased risk of future VTE, with incidence rates per 1000 person-years of 1.5, 1.9, and 4.5 for normal kidney function, mildly decreased renal function, and stage 3 or 4 CKD. The age, sex and race-adjusted relative risk of VTE with stage 3 or 4 kidney disease was 2.1 [95% confidence interval (CI) 1.5-3.0]. In fact, the risk began to rise when the eGFR was less than 75 ml/min/1.73 m², which is above the threshold defining stage 3 or 4 CKD. The investigators also evaluated the association of cystatin C, a novel marker of renal function, with risk of VTE. An independent association was not observed. This may have been due to insufficient statistical power, as cystatin C was measured in a smaller number of participants. The main limitation of this study is that estimation of renal function was measured on average 12 years before the index event. Thus, change in renal function during the follow-up time would have resulted in misclassification of the exposure status, and underestimation of the true risk of VTE in people with CKD. Thus, it is likely that the true risk associated with stage 3 or 4 kidney disease is likely greater than two-fold increased.

In the LITE study mildly decreased kidney function was associated with a 1.3-fold increased risk of VTE, but this was not independent of cardiovascular risk factor levels. In contrast, Mahmoodi and colleagues [14•] recently reported that microalbuminuria was independently associated with increased VTE risk in a community cohort of 8574 men and women, associated with a two-fold increased risk (95% CI 1.3–3.0). However, the investigators did not exclude participants with abnormal eGFR from the analysis so the impact of stage 1 kidney disease itself was not addressed. Since microalbuminuria in the absence of kidney damage (stage 1 CKD) is very common in the general population, if this finding can be confirmed by others, the proportion of VTE attributed to kidney disease in general would be high.

Nephrotic syndrome and venous thromboembolism

Multiple small studies consistently suggested that nephrotic syndrome is a risk factor for VTE [15,16,17•,18,19•]. Of these, the largest study was conducted using data from the US National Hospital Discharge Survey [19•]. Of 925 000 patients discharged from hospitals between 1979 and 2005 with nephrotic syndrome, 19 000 (2%) had VTE events (0.5% with pulmonary embolism or renal vein thrombosis and 1.5% with DVT). Among 898 253 000 patients discharged without a diagnosis of nephrotic syndrome, approximately 11 500 (1.3%) had VTE events. Compared to patients without nephrotic syndrome, those with nephrotic syndrome had a 39% increased risk of DVT and a 72% increased risk of pulmonary embolism. On the contrary, renal vein thrombosis in the same study was rare and not significantly different between nephrotic and nonnephrotic patients.

Renal transplantation and venous thromboembolism

To date, few studies have evaluated the risk of VTE in patients with renal transplant. Using the US Renal Data System database, consisting of 28 924 renal transplant patients between 1996 and 2000, Abbott and colleagues [20] reported that VTE was common in this population, with an incidence per 1000 persons of 2.9 episodes at 1 year and 4.3 episodes at 2 years. In a multivariable adjusted model, those with eGFR less than 30 ml/min/1.37 m² after transplant had a two-fold higher risk of VTE than those whose eGFR was higher [20]. In another study of 484 renal transplant patients 9% developed a VTE at a median follow-up of 17 months [21]. Patients were screened for VTE and 40% of cases were asymptomatic. This study also noted a high incidence of recurrent VTE after anti-coagulation was discontinued. Compared to age and sex-matched controls with normal renal function who had a first VTE, renal

transplant patients who discontinued anti-coagulation therapy had a 10-fold higher risk of recurrent VTE, highlighting the importance of careful consideration of treatment strategies in this population, and the need for further study.

Mechanisms linking chronic kidney disease and venous thromboembolism

Although exact mechanisms are unclear, it is believed that CKD patients have underlying hemostatic derangements predisposing to VTE. Much of the work has focused on activation of procoagulant markers, decreased endogenous anticoagulants, enhanced platelet activation and aggregation, and decreased activity of the fibrinolytic system.

Overview of hemostasis

A review of normal hemostasis is essential in order to understand the hemostatic derangement in the CKD population. Following vascular injury, a series of dynamic and interwoven steps occurs leading to hemostasis. Central to hemostasis is the generation of thrombin, which is critical in converting fibrinogen to insoluble fibrin. At the site of vascular injury, tissue factor is exposed, which then binds and activates factor VII. This results in activation of factor X and factor IX and conversion of prothrombin to thrombin. This cascade is known as the extrinsic pathway.

Through the extrinsic pathway, a limited amount of thrombin is generated. At this initial stage, a fibrin clot that is formed is susceptible to fibrinolysis. To maintain coagulation, more thrombin is generated through a positive feedback loop. That is a small amount of thrombin generated initially activates platelets, factor V, factor VIII, and factor XI, leading to amplification of thrombin.

Whereas procoagulant reactions are ongoing, termination of the clotting cascade occurs simultaneously by activation of endogenous anticoagulants, including antithrombin, the protein C and S pathway, and tissue factor pathway inhibitor. This phase is critical in modulating the extent of clot formation. If left unchecked, hemostatic response could lead to thrombosis and vascular damage.

Following hemostasis, the organized clot must be removed. This is accomplished by conversion of plasminogen to plasmin. Plasmin can cleave polymerized fibrin, fibrinogen, and a variety of plasma proteins and clotting factors, thereby removing organized clots.

Activation of procoagulation

To understand mechanisms that might explain an increased risk of VTE in CKD, several epidemiologic studies have compared the levels of procoagulant markers in patients with and without kidney disease. In general, patients with ESRD and predialysis renal failure, nephrotic syndrome, and even mild CKD have elevated levels of D-dimer, C-reactive protein (CRP), fibrinogen, factor VII, and factor VIII and von Willebrand factor [22,23,24]. It is presumed that the elevated levels are due to increased synthesis out of proportion to urinary losses. Lower levels of factors IX, XI, and XII demonstrated in ESRD and nephrotic syndrome were believed to be due to increased urinary loss. The exact mechanisms on how these changes in proteins mediate a VTE risk are unclear. To date, factors VII, VIII [25,26], IX [27], and XI [28], fibrinogen [29], and D-dimer [30] have been correlated with VTE risk in the general population. Studies of procoagulant factors and VTE risk specific to the type of renal disease are not available.

Decreased endogenous anticoagulants

Antithrombin, protein C, and protein S are anticoagulant proteins and inherited deficiency states increase VTE risk. The evidence that these endogenous anticoagulants play a role in increasing VTE risk in the CKD population is inconclusive. Studies have consistently reported lower levels of antithrombin in patients with nephrotic syndrome [31]. This is presumably due to increased urinary loss of antithrombin out of proportion to synthesis. Clinical correlation of antithrombin deficiency and VTE risk in nephrotic syndrome was demonstrated in some studies [17,32], but not others [33]. On the contrary, a few small studies showed that levels of protein C and protein S were increased in patients with nephrotic syndrome compared to healthy adults, suggesting protection against VTE [34,35]. We are not aware of studies relating levels of protein C or protein S to VTE risk in CKD patients.

Enhanced platelet activation and aggregation

Markers of platelet activation, such as circulating P-selectin concentration, are increased in nephrotic syndrome patients [36,37]. With vascular injury, nearby intact endothelial cells secrete arachidonic acid. Arachidonic acid, normally bound to albumin, is converted to thromboxane A2 by the enzyme cyclooxygenase-1 in platelets. Patients with nephrotic syndrome usually have hypoalbuminemia, resulting in increased availability of thromboxane A2 [38,39]. Platelet aggregation then ensues because thromboxane A2 is a potent platelet agonist and vasoconstrictor. It is hypothesized that patients with nephrotic syndrome could have increased VTE risk mediated by this mechanism. Although high plasma P-selectin levels are predictive of VTE in patients with cancer [40], and recurrent VTE in patients with prior VTE events [41], there are no population-based studies addressing relations of P-selectin and VTE risk in healthy patients or those with CKD or nephrotic syndrome.

Decreased activity of fibrinolytic system

Data on a role of hypofibrinolysis in mediating VTE risk are conflicting [42,43]. Prior studies have focused on the role of plasminogen and plasmin-antiplasmin complex. In nephrotic patients, albumin and plasminogen levels are inversely correlated [44], and this might lead to decreased fibrinolytic activity. Alpha-2 antiplasmin is released into the circulation and rapidly inactivates plasmin by forming plasmin-antiplasmin complex. This complex helps making clot resistant to lysis. One study noted higher plasmin-antiplasmin complex with declining creatinine clearance, suggesting a state of reactive fibrinolysis [24]. This finding may be one of the mechanisms explaining an increased VTE risk in CKD patients, but specific studies addressing this question are not available.

Conclusion

The risk of VTE is increased across the spectrum of CKD, including mild and more advanced CKD, nephrotic syndrome, ESRD and after kidney transplant. This increased risk may be due to underlying hemostatic derangements, including activation of procoagulants, decreased endogenous anticoagulants, enhanced platelet activation and aggregation, and decreased fibrinolytic activity. The pathogenesis likely differs depending on the cause of the kidney disease (nephrotic syndrome, nonnephrotic and ESRD). Environmental factors and comorbid condition are certain to play a modulating role, although few specific data are available. Future prospective studies should evaluate specific hemostatic abnormalities and environmental risk factors across the spectrum of CKD in relation to risk of VTE, and confirm an association of stage 1 CKD with risk of VTE. This would allow study of application of risk stratification tools that might be further studied in trials of preventive treatments in this special population.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 521).

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Table 1
Definition and prevalence of chronic kidney disease

Stage	Description	GFR (ml/min/1.72 m ²)	Prevalence in US ^a
0	Normal GFR, no kidney damage		87%
1	Kidney damage with normal GFR	≥90 ^b	1.8%
2	Kidney damage with mildly decreased GFR	60–89	3.2%
3	Moderately decreased GFR	30–59	7.7%
4	Severely decreased GFR	15–29	0.3%
5	Kidney failure	<15 (or dialysis)	–

^aData from NHANES 1999–2004 survey of adults aged 20 years and older. Stage 5 not studied [3].

^bPersistent microalbuminuria.