End-stage renal disease and thrombophilia

Alexander Bauer; Verena Limperger; Ulrike Nowak-Göttl
Institute of Clinical Chemistry, Thrombosis & Hemostasis Treatment Center, University Hospital Schleswig-Holstein, Campus Kiel & Lubbock, Germany

Keywords
Chronic kidney disease, thrombosis, organ failure, thrombophilia

Summary
Chronic kidney disease is an established risk factor for arterial and venous thromboembolism (TE). Whereas the overall risk of TE in moderately decreased kidney function is approximately 2.5-fold higher compared to patients with normal renal function, the risk increase is 5.5-fold in patients with severe renal dysfunction. In patients with renal dysfunction and arterial thrombosis (OR: 4.9), malignancy (OR: 5.8) surgery (OR: 14.0) or thrombophilia (OR: 4.3) the risk to suffer from venous TE is higher compared to the risk associated to the baseline renal dysfunction alone. The treatment options for end-stage renal diseases include hemodialysis, peritoneal dialysis and kidney transplantation. During all treatment modalities thrombotic complications have been described, namely catheter malfunction and shunt thrombosis in patients undergoing hemodialysis in up to 25% of patients, and TE, pulmonary embolism or graft vessel thrombosis in approximately 8% of patients. The reported incidence of reno-vascular thrombosis following renal transplantation leading to hemorrhagic infarction with organ rejection or organ loss varied between 2–12%. Keeping in mind the multifactorial etiology of TE in patients with kidney dysfunction a general screening for thrombophilia in this patient group is not indicated. Selected screening on an individual patient basis should be discussed if the family history for TE is positive or the patient itself had suffered one thrombosis before the onset of the renal disease or multiple TEs during hemodialysis or post kidney transplantation in patients waiting for living donor kidney transplantation.

Schlüsselwörter
Chronisches Nierenversagen, Thrombose, Organversagen, Thrombophilie

Zusammenfassung
Die chronische Niereninsuffizienz (chronic kidney disease; CKD) stellt einen bekannten Risikofaktor für die Entwicklung einer arteriellen und venösen Thromboembolie (TE) dar. Das Risiko für eine TE ist bei moderat eingeschränkter Nierenfunktion ca. 2,5-fach erhöht und steigt mit zunehmender Insuffizienz auf etwa das 5,5-Fache. Vergleicht man Patienten mit einer chronischen Niereninsuffizienz mit Patienten, die zusätzlich folgende Risikofaktoren aufweisen, erhöht sich das TE-Risiko erheblich: CKD und arterielle Thrombose: OR 4.9, CKD und maligne Grunderkrankung: OR 5.8, CKD und chirurgischer Eingriff: OR14.0; CKD und angeborene Thrombophilie (OR 4.3).


Da TE häufig multifaktoriell bedingt sind, erscheint ein generelles Screening auf Thrombophilie in diesem Patientenkollektiv nicht indiziert. Ein Screening sollte diskutiert werden bei Patienten, die entweder TEs vor Auftreten ihrer Nierenkrankheit entwickelt haben oder die eine positive Familienanamnese hinsichtlich VTE aufweisen. Auch Patienten, die unter Dialyse oder nach Transplantation multiple TEs erleiden und solche, die auf der Warte liste für eine Nierentransplantation (insbesondere Lebendspende) stehen, sollten hinsichtlich Thrombophilie untersucht werden.

Chronic kidney disease (CKD) is defined as a wide range of renal disturbances, including gradual to permanent loss of kidney function over a period of time. End-stage renal kidney disease (ESRD) is known as a total or near-total loss of kidney function. CKD and ESRD are both established risk factors for arterial and venous thromboembolism (TE) (1). Common causes of CKD are interstitial nephritis, glomerulonephritis, diabetes mellitus and nephrosclerosis, whereas polycystic kidney disease and further inherited diseases are rare (2–4). The treatment options for ESRD include hemodialysis (HD), peritoneal dialysis and kidney transplantation (KT). During all treatment modalities thrombotic complications have been described,
namely catheter malfunction and arteriovenous fistula/shunt thrombosis in up to 25% patients undergoing HD (5, 6), TE, pulmonary embolism or graft vessel thrombosis occurred in approximately 8% of patients with CKD or ESRD (7, 8). The reported incidence of reno-vascular thrombosis following renal transplantation leading to organ loss varied between 2–12% (9–11). The pathophysiology of early arteriovenous fistula dysfunction is generally attributed to low-flow states, hypotension and occurrence of hematomas, whereas late fistula failure is discussed in association with de novo TE, secondary to neointimal hyperplasia or stenosis of the graft vein anastomosis (12). Vascular occlusion following kidney transplantation generally occurs within 48 hours after KT but may also be diagnosed up to 14 days later with an increased risk during the first 5 months (10). Apart from numerous risk factors for TE, such as malignancy, surgery, obesity, immobilization, diabetes, chronic nicotine abuse, higher age (> 45 years) and estrogen administration in women, in patients undergoing KT immunosuppressive medications, donor type, dialysis modalities prior to KT as well as surgical techniques have been reported to increase the likelihood of thrombosis-associated graft loss (13). In addition, abnormal anatomical conditions, namely differences in vessel diameter between donor and recipient, presence of multiple renal arteries, donor renal artery stenosis or atherosclerosis, surgical trauma, prolonged cold ischemia, reperfusion trauma, hypotonia or acute organ rejection prone patients to TE following kidney transplantation (14). The risk for TE following KT is also discussed in association with platelet dysfunction and acquired or genetic hypercoagulable states (15). Acquired thrombophilia included antithrombin-, protein C- and protein S-deficiency states, elevated levels of fibrinogen, factor VIII, homocysteine and lipoprotein (a), impaired fibrinolysis, as well as the presence of lupus anticoagulants and or anti-ß2 glycoprotein I or anticardiolipin antibodies (►Tab. 1) (15, 16).

Based on literature data reported between 1993 and 2014 also the presence of inherited prothrombotic risk factors showed an increased odds ratio to contribute to the thrombotic events documented in patients with ESKD (►Tab. 1). This issue will be discussed in this manuscript.

### Inherited thrombophilia

**Associated with catheter malfunction and arteriovenous fistula/shunt thrombosis**

Vascular access represents a lifeline for patients undergoing hemodialysis. A failure or malfunction of vascular complications among patients receiving regular HD is associated with increased morbidity, mortality and costs. Whereas the main causes of shunt thrombosis or stenosis are associated with high-shear-stress-rate-induced vascular injury or intimal hyperplasia studies on the prevalence of acquired/inherited thrombophilia directly associated with these complications are contradictory. Reported studies are conflicting with some suggesting a significant association (17–27), whereas others having not (6, 28–32). This discrepancies are mainly due to different studies types (retrospective versus prospective), limited by small sample size, absence of control groups, investigation of different thrombophilic risk factors and non-adjustment for known anatomical and/or clinical risk factors described. In 2005 Knoll and coworkers could demonstrate in a prospective Canadian cohort that 107 of 419 consecutively enrolled patients developed access TE during the follow-up (25). After controlling for known clinical risk factors and the drug treatment modalities applied (gender, diabetes, access type, angiotensin-converting enzyme inhibitor use, warfarin use, any B-vitamin or folic acid use, location of access, time with dialysis access, previous history of shunt TE, hemoglobin, albumin and urea reduction ratio) the adjusted odds ratio of shunt TE remained significantly enhanced for patients with any thrombophilia compared to those without (odds ratio [OR/95% CI]: 2.42 /1.47–3.99). Furthermore, the authors could demonstrate that the odds ratio of shunt TE increased significantly with each additional thrombophilia. For the individual thrombophilic risk factors the adjusted odds ratios were as follows:

- Factor V G1691A mutation (3.94),
- elevated factor VIII (2.4),
- elevated lipoprotein (a) (1.97) and
- elevated total homocysteine (2.43).

Data of this prospective study are in line with previously published retrospective studies by Klamroth and colleagues in a German cohort and results obtained from Swedish patients (26, 27). Both studies confirmed in 2013 the prospectively obtained findings by Knoll et al. (25) that the presence of any thrombophilia versus no thrombophilia was associated with an increased odds ratio to develop access TE. The odds for severe TE were approximately 2 in both studies.

### Associated with vascular complications after kidney transplantation

Whereas the overall risk of TE in moderately decreased kidney function is approxi-
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mately 2.5-fold higher compared to patients with normal renal function, the risk increase is 5.5-fold in patients with severe renal dysfunction (33). In addition, it has been recently shown in a case control study from the Netherlands (2013) that in patients with renal dysfunction combined with arterial thrombosis (OR: 4.9), malignancy (OR: 5.8) surgery (OR: 14.0) or thrombophilia (FVG1691A or Prothrombin G20210A; OR: 4.3) the risk to suffer from venous TE is higher compared to the risk associated to the baseline renal dysfunction alone (33).

Whereas the latter study has focused on CKD-related TE in general, renovascular or renal allograft thrombosis is a rare complication that often resulted in kidney or graft loss. Although the rate of renal allograft survival has improved over the last decades, 3 to 11% of transplants are still lost within 12 months following KT, mainly due to acute rejections including vascular damage (34–37). In addition, arterial or venous TEs of the allograft are frequently associated with rapid organ loss (39). In children following KT the frequency of venous VT is approximately 15% with a high rate of graft failure (16). Apart from micro- or macrovascular thrombosis fibrin formation or occlusive glomerulonephritis represent hypercoagulable states, which are discussed as possible link towards acquired or inherited thrombophilia, possibly leading to acute or chronic organ rejection of vascular organ loss (13, 14, 34–37, 39–42).

Of note, patients with autosomal dominant polycystic kidney disease in general have a better graft survival but suffer from a higher thrombotic complication rate (43). As underlying mechanism for the higher TE rate the excessive activation of the alternative complement pathway with enhanced epithelial cell proliferation, tubulo-interstitial inflammatory cell infiltration and fibrosis may be discussed (44).

Chronologically, a case of allograft TEs associated with thrombophilia was first described in 1993 by Koester and coworkers focusing on protein S-deficiency (45). Next, the role of the factor V G1691A mutation with an increased risk of graft thrombosis was elucidated between 1998 and 2001 (13, 40–42), followed in 1999 by association studies investigating the role of the prothrombin G20210A mutation (42, 46, 47). During that study period overall the risk of micro- and or macrovascular graft TE was higher when inherited thrombophilic risk factors were present compared to patients with no thrombophilia. Dependent on the study design, i.e. on univariate or multivariate analysis the odds ratio to suffer from clinical significant graft TE varied between 2 to 10 (42). Although hyperhomocysteinemia > 30 mmol/l mainly due to total homocysteine accumulation is often diagnosed in patients with CKD and ESRD the common MTHFR
C677T variant plays a minor role in reno-vascular TE (14, 42). However, in individuals homozygous for the MTHFR T677T genotype the risk of vascular rejection was increased (42). Retrospective cohort studies reporting vascular graft thrombosis between 2007 and 2011 showed a lower incidence of vascular complications following KT (32, 38, 48) and a lower rate of inherited thrombophilic gene mutations associated with graft thrombosis, dismissing that change of treatment modalities may have influenced this shift (32, 48, 49).

Conclusion

Prothrombotic genes alone have an estimated 2-fold increased risk to contribute to the thrombotic events occurring in patients with end-stage renal diseases. However, keeping in mind the multifactorial etiology of TE in patients with kidney dysfunction a general screening for thrombophilia in this patient group is not indicated or recommended. Selected screening only on an individual patient basis should be discussed if the family history for TE is positive or if the patient itself had suffered one thrombosis before the onset of the renal disease or from multiple TEs during hemodialysis or post kidney transplantation (50, 51). Screening for inherited or acquired thrombophilia is should be performed in selected patients waiting for deceased or living donor kidney transplantation.

Conflict of interest

The authors declare no conflict of interest.

References


