Thrombophilia and Arteriovenous Fistula Survival in ESRD

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Summary

Background and objectives The role of thrombophilia in failing arteriovenous fistula (AVF) among patients with ESRD undergoing hemodialysis is not established. This study aimed to assess whether AVF primary patency is associated with thrombophilia and coagulation abnormalities.

Design, setting, participants, & measurements This observational study screened 219 patients between 2002 and 2004 for thrombophilia before AVF surgery. Thrombophilia included factor V Leiden and prothrombin G20210A mutations, protein C and antithrombin activities, and protein S. Coagulation abnormalities included high factor VIII:C, homocysteine, fibrinogen, and d-dimer levels; presence of antiphospholipid antibodies; and short thrombin time. We reviewed patient charts for comorbid conditions, AVF maturation and interventions, kidney transplantation, and patient survival (mean follow-up duration, 3.6 [range, 2.3–5.8] years). Primary patency from the AVF placement and functional primary patency from the first AVF cannulation were analyzed with Kaplan-Meier and Cox proportional hazards models.

Results Thrombophilia was present in 9% of the patients, and coagulation abnormalities occurred in 77%. One-year primary patency was 68%; 46% of the AVF failures occurred before the initiation of hemodialysis. Female sex (hazard ratio [HR], 2.6; 95% confidence interval [CI], 1.7–4.1) and thrombophilia (HR, 2.2; 95% CI, 1.2–4.2) were independent risk factors for loss of primary patency. Thrombophilia mutations or low antithrombin level (HR, 3.8), female sex (HR, 2.5), and diabetes (HR, 1.9) were associated with shortened functional primary patency of AVF.

Conclusions Against the background of frequent coagulation abnormalities, thrombophilia and female sex predispose patients with ESRD to access failure, mostly due to thrombosis or stenosis.

Introduction

Vascular access represents a lifeline for patients undergoing hemodialysis (HD). A failure of vascular access among patients receiving regular HD is associated with increased morbidity, mortality, and costs. In fact, in the United States the annual costs of access failure are approximately $1 billion (1). The main causes of access dysfunction—thrombosis and stenosis—are associated with vascular injury and intimal hyperplasia caused by high-shear-rate conditions in the access (2,3).

The overall prevalence and effect of thrombophilia in patients with ESRD are as yet unclear. Studies on inherited or acquired thrombophilia in access thrombosis are scarce among patients with ESRD, and the results are contradictory. This is due to limited patient numbers, retrospective thrombophilia screening, and differences in definition and inclusion of individual types of thrombophilia (4–11). One large retrospective study of 419 patients undergoing HD found at least one thrombophilic disorder in 43% of patients with ESRD, and any thrombophilic disorder increased the risk for access thrombosis (2).

Our aim was to analyze the prevalence and effect of thrombophilia and coagulation abnormalities in patients with ESRD undergoing native arteriovenous fistula (AVF) surgery. We evaluated the effect of thrombophilia and coagulation abnormalities upon AVF survival (i.e., primary patency and functional primary patency).

Materials and Methods

Study Design

This observational study was carried out at Helsinki University Central Hospital, Finland, which provides vascular surgery for a population of 1.2 million. Between 2002 and 2004, 280 patients with ESRD underwent routine prospective screening for thrombophilia and coagulation abnormalities 1 month before their vascular access surgery. Of those 280 patients, we included 219 consecutive patients who underwent creation of an AVF, without exclusion criteria. Exclusion criteria were lack of preoperative thrombophilia screening, arteriovenous graft surgery, reconstruction of preexisting vascular access, surgical
revision of the AV anastomosis, and cases in which the access was not needed for HD during follow-up. Clinical demographic characteristics, cause of kidney disease, comorbid conditions, and medications were retrieved from the patient records. Patients were followed until the end of 2007, and the mean follow-up time was 3.6 (range, 2.3–5.8) years. The study was approved by the institutional review board and ethics committee.

**AVF Surveillance**

The main objective of the study was to assess primary patency of AVF from the placement of fistula until the need for intervention to maintain patency, fistula thrombosis, or abandonment of the access. Functional primary patency of AVF was recorded from the initial fistula cannulation for HD until the need for the first vascular intervention or abandonment of the AVF.

Preoperative duplex scanning facilitated the choice of vascular access and helped rule out the presence of preexisting postphlebitic venous disease. During the access surveillance, primary patency, presence of thrombosis, or critical stenosis was established by duplex scanning and, subsequently, with angiography when needed. During HD, the AVF function was regularly assessed every week and when any difficulty occurred. The AVF assessment included recording of success of puncture, recirculation, blood flow, online measurements of arterial and venous pressure, and puncture site bleeding. Duplex scanning or angiography or both were performed upon any suspicion of malfunction or insufficient flow volume, even in the absence of clinical signs of insufficient dialysis. Only vascular lesions that required interventions and access abandonment were registered as adverse outcome of primary patency.

**Screening and Definitions for Thrombophilia and Coagulation Abnormalities**

**Thrombophilia Screening.** Thrombophilia screening included laboratory assessment of congenital and acquired coagulation abnormalities: factor V Leiden (R506Q) and prothrombin G20210A mutations (cyclic mini-sequencing), activated protein C resistance (Coatest APC Resistance V; Chromogenix, Milan, Italy), protein C and antithrombin activity (Berichrom Protein C, normal range, 74%–141%; Berichrom Antithrombin III A, normal range, 84%–108%; Siemens, Healthcare Diagnostics, Marburg, Germany), and free protein S antigen (Instrumentation Laboratory, Milan, Italy; normal ranges: men, 66%–150%; women, 50%–137%).

**Definition of Thrombophilia.** Thrombophilia was defined as one of the following: the presence of homozygous or heterozygous factor V Leiden or prothrombin mutation, low antithrombin activity (≤60%), and decreased activities of protein C and protein S. Decreased activities were defined at their lowest fifth percentile (protein C <74% and protein S <58% in men) and only in patients without vitamin K antagonists (these agents impair synthesis of protein C and protein S).

**Acquired Coagulation Abnormalities.** Acquired coagulation abnormalities included high levels of factor VIII:C, fibrinogen, d-dimer, and homocysteine; shortened thrombin time; and presence of antiphospholipid antibodies. The latter were analyzed separately from thrombophilia because they may not be permanent and may be modified by dialysis. Cutoff values for these were set within the 75th quartiles (i.e., clearly above the references for factor VIII:C [>206%], fibrinogen [>5.9 g/L], d-dimer [>2.0 mg/L]), and homocysteine [≥35 μmol/L], and the lowest quartile of thrombin time (<17 seconds). The tests for antiphospholipid antibodies (lupus anticoagulant, cardiolipin, or β2-glycoprotein I antibodies) included lupus anticoagulant (DVVtest 10 test kit, American Diagnostica, Pfungstadt, Germany; Platelin, HemosIL APTT-SP, Instrumentation Laboratory, Milan, Italy) with plasma cardiolipin and β2-glycoprotein I antibodies (Varelisa, cardiolipin IgG antibodies and β2-glycoprotein I IgG antibodies, Phadia GmbH, Freiburg, Germany; normal range for both <15 U/ml). The latter was available for 88 patients from 2004 in our institution.

We measured prothrombin time and international normalized ratio (Nycostest prothrombin time reagent, Axis-Shield PoC AS, Oslo, Norway; normal ranges, 70%–130% and 0.9–1.1, respectively), thrombin time (BC-Thrombin reagent, Siemens; normal range, 17–25 seconds), factor VIII coagulant activity, factor II:C (Pathrombin SL and Coagulation factor VIII-deficient plasma, Siemens; normal range, 52%–148%), fibrinogen (modified Clauss method, Multifibrin U, Siemens; normal range, 1.7–4 g/L), d-dimer (immunoturbidimetric assay, Tina-quant, d-dimer, Roche Diagnostics, Mannheim, Germany; normal, <0.5 mg/L), and homocysteine (Homocysteine Liquid Stable reagent, Axis-Shield, Dundee, United Kingdom; normal range, 4–15 μmol/L). Behring Coagulation System-XP (Siemens) was used in automated analyses, and the Evolis analyzer (ELISA microplate system, Bio-Rad, Hemel Hempstead, United Kingdom) for measuring cardiolipin and β2-glycoprotein I antibodies. D-Dimer and homocysteine were analyzed with the Modular analyzer (Roche Diagnostics).

**Statistical Analyses**

The main endpoints were primary patency (from the fistula placement) and functional primary patency (from the initial cannulation) of AVF until the need of first vascular intervention or abandonment of the access or end of follow-up.

The distribution of age, sex, body mass index, smoking, cause of ESRD, transplantation history, access type and flow after surgery, comorbid conditions, use of antithrombotics, statins, antihypertensive medication, preoperative dialysis, and laboratory variables across categories were analyzed by chi-squared tests (Fisher exact test when necessary) or Mann-Whitney U test for continuous variables. Only factors with \( P \) values ≤0.2 in correlation analysis by chi-squared tests were subjected to Kaplan-Meier and Cox regression analyses as independent risk factors for access failure.

In the regression analyses, patients without AVF failure or loss of functional primary patency were censored at 2 months after fistula placement in case of maturation failure without manageable specific lesions, at the time of death, at renal transplantation, or at the end of follow-up. Risk factor differences between the groups in the survival analysis were tested with the Breslow method. All significant factors in AVF survival analyses were further examined by
distribution analysis to exclude bias due to censoring times between the groups. Statistical analysis was based on PASW Statistics 18 software (SPSS Inc., Chicago, IL). Significance was set at \( P<0.05 \).

**Results**

**Patient Characteristics, Thrombophilia, and Coagulation Abnormalities**

Clinical demographic characteristics, cause of kidney disease, medications, and AVF data for the 219 patients with ESRD are presented in Tables 1 and 2. Half of the patients had a history of coronary heart disease, peripheral arterial disease, or stroke. A high proportion (88%) of the patients (Table 2) used an antithrombotic medication, and 19% of the patients were receiving a combination of two antiplatelet agents or an antiplatelet agent and low-molecular-weight heparin at the time of surgery. In all, 9% of the patients presented with thrombophilia (Table 3). Factor V Leiden was encountered in seven (3%) patients and prothrombin mutation in one patient. Low protein C or protein S activity was found in 5% of the patients, but only male patients had low protein S activity. Antithrombin activity was low (≤60%) in four patients.

In addition, 11% of patients were positive for antiphospholipid antibodies (lupus anticoagulant, cardiolipin, or β2-glycoprotein I antibodies), and positivity occurred in more men than women (14% versus 3%; \( P=0.008 \)). Other coagulation abnormalities were present in most (77%) patients (Table 3). Coagulation factor VIII:C (median, 171%; interquartile range [IQR], 59%), fibrinogen (median, 5.2 g/L; IQR, 1.6 g/L), D-dimer (median, 0.9 mg/L; IQR 1.5 mg/L), and homocysteine (median, 27 μmol/L; IQR, 15 μmol/L) levels were all markedly above the normal reference ranges. Moreover, thrombin time was short (<17 seconds) in 25% of patients.

**AVF Outcome and Primary Patency**

Overall, 46% of AVF failures (i.e., insufficient maturation, thrombosis, or stenosis) had already occurred before HD was initiated. Eleven patients had maturation failure without specific manageable vascular lesions. Most of these were women (73%) and had both diabetes and lower-extremity atherosclerosis (73%); 36% had an upper-arm fistula. Three patients died before the initiation of HD. The 1-year primary patency rate was 68%, and thrombosis or stenosis led to AVF failure in 82 patients (37%) during the follow-up period (mean, 3.6 years; range, 2.3–5.8 years) (Figure 1).

According to transient-time ultrasonography, the immediate postoperative blood flow through the fistula was not associated with AVF patency (data not shown). Patient groups with and without AVF failure were similar with regard to clinical characteristics, comorbid conditions, mortality, and access details (Tables 1 and 2). The only exception was the overrepresentation of women among patients with AVF failure (51% versus 23%; \( P<0.001 \)). Kidney transplantation was performed equally in patients with or without AVF failure during the follow-up. Mortality was 11% at 1 year.

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**Table 1. Clinical characteristics and comorbid conditions of 219 patients with ESRD**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) (yr)</td>
<td>57 (16–83)</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>146 (67)</td>
</tr>
<tr>
<td>Median body mass index (range) (kg/m²)</td>
<td>25 (15–42)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>60 (27)</td>
</tr>
<tr>
<td>Cause of kidney disease, n (%)</td>
<td>60 (27)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>73 (33)</td>
</tr>
<tr>
<td>Inflammatory disease*</td>
<td>74 (34)</td>
</tr>
<tr>
<td>Polycystic kidney disease, obstructive nephropathy</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Renovascular disease, nephro sclerosis, or other</td>
<td>39 (18)</td>
</tr>
<tr>
<td>Comorbid conditions, n (%)</td>
<td>80 (38)</td>
</tr>
<tr>
<td>Hypertension on medication</td>
<td>84 (38)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>80 (38)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>71 (32)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>62 (28)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>28 (13)</td>
</tr>
<tr>
<td>History of venous or arterial thrombosis, n (%)</td>
<td>13 (6)</td>
</tr>
<tr>
<td>Deep vein thrombosis/pulmonary embolism</td>
<td>31 (14)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>33 (15)</td>
</tr>
<tr>
<td>Any lower extremity amputation</td>
<td>11 (5)</td>
</tr>
<tr>
<td>Previous transplantation, n (%)</td>
<td>12 (6)</td>
</tr>
</tbody>
</table>

*CGN (46%), IgA nephropathy (18%), amyloidosis (15%), tubulointerstitial nephritis (14%), or chronic pyelonephritis (8%).

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**Table 2. Medication, vascular access, and preoperative dialysis in 219 patients with ESRD**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td>164 (75)</td>
</tr>
<tr>
<td>Aspirina</td>
<td>27 (12)</td>
</tr>
<tr>
<td>LMWH</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>14 (6)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>5 (2)</td>
</tr>
<tr>
<td>No antithrombotic medication</td>
<td>27 (12)</td>
</tr>
<tr>
<td>Statin</td>
<td>121 (55)</td>
</tr>
<tr>
<td>HD [duration &gt;3 mo]</td>
<td>93 (43) [30, 32%]</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td>5 (2) [5, 100%]</td>
</tr>
<tr>
<td>First access operation</td>
<td>198 (90)</td>
</tr>
<tr>
<td>Ongoing preoperative dialysis</td>
<td>98 (45)</td>
</tr>
<tr>
<td>Anatomic location</td>
<td>91 (91)</td>
</tr>
<tr>
<td>Radiocephalic (wrist)</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Median access flow (range) (ml/min)b (n=209)</td>
<td>180 (10–855)</td>
</tr>
</tbody>
</table>

LMWH, low molecular-weight heparin; HD, hemodialysis.

*a* For 30 patients, aspirin was initiated in association with the access surgery.

*b* According to transient-time ultrasonography immediately after surgery.
According to Kaplan-Meier analysis, AVF patency was significantly lower in association with three clinical factors. First, in women compared with men, the AVF survival was shortened to 25 months (95% confidence interval [CI], 18–32 months) versus 45 months (95% CI, 41–49 months). Second, patients with thrombophilia had shorter AVF survival than patients without thrombophilia: 19 months (95% CI, 10–27 months) versus 40 months (95% CI, 36–44 months), respectively. Finally, AVF survival was 25 months in patients with a history of vascular access (95% CI, 14–35 months) versus 40 months (95% CI, 36–44 months) in patients having their first vascular access. Positivity for antiphospholipid antibodies was not associated with primary patency of AVF. In the multivariate Cox analysis, female sex (hazard ratio [HR], 2.6; 95% CI, 1.7–4.1) and the presence of thrombophilia (HR, 2.2; 95% CI, 1.2–4.2) were independent risk factors for shortened primary patency of AVF (Figure 2).

### Functional Primary Patency of Arteriovenous Fistula

In 180 patients (82%), AVF could be used for HD. Among these patients, the 1-year rate of primary functional patency for AVF was 80% (66% of all created AVFs) (Figure 1). Percutaneous transluminal angioplasty was performed in eight patients to enhance patency before initiation of dialysis. Median duration of functional primary patency for radial and brachial AVFs were similar: 18 (IQR, 26) months versus 11 (IQR, 31) months, respectively. One third of the patients with thrombophilia developed AVF failure before HD. Yet the presence of thrombophilic gene mutations or low antithrombin levels (60%) (n=9) was associated with a shortened functional primary patency: 19 months (95% CI, 7–31 months) versus 47 months (95% CI, 43–51 months) (P=0.01). In women, the functional patency was shortened: 34 months (95% CI, 25–42 months) versus 50 months (95% CI, 45–54 months) in men (P=0.003). In the multivariate analysis, thrombophilic gene mutations or low antithrombin levels (HR, 3.8; 95% CI, 1.5–9.9), female sex (HR, 2.5; 95% CI, 1.4–4.5), and diabetes (HR, 1.9; 95% CI, 1.1–3.5) independently shortened the functional primary patency.

### Discussion

AVF failure, mainly due to thrombosis or stenosis, occurred in 37% of the 219 patients in this study within the mean follow-up of 3.6 years. Almost half of the events had already occurred before the initiation of dialysis, and up to 84% occurred during the first year. After successful
initiation of HD, only a few AVFs were abandoned, as previously reported (12). The most significant risk factors for primary patency failure of AVF were female sex, history of previous vascular access, and thrombophilia. Similarly, female sex, the presence of thrombophilic gene mutation, and low antithrombin and diabetes were associated with the loss of functional primary patency.

In this study, thrombophilia prevalence (9%) was equal to that in general population (13) and was similarly distributed between men and women. We followed a conservative strategy and analyzed acquired coagulation abnormalities separately because they may be transient and influenced by dialysis. Acquired coagulation abnormalities were highly prevalent, occurring in 77% of the patients. Antiphospholipid antibodies were more common in men but did not seem to affect the AVF outcome. High incidence of thrombophilia is reportedly associated with risk of thrombosis after access surgery or revascularization among patients with ESRD and those with other vascular conditions (2,11,14). The difference in thrombophilia prevalence among the studies reflects various definitions of thrombophilia.

Thrombosis and stenosis of AVF both compromise the primary patency and coincide, but they cannot always be distinguished. The clinical consequences are also rather similar: insufficient maturation or a need for intervention or access abandonment. In fact, thrombosis, atherosclerosis, and inflammation form a pathogenic continuum in cardiovascular disease (15,16). Inflammatory mechanisms upregulate procoagulants, downregulate anticoagulants, and inhibit fibrinolysis, resulting in prothrombotic states (15–17). Furthermore, acquired coagulation abnormalities (i.e., elevated factor VIII:C level, short thrombin time, and high fibrinogen and D-dimer levels) were frequent in our patients with ESRD (Table 3) and failed to differentiate problems in access thrombosis or stenosis. Remarkably, these acquired abnormalities have been reported to correlate with cardiovascular mortality and other thrombotic events in ESRD (18–20). In this study, in addition to high prevalence of cardiovascular disease (49%), a history of venous thromboembolism (6%) was relatively frequent (Table 1). Further studies are needed to assess the effect and management of the coagulation abnormalities on high cardiovascular mortality and morbidity in ESRD.

The 1-year rate of primary patency of AVF was 68%, and the rate of initial functional primary patency for HD was 86%. Our relatively high success rate may reflect careful patient selection for HD, large patient volume, duplex mapping of suitable veins for vascular access, scrutinized vascular technique, and frequent use of antithrombotics (88%). Additionally, 90% of the patients were having their first access operation. In fact, AVF is the most common access type in Finland (79%) compared with grafts (3%) and a permanent (tunneled) catheter (16%) (Finnish Registry for Kidney Diseases. Report 2008. Helsinki, Finland, 2009; http://www.musili.fi/smri/eng). General risk factors for access failure include female sex, diabetes, and history of access dysfunction (21–26). In this study, diabetes was associated only with the impaired functional primary patency of AVF. Among women, the underlying reasons for access failure are unclear. One hypothesis is the subcutaneous adipose tissue and small vessel size; in fact, in women, upper-arm fistulas seem to succeed better than forearm fistulas (21,22). Women are also subjected to increased risk for arterial thrombosis, such as myocardial infarction, despite taking aspirin (27).

Some patients with ESRD carry a particularly high risk for recurring access thrombosis or stenosis (5,28,29). These patients with hypercoagulable states or combined thrombophilia should be preoperatively identified to tailor antithrombotic therapy and intensify surveillance, especially during the first, most vulnerable months after surgery. However, the optimal prophylaxis for access thrombosis and stenosis is not settled despite extensive efforts (29–35).

Limitations of this study include moderate sample size and descriptive data on medications that could not be compared. Furthermore, the results represent a single center experience of a racially homogeneous cohort and
may not be generalizable to other populations. The magnitude of risk of undiagnosed thrombophilia is difficult to interpret because of the frequent use of antithrombotic treatment in this study.

Routine thrombophilia screening is not recommended before access surgery. However, certain risk factors, such as prior access failure, history of thrombosis at a young age, or unprovoked venous and arterial thrombosis, should raise the suspicion of thrombophilia and necessitate laboratory testing. Thrombophilia appears as an additional risk indicator for AVF failures. Known thrombophilia should alert clinician to enhance and target antithrombotic therapy and surveillance of the access. However, the optimal clinical management requires further studies. We suggest that the surrogate markers of coagulation (e.g., fibrinogen, factor VIII, and D-dimer may be valuable in designing antithrombotic medication, as reported in cardiovascular disease and venous thromboembolism (36,37). Against the background of common acquired coagulation abnormalities, thrombophilia and female sex predispose patients with ESRT to problems with patency of the vascular access. Optimization of the antithrombotic therapy, particularly in association with the initial access surgery and vascular interventions, may improve the outcome. Overall, antithrombotic treatment among HD patients demands more attention. Multicenter randomized trials should assess whether access survival can be improved with tailored antithrombotic therapies while maintaining the balance with bleeding risks.

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Disclosures
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