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DIALYSIS – TRANSPLANTATION

Hyperhomocysteinemia, anticardiolipin antibody status, and risk for vascular access thrombosis in hemodialysis patients

BRADEN J. MANNS, ELLEN D. BURGESS, HOWARD G. PARSONS, JEFFREY P. SCHAEFER, M.E. HYNDMAN, and NAIRNE W. SCOTT-DOUGLAS

Department of Medicine, and Department of Pediatrics and Medical Genetics, University of Calgary, Calgary, Alberta, Canada

Hyperhomocysteinemia, anticardiolipin antibody status, and risk for vascular access thrombosis in hemodialysis patients.

Background. Vascular access failure is an important cause of morbidity in end-stage renal failure patients on hemodialysis. Currently, little is known about risk factors that predispose certain hemodialysis patients to recurrent access thrombosis. Hyperhomocysteinemia (common in patients with renal failure) predisposes people with normal renal function to recurrent and early-onset venous thrombosis, although the effect on vascular access thrombosis is currently unknown. Previous studies have suggested that high titers of IgG anticardiolipin antibody (IgG-ACA) predispose hemodialysis patients to access thrombosis. This cross sectional study was designed to assess for an association between two predictive variables, hyperhomocysteinemia and elevated titers of IgG-ACA, and vascular access thrombosis in patients undergoing chronic hemodialysis.

Methods. Risk factors for vascular access thrombosis were documented, and the number of episodes of access thrombosis was recorded for the previous three years in patients undergoing hemodialysis. Midweek predialysis total homocysteine and IgG-ACA levels were measured in all subjects.

Results. Of the 118 patients who were enrolled, 75.4% had a native arteriovenous fistula. Episodes of vascular access thrombosis were recorded for the previous three years; 34 (28.8%, 95% CI 20.9 to 37.9%) patients had 72 episodes of access thrombosis over the period of risk. Mean homocysteine levels were not significantly different between these 34 patients (28.6 μmol/liter, 95% CI 24.5 to 32.7) and the patients who had no episodes of graft thrombosis (29.8 μmol/liter, 95% CI 26.7 to 32.9). Sixty-seven unselected patients had IgG-ACA levels drawn for analysis, and all assays were negative. The only variable that was associated with a higher risk for graft thrombosis was the type of vascular access placed (odds ratio 4.0, 95% CI 1.6 to 9.6 for patients with a synthetic graft compared with those with an arteriovenous fistula).

Conclusions. No association was found between homocysteine levels or anticardiolipin antibody and vascular access thrombosis in our patient population.

Vascular access is necessary for hemodialysis. Long-term access is best achieved with a native arteriovenous fistula (AVF) [1–4], but inadequate arterial and venous anatomy frequently necessitate creation of a synthetic polytetrafluoroethylene (PTFE) graft, which has a higher rate of graft failure. In fact, patency rates at one and two years for PTFE grafts are only 50% to 65% and 50%, respectively [1, 2, 4–6]. The most common cause of vascular access failure is graft thrombosis [7]. Because patients may be supported on hemodialysis for years to decades, graft thrombosis is a major clinical problem, accounting for an average of 17% of hemodialysis patient admissions to one center [8]. In addition to the significant morbidity created by access failure, it has been estimated that $500 million is spent each year in the United States to create and maintain vascular access [9].

Little is known about risk factors for vascular access thrombosis [1]. It is accepted that low blood flow through the graft resulting from stenosis or neointimal hyperplasia at the site of the venous anastomosis increases the likelihood of thrombosis [5, 10]. However, this is only a marker for thrombosis and not a risk factor for its development. Currently, the only definite risk factor for vascular access thrombosis is placement of a synthetic graft rather than a native AVF [2–4, 11]. Risk factors that have been suggested in single studies but not confirmed by other analyses include the presence of diabetes [3], the location of the graft [4], the age of greater than 65 years [11], the time until use of graft after surgical creation [4], hypoalbuminemia [2], and elevated lipoprotein(a) [13].

Hyperhomocysteinemia has been reported to be associated with early-onset venous thrombosis [14] and recurrent venous thrombosis [15] in patients without end-stage renal disease (ESRD). Patients with chronic renal failure have homocysteine levels twofold to fourfold higher than patients with normal renal function [16–19]. Currently, no published studies have measured the association between hyperhomocysteinemia and vascular access thrombosis in patients on hemodialysis.

Immunoglobulin-G anticardiolipin antibody (IgG-ACA) is strongly associated with venous and arterial thrombosis in patients with normal renal function [20]. Elevated titers of IgG-ACA have been reported in he-

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modialysis patients [21]. There are conflicting reports regarding the association between elevated titers of ACA and vascular access thrombosis in patients on hemodialysis [21–25]. In one study by Prakash, Miller and Suki, the odds ratio for experiencing more than two episodes of graft thrombosis over a 2.5 year period in patients with an elevated IgG-ACA level was 3.7 (95% CI 1.2 to 11.8) [23]. This relationship was only noted among patients with synthetic grafts.

The purpose of this study was to determine whether hyperhomocysteinemia and/or elevated levels of IgG-ACA are associated with vascular access thrombosis in patients with ESRD undergoing chronic hemodialysis.

METHODS

Subjects and protocol

The Conjoint Medical and Research Ethics Board at the University of Calgary approved the study protocol. All study subjects provided written informed consent. This was a cross-sectional study involving patients with ESRD receiving hemodialysis in a centralized dialysis unit.

In our dialysis unit, approximately 75% of patients had native AVFs, and no patients used bioincompatible dialysis membranes. Eighty-seven percent of patients used polysulfone, 8.6% used cellulosynthetic, 3.6% used cellulose acetate, and 0.9% used polyacrylonitrile membranes. No dialyzer reuse occurred in this unit. The average blood flow was 300 to 400 ml/min. The average length of each dialysis was four hours, and the adequacy of dialysis was assessed on a monthly basis using the Kt/V. At the time that this study was completed, there was no routine screening program in place to detect venous outlet stenosis. In our unit, if thrombosis of a synthetic graft occurred, a surgical declotting procedure was performed if possible, and venous outlet stenosis was treated with a coronary dilator intraoperatively. Eighty-four percent of patients in our dialysis unit were on supplementation with a multivitamin containing 1 mg of folic acid, 6 μg of vitamin B12, and 10 mg of vitamin B6, either on a daily basis or three times per week.

Exclusion criteria for this study were refusal or inability to give informed consent, never having had a functioning permanent hemodialysis access (that is, AVF or PTFE graft), and the requirement for short-term (that is, less than two months) dialysis only. Of 221 patients who were dialyzed in this unit, 183 patients were eligible for this trial on the basis of having a permanent access. Of the eligible patients, 131 patients (72%) provided informed consent. Of those, 118 patients had all of the necessary blood work completed.

Midweek predialysis blood samples were collected from all participants for total homocysteine and IgG-ACA levels. Information was recorded for each patient regarding history of vascular access thrombosis in the past three years, as well as possible risk factors for access thrombosis. All information was confirmed by careful review of each participant's hospital chart, surgical record, and outpatient dialysis record.

Outcome variables

Risk factors for vascular access thrombosis. Information on type of vascular access (native AVF or PTFE graft), graft location, patient race and age, and etiology of renal failure was recorded. Diabetes mellitus was considered present if the patient was on insulin, oral hypoglycemics, or a diabetic diet, or if the patient's fasting or random plasma glucose was more than 7.8 mmol/liter or more than 11.1 mmol/liter, respectively. A patient was considered a smoker if they were a current smoker, an ex-smoker if they had smoked in the past, or a nonsmoker if they had never smoked. The use of interdialytic anticoagulants (such as coumadin) was recorded.

Diagnosis of vascular access failure and thrombosis. Vascular access failure was defined as failure of the access due to any cause requiring surgical intervention. Radiological intervention (such as angioplasty) was not recorded for this study, although in our dialysis unit, radiologists do not perform declotting or thrombolysis procedures. For the purposes of this study, vascular access failure was divided into primary and secondary graft failure. Primary graft failure was defined as the failure of patency within the first 30 days after placement [7], which is generally considered a surgical problem. We only considered secondary graft failure for the purposes of this analysis, and we classified the cause of secondary vascular access failure as being related to thrombosis or to other causes (such as infection or pseudoaneurysm).

Vascular access thrombosis was defined as the lack of blood flow by palpation and auscultation [10]. The presence of thrombus was confirmed by angiography or surgery. In order to account for the fact that many subjects in this study had their vascular access for less than three years and therefore were at risk of thrombosis for a shorter period, we also calculated rates of graft thrombosis per year. Patients were divided into three groups based on their rates of graft thrombosis: a thrombosis-free group with no episodes of graft thrombosis per year, an infrequent thrombosis group with more than zero but less than one episode of graft thrombosis per year, and a recurrent thrombosis group with more than one episode of graft thrombosis per year.

Laboratory investigations

Homocysteine. Plasma total homocysteine concentrations were determined by reverse phase high pressure liquid chromatography (HPLC) using the method developed by Vester and Rasmussen [26] and further modified by Ubbink et al [27]. Ingestion of food has little effect on homocysteine levels [27, 28], whereas hemodialysis

may decrease levels by 30% [28]. Hence, predialysis nonfasting midweek levels were measured for all patients. Blood samples were collected and spun to plasma within 30 minutes of collection. Samples were stored at −70°C, and all assays were conducted in one batch. The reference range as determined in our research laboratory for patients with normal renal function was 7.0 to 14.2 μmol/liter (mean 10.6 μmol/liter, SD 1.6 μmol/liter).

Anticardiolipin antibody (ACA). IgG-ACA levels were measured using a commercial ELIZA kit (Hemagen, Waltham, MA, USA). Positive and negative controls were included in each batch assay. Normal values were less than 10 IgG phospholipid units (GPL). Positive assays are graded into low, moderate, and highly positive as follows: 11 to 20 GPL, 21 to 80 GPL, and more than 80 GPL [29].

Statistical methods

Baseline variables were described using mean, geometrical mean, or proportions and confidence intervals where appropriate. The primary hypothesis of this study—hyperhomocysteinemia is associated with vascular access thrombosis in patients with ESRD on hemodialysis—was tested using three complementary statistical methods. First, a two-sample, two-sided *t*-test was used to compare mean homocysteine levels between patients with and without an episode of graft thrombosis over the period at risk. Second, one-way analysis of variance was used to assess for a difference between mean homocysteine levels in the thrombosis-free group, the infrequent thrombosis group, and the recurrent thrombosis group. Finally, logistic regression was done using a history of one or more episodes of graft thrombosis as the outcome variable. Backward elimination was then performed by sequentially removing predictor variables where the *P* value was more than 0.10.

The secondary hypothesis of this study—the presence of IgG-ACA is associated with vascular access thrombosis in patients with ESRD on hemodialysis—was tested using Fisher's exact test.

Results were considered significant if the *P* value was less than 0.05. Ninety-five percent confidence intervals were used for means, whereas binomial exact 95% confidence intervals were used for proportions.

RESULTS

All of the 118 patients enrolled in this study had all of the necessary blood work collected. Baseline patient characteristics are described in Table 1. Approximately three quarters of the patients had a native AVF, whereas one quarter of patients had a synthetic PTFE graft. Seventy-nine percent of sampled patients were white, 8% Asian, 4% Native Indian, 2% African American, and 7% other. The etiology of renal failure was diabetes mellitus 26%, glomerulonephritis 20%, hypertension 7%, polycystic kidney disease 7%, reflux nephropathy 4%, interstitial nephritis 3%, other 19%, and unknown 14%. The mean homocysteine level was 29.4 μmol/liter (95% CI 26.8 to 32.0; range 11.2 to 116.8). Mean red blood cell folate and vitamin B12 levels were 1699 μmol/liter (95% CI 1574 to 1804; normal more than 250), and 448 pmol/liter (95% CI 405 to 491; normal more than 130), respectively.

Table 1. Baseline patient characteristics for the entire group and for those with an anticardiolipin antibody assay

Patient characteristic	All patients (95% CI)	Subgroup in which IgG-ACA was assayed (95% CI)
Number of patients	118	67
Age *mean in years*	61.0 (58.2–63.8)	60.9 (56.9–64.9)
Sex *male*	68.6% (59.5–76.9)	65.5% (53.1–76.8)
Type of graft		
AVG	75.4% (66.7–82.9)	83.6% (72.5–91.5)
PFTE graft	24.6% (17.1–33.3)	16.4% (8.5–27.5)
Diabetic	36.1% (27.2–44.9)	25.5% (15.5–37.5)
Smoking status		
Never	42.0% (32.5–50.9)	41.8% (29.8–54.5)
Ex-smoker	41.2% (31.8–50.1)	36.4% (24.5–48.5)
Smoker	15.8% (10.0–24.0)	21.8% (13.1–34.2)
Graft location (proximal to elbow)	14.4% (8.6–22.1)	15.5% (7.4–25.7)
Erythropoietin use	79.5% (70.3–85.8)	85.5% (74.3–92.6)
Interdialytic use of anticoagulants	11.0% (6.0–18.1)	13.4% (6.3–24.0)
Use of folic acid supplementation[a]	84.0% (76.0–90.0)	87.3% (64.2–85.7)
Mean homocysteine *μmol/liter*	29.4 (26.8–32.0)	29.4 (26.6–32.2)

Abbreviations are: AVF, arteriovenous fistula; PTFE, polytetrafluoroethylene.
[a] Mean dose 0.57 mg folic acid/day (0.47–0.67)

Of the 118 study patients, 50 (42.4%, 95% CI 33.3 to 51.8%) patients had 117 episodes of vascular access failure requiring surgical intervention. Thirty-four (28.8%, 95% CI 20.9 to 37.9%) patients had 72 episodes of thrombosis as the cause of vascular access failure. Access thrombosis was analyzed for the three years preceding this study. Because some subjects had had their access for less than three years, the mean observation time over which subjects were at risk for thrombosis was actually two years (95% CI 1.84 to 2.16 years). Table 2 demonstrates absolute numbers and rates of vascular access thromboses for patients in this study according to type of vascular access.

Mean homocysteine levels were not significantly different between those patients who had at least one documented episode of vascular access thrombosis (28.6 μmol/liter, 95% CI 24.5 to 32.7) and those patients who had no episodes of access thrombosis (29.8 μmol/liter, 95% CI 26.7 to 32.9; mean difference 1.2 μmol/liter; 95% CI −4.5 to 7.0). Similarly, when patients with homocysteine levels below the median were compared with those

Table 2. Number and rates of graft thrombosis according to type of vascular access

	All grafts (95% CI)	AVF (95% CI)	PTFE graft (95% CI)
Number of graft thromboses in period at risk			
0 episodes	71.2% (62.1–79.1)	78.7% (68.7–86.6)	48.3% (29.5–67.5)
1 episode	15.3% (9.3–23.0)	14.6% (8.0–23.7)	17.2% (5.8–35.7)
2 episodes	5.9% (2.4–11.8)	3.4% (0.7–9.5)	13.8% (3.9–31.6)
>2 episodes	7.6% (3.5–14.0)	3.4% (0.7–9.5)	20.7% (8.0–39.7)
Rates of graft thromboses/year			
0 episodes/year	71.8% (62.1–79.1)	78.7% (68.7–86.6)	48.3% (29.5–67.5)
>0 and <1 episode/year	16.1% (10.0–24.0)	14.6% (8.0–23.7)	20.7% (8.0–39.7)
> or =1 episode/year	12.7% (7.3–20.1)	6.7% (2.5–14.1)	31.0% (15.3–50.8)

Table 3. Mean homocysteine levels in the thrombosis-free, infrequent thrombosis, and recurrent thrombosis groups according to type of vascular access

	Mean homocysteine (95% CI), *μmol/liter*		
Rate of thrombosis during time at risk	All subjects (N = 118)	Native AVF (N = 89)	PTFE graft (N = 29)
0 episodes/year	29.8 (27.0–32.5)	28.4 (25.9–30.9)	36.6 (27.2–46.4)
>0 and <1 episode/year	26.3 (24.6–28.0)	25.7 (24.0–27.4)	27.5 (22.7–32.3)
>1 episode/year	31.5 (28.8–34.2)	35.5 (32.3–38.7)	28.9 (22.6–34.2)
ANOVA	P = 0.52	P = 0.24	P = 0.54

Table 4. Multiple logistic regression using previously reported risk factors to predict for one or more episodes of graft thrombosis (prior to backwards elimination)

Risk factors	Odds ratio	95% CI	P value
Plasma homocysteine	0.99	0.96–1.02	0.682
Age *years*	0.98	0.95–1.01	0.137
PTFE graft	4.20	1.51–11.7	0.006
Current smoker	2.41	0.90–6.42	0.079
Graft proximal to elbow	1.28	0.80–2.06	0.308
Peripheral vasc. dis.	1.39	0.44–4.40	0.578
Diabetes mellitus	0.86	0.32–2.33	0.765

above the median level, the percentage having had an episode of access thrombosis was not different (30.0%, 95% CI 18.8 to 43.2 vs. 27.6%, 95% CI 16.6 to 40.9). When the mean homocysteine levels were compared for the thrombosis free, the infrequent thrombosis, and the recurrent thrombosis groups using analysis of variance, there was no significant difference (Table 3). This analysis was repeated separately for patients with native AVFs and synthetic grafts, and there also was no significant association found between homocysteine levels and rates of thrombosis for the two types of vascular accesses (Table 3).

Logistical regression analysis, using a history of access thrombosis as the outcome variable and controlling for previously postulated risk factors for access thrombosis as predictor variables, did not reveal homocysteine to be independently associated with access thrombosis (Table 4). After performing backward-elimination logistical regression using the model in Table 4 as a starting point, the only variable that was independently associated with access thrombosis was the type of access created (odds ratio 4.0, 95% CI 1.6 to 9.6 for patients with a synthetic graft).

There was a trend toward an association between younger age and increased rates of vascular access thrombosis. The odds ratio of having one or more episodes of access thrombosis for patients over the age of 65 was 0.47 (95% CI 0.21 to 1.07, P = 0.07). There was no association found between vascular access thrombosis and smoking, diabetes, graft location, or presence of peripheral vascular disease.

Sixty-seven unselected patients had IgG-ACA levels drawn for analysis. All IgG-ACA assays were negative (mean 2.4 GPL, SD 1.3; normal IgG-ACA less than 10 GPL). Because of the uniformly negative test results, no further assays were conducted, as it was very unlikely any association would be demonstrated with further testing. The baseline characteristics of these 67 patients were similar to the overall group (Table 1), and the rate of access thrombosis was also not different. Therefore, this subgroup appeared to be representative of the overall sample.

DISCUSSION

Despite the fact that the majority of patients enrolled in this study had native AVFs, vascular access thrombosis was still a major problem and occurred in nearly one third of patients over the average risk time of two years. Access thrombosis was much more common in patients

with synthetic grafts. Thirty-one percent of the patients with synthetic grafts had more than one episode of thrombosis per year at risk compared with only 6.7% of patients with AVFs. Our results are similar to those found in the Canadian Hemodialysis Morbidity Study, a large multicenter prospective cohort study of first permanent vascular access survival among incident hemodialysis patients, which demonstrated a 55% reduction in episodes of graft thrombosis for patients with AVFs compared with synthetic grafts [2].

There was a trend toward an increased risk of access thrombosis in patients younger than 65 years of age, which was strongest for patients with an AVF. This is unlike the findings of a cross-sectional study done using *United States Renal Data System* data, which noted a lower risk of vascular access failure among patients under the age 65 who were using native AVFs [11].

Despite previous reports that hyperhomocysteinemia, in patients with normal renal function, is associated with early-onset venous thrombosis [14] and recurrent venous thrombosis [15], our study found no association between homocysteine levels and vascular access thrombosis. There also was no trend demonstrated toward increasing homocysteine levels in those patients who experienced recurrent vascular access thrombosis. There was no significant effect of elevated homocysteine levels on access thrombosis noted for patients with native AVFs or synthetic grafts. We feel this study had adequate power to detect a clinically important association between hyperhomocysteinemia and access thrombosis if one had been present. With a sample size of 118, using a two-sided *P* value and using variability estimates for homocysteine as determined in our data set, our study had a power of 0.82 to detect a difference in homocysteine levels of 25% between patients with and without a history of graft thrombosis.

Since conducting our study, there have been three retrospective reports published on the association between homocysteine and access thrombosis, all with fewer patients than this report. Two have been in abstract form and, in general, have supported the findings of this study. The first abstract reported no association between hyperhomocysteinemia and recurrent vascular access thrombosis in hemodialysis patients with synthetic grafts ($N = 45$) [30], whereas the second noted a small inverse relationship between hyperhomocysteinemia and vascular access thrombosis ($N = 98$) [31]. A recent, small study by Ducloux et al ($N = 39$) revealed significantly higher homocysteine levels in patients with recurrent access thrombosis compared with those with one or less episodes of thrombosis [32]. Although the results were statistically significant, it is unclear what type of vascular access was studied, and concern should be given to such a small sample size.

Our study included patients with both AVFs and synthetic grafts. There was no association found between hyperhomocysteinemia and access thrombosis for either type. At the time of this study, our dialysis unit had no screening program to detect or correct venous outlet stenosis. The lack of a screening program, in fact, provided the best opportunity to demonstrate an association between homocysteine levels and access thrombosis if one had existed, since a prophylactic regimen correcting all venous outlet stenoses may have dramatically reduced the number of access thromboses [33]. Because thrombosis is usually preceded by venous outlet stenosis for synthetic grafts or draining vein stenosis for AVFs, our study suggests that hyperhomocysteinemia does not predispose to vascular disease or stenosis in veins as it does in arteries.

Previous studies have reported elevated IgG-ACA levels in 0.7 to 69% of patients with ESRD on hemodialysis [21]. Sitter and Schiffl have reported elevated IgG-ACA titers more commonly in patients on hemodialysis, occurring in 17% of patients on hemodialysis and in only 5% of patients on peritoneal dialysis [21]. Garcia-Martin et al found that patients dialyzing with cuprophane membranes had a higher prevalence of positive ACA assays than those dialyzed with more biocompatible membranes [34]. Prakash et al found significant titers of IgG-ACA in 22% of patients with a synthetic graft and only in 6% of patients with native AVFs [23]. These three observations suggest that production of the ACA may be a reaction to material present in the synthetic graft or to foreign substances to which the patient is exposed during hemodialysis.

Previous retrospective studies have reported an association between elevated IgG-ACA levels and vascular access thrombosis in patients on hemodialysis [21, 23–25]. No prospective studies have confirmed this finding, which has been noted mostly in patients dialyzing with synthetic grafts. In our study, we measured IgG-ACA levels because it is the isotype that correlates best with thrombosis in patients with SLE and primary antiphospholipid syndrome [20, 23]. No patients in our study had an elevated IgG-ACA level, and hence, there was no demonstrable association found between ACA and vascular access thrombosis. It is noteworthy that only 16.4% of patients in our study had synthetic grafts and that no patient used a cuprophane dialysis membrane.

The results of our study suggest that high titers of IgG-ACA are not an important predisposing factor to graft thrombosis in patients who use predominantly native AVFs and biocompatible membranes.

In summary, this study demonstrates a high risk of graft thrombosis in patients undergoing hemodialysis. The only definite association noted for graft thrombosis in this study was the type of graft placed. There was no association found between homocysteine levels or ACA and vascular access thrombosis in our patient population. Currently, there does not appear to be a role for mea-

surement of homocysteine or IgG-ACA levels in hemodialysis patients to predict risk for vascular access thrombosis. The patient factors that predispose certain patients to vascular access thrombosis remain largely undetermined.

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Reprint requests to Nairne Scott-Douglas, Foothills Hospital, 1403–29th Street NW, Calgary, AB, T2N-2T9, Canada.
E-mail: nairne.scott-douglas@crha-health.ab.ca

APPENDIX

Abbreviations used in this article are: AVF, arteriovenous fistula; ESRD, end-stage renal disease; CI, confidence interval; GPL, IgG phospholipid units; HPLC, high pressure liquid chromatography; IgG-ACA, immunoglobulin G–anticardiolipin antibody; PTFE, polytetrafluoroethylene.

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