Association of plasma fibrinogen concentration with vascular access failure in hemodialysis patients

In Suk Song¹, Won Seok Yang¹, Soon Bae Kim¹, Jong-Ho Lee³, Tae-Won Kwon² and Jung Sik Park¹

¹Nephrology Section, Department of Medicine, ²Vascular Surgery, Asan Medical Center, College of Medicine, University of Ulsan, Seoul, and ³Nephrology Section, Department of Medicine, Gil Medical Center, Gachon Medical College, Inchon, Korea

Abstract

Background. Elevated plasma fibrinogen is an important risk factor for coronary artery disease in the general population and patients with chronic renal failure. High plasma fibrinogen may trigger thrombus formation in arteriovenous fistulas. We performed a prospective, cohort study to evaluate the association of plasma fibrinogen concentration with vascular access failure in patients undergoing long-term haemodialysis.

Methods. Between September 1989 and October 1995, 144 patients underwent a vascular access operation. In March 1997, 102 patients (56 M, 46 F) who had been followed up for more than 18 months (median; 37 months, range; 18–102 months) were included in the study. The median age of the patients was 52 years (range; 19–78 years). In 35 patients, renal disease was secondary to diabetes mellitus. The type of vascular access was a polytetrafluoroethylene (PTFE) graft in 17 patients. Seventy-seven patients received recombinant human erythropoietin (r-HuEPO) therapy during the follow-up period. Plasma fibrinogen, albumin, total cholesterol, hematocrit, platelets and creatinine were measured at the time of operation. Vascular access failure was defined as the occurrence of complications requiring transluminal angioplasty, thrombolytic therapy or surgical repair.

Results. Thirty-eight patients had at least one vascular access failure and the incidence was 0.3 (range; 0–2.4) episodes per patient-year. The survival rate of vascular access was 78% (native fistula; 80%, PTFE graft; 71%) after 12 months and 70% (native fistula; 73%, PTFE graft; 51%) after 24 months. Older age, a PTFE graft, r-HuEPO therapy, higher hematocrit, lower albumin and higher fibrinogen levels were significantly associated with vascular access failure, whereas gender, diabetes mellitus, total cholesterol and platelet count were not. Plasma fibrinogen was inversely correlated with albumin (r = −0.38, P = 0.001). The cumulative vascular access survival was significantly lower in patients with high plasma fibrinogen levels (≥460 mg/dl) compared with patients with low levels (<460 mg/dl) (P = 0.007). Independent risk factors for vascular access failure analysed by Cox’s proportional hazards model were older age (RR; 1.36 by 10-year increment), higher fibrinogen level (RR; 1.20 by 100 mg/dl increment), PTFE graft (RR; 2.28) and r-HuEPO therapy (RR; 3.79).

Conclusion. High plasma fibrinogen level is an independent risk factor for vascular access failure in haemodialysis patients.

Key words: fibrinogen; haemodialysis; risk factor; vascular access failure

Introduction

Reliable vascular access is the Achilles’ heel of long-term maintenance haemodialysis and a vascular access problem is the most common complication encountered in patients undergoing long-term haemodialysis. A recent study showed that more than 20% of all hospitalizations of haemodialysis patients were due to vascular access complications [1]. Thrombosis is a leading cause of vascular access failure and usually results from stenosis caused by progressive neointimal hyperplasia in the venous outflow system [2]. In addition, hypercoagulability, as well as low blood flow rate resulting from hypotension, hypovolemia or stenosis of central vein drainage, is thought to be important in the formation of thrombosis. Hypercoagulability, caused by an alteration in coagulation factors, was reported to occur frequently in patients with chronic renal failure [3]. Haemostatic activation was also found in arteriovenous fistulas following endothelial injury [4] through excessive intraluminal pressure, turbulent flow and frequent needle insertion during haemodialysis.

In several prospective studies, plasma fibrinogen was reported to be an independent risk factor for initial
[5] and recurrent [6] coronary artery disease in the general population, for vascular complications in diabetes [7] and for atherosclerotic cardiovascular disease in chronic renal failure patients [8]. In the presence of low fibrinogen concentrations, the risk of coronary events remained low even in patients with high serum cholesterol levels [9]. High plasma fibrinogen may also serve as a trigger for thrombus formation in arteriovenous fistulas. However, little has been evaluated regarding the relationship between the level of plasma fibrinogen and the occurrence of vascular access failure. We performed a prospective cohort study to evaluate the association of plasma fibrinogen concentration with vascular access failure in patients undergoing long-term haemodialysis.

Subjects and methods

This prospective cohort study was initiated at Asan Medical Center in September 1989. Patients with end-stage renal disease (ESRD) were eligible for entry into the study if they underwent a vascular access operation at our center and survived for more than 3 months. One-hundred and forty-four patients were enrolled until October 1995. Forty-two patients were excluded for the following reasons: 26 patients received renal transplants, three patients switched to peritoneal dialysis and 13 patients expired. The remaining 102 patients (70.8% of enrollment) were followed for more than 18 months until March 1997. The median duration of follow-up was 37 months (range; 18–102 months). Patients were haemodialysed three times a week with a bicarbonate bath using Cobe Centry system 3 dialysis machines (Cobe, Lakewood, CO) through 16-gauge dialysis needles. Blood flow rates ranged from 200 to 250 ml/min. All patients received heparin in each dialysis session and 17 patients who received a polytetrafluoroethylene (PTFE) graft were given 100 mg of aspirin daily. Vascular access failure was defined as the occurrence of complications requiring transluminal angioplasty, thrombolytic therapy or surgical repair.

Clinical data included age, gender, history of diabetes mellitus, access type (native arteriovenous fistula vs PTFE graft) and recombinant human erythropoietin (r-HuEPO) therapy during the follow-up period. The doses of r-HuEPO were adjusted to maintain the haematocrit level between 30% and 33%. Fasting blood was drawn at the time of access operation. Serum albumin, cholesterol and creatinine were measured as the occurrence of complications requiring transluminal angioplasty, thrombolytic therapy or surgical repair.

Statistical analysis was performed using SPSS Windows version 6.0 (SPSS Inc, Chicago, IL). Continuous variables were compared using Student’s t-test and categorical variables were compared using the χ² test. Relationships between variables were evaluated by Pearson’s correlation. The data are expressed as mean ± SD and P-values less than 0.05 are considered to be statistically significant. In the multivariate analysis, the independent correlates of vascular access failure were determined with the Cox’s proportional hazards model. Data presented include the relative risk (RR) ratios and their 95% confidence intervals (95% CI). The cumulative vascular access survival curves of patients with high plasma fibrinogen levels (≥460 mg/dl) and those with low levels (<460 mg/dl) were obtained by the Kaplan–Meier method and compared using a log-rank test.

Results

The baseline characteristics of the patients are shown in Table 1. The median age of the patients was 52 years (range; 19–78 years). The median duration of haemodialysis was 37 months (range; 18–102 months). In 35 patients (34%), renal disease was secondary to diabetes mellitus. A PTFE graft served as vascular access in 17 patients (17%). Seventy-seven patients (76%) received r-HuEPO therapy. Thirty-eight patients had at least one vascular access failure during the follow-up period, and the frequency of vascular access failure was 0.3 episodes per patient-year (range; 0–2.4).

Vascular access survival was 78% (native fistula; 80%, PTFE graft; 71%) after 12 months and 70% (native fistula; 73%, PTFE graft; 51%) after 24 months.

Comparisons of clinical and biochemical data of patients with and without vascular access failure are shown in Table 2. Older age, a PTFE graft, r-HuEPO therapy, higher hematocrit, lower albumin and higher fibrinogen levels were significantly associated with vascular access failure, whereas gender, diabetes mellitus, total cholesterol and platelet count were not. Comparisons of clinical and biochemical data according to fibrinogen level are shown in Table 3. In patients with high plasma fibrinogen levels (≥460 mg/dl), serum albumin was lower and vascular access failure
The incidence of vascular access failure was 0.3 episodes per patient-year in our patients. This is similar to the value given in previous reports [11,12]. Of the variables included in the analysis, age, a PTFE graft, r-HuEPO therapy and high plasma fibrinogen level were independent risk factors for vascular access failure.

The cumulative vascular access survival of a PTFE graft after 24 months was 51%, which was significantly worse than that of a native fistula (73%). PTFE graft and age have been consistently reported as risk factors for vascular access failure in previous studies [12–14]. In the study by Besarab et al., most of the thromboses occurred in a PTFE graft [12]. Churchill et al. [11] reported that the incidence of vascular access failure of a PTFE graft (32.3–39.9%) is about twice that of a native fistula (14.4–18.4%) during 12 months of follow-up after arteriovenous fistula surgery. After follow-up for 14 months in 124 patients who underwent arteriovenous fistula operation, Goldwasser et al. [13] also reported that old age and PTFE graft were associated with increased arteriovenous fistula thrombosis. Considering that the PTFE grafts were usually placed in those with failed arteriovenous fistula or with poor arteries and veins, it is not surprising that a PTFE graft was a risk factor for vascular access failure.

r-HuEPO may cause thrombosis by increasing haematocrit and blood viscosity, altering haemostasis and enhancing platelet function [15]. Results of studies regarding the association of increased vascular access failure with r-HuEPO therapy have been inconsistent. Besarab et al. [12] investigated the rate of thrombotic events in 164 dialysis patients receiving r-HuEPO for more than 2 months and were unable to detect any evidence of increased frequency of thrombosis either for a PTFE graft or for a native fistula. On the contrary, Dy et al. [16] performed a cohort study of 46 dialysis patients before and after treatment with r-HuEPO for 12 months and reported a greater incidence of graft thrombosis in the r-HuEPO period. A similar finding was also reported by the Canadian Erythropoietin Study [17]. The result of the present study is in agreement with the latter studies. In the study by Besarab et al. [12], r-HuEPO was given for a longer duration than in the present study. Thus, it may be possible that prolonged administration of r-HuEPO predisposes to thrombosis of arteriovenous fistula.

Several reports found diabetes to be associated with an increased risk of vascular access failure, but we failed to show diabetes as an independent risk factor. This discrepancy may be explained by differences in the patient population and analytic method. The study by Windus et al. [18] included a larger number of patients with diabetes (51 vs 34%), older age (61 vs 52 years) and higher rate of synthetic graft use due to inadequate native arteriovenous fistula (100 vs 17%) than the present study. Tang et al. [19] reported that...
although vascular access failure occurred more frequently in diabetic patients, it was more prevalent with a PTFE graft than a native fistula (65 vs 20%), even in diabetic patients. In the report by Goldwasser et al. [13], diabetes was associated with vascular access failure with a univariate analysis, but was not an independent risk factor with a multivariate analysis. Thus, the increase incidence of vascular access failure in diabetic patients may depend on the presence of confounding variables, such as age and the use of a PTFE graft.

To our knowledge, there has been only one study evaluating fibrinogen as a risk factor for vascular access failure. The study by de Marchi et al. [20] evaluated 30 non-diabetic patients with a native fistula and fibrinogen was not found to be a risk factor for fistula dysfunction. However, we found very high fibrinogen levels to be an independent risk factor for vascular access failure in our present study which had a larger number of patients, including those with a PTFE graft and diabetes. Fibrinogen is a acute phase protein. It is very difficult to determine when to measure fibrinogen levels associated with a vascular access problem. Therefore, we evaluated the influence of baseline fibrinogen on vascular access failure similar to studies investigating the effect of fiberoogen on atherosclerosis [6,21,22]. Baseline fibrinogen was found to be a predictable factor for cardiac events in patients with angina pectoris after 9 years follow-up in Thompson et al.’s study [6] and for vascular access failure after 102 months follow-up in our study. High fibrinogen is thought to contribute to intravascular thrombosis by several mechanisms [23]. First, fibrinogen is the major determinant of plasma viscosity and induces reversible red-cell aggregation. Secondly, fibrinogen binds to the glycoprotein IIb/IIIa receptor, leading to aggregation of platelets which serve as the primary haemostatic mechanism following vascular injury. Thirdly, fibrinogen can evolve into mural thrombi and stimulate smooth muscle cell proliferation and migration. These mechanisms may contribute to the higher risk of vascular access thrombosis in haemodialysis patients.

In haemodialysis patients, cardiovascular disease is more frequently found in those with low serum albumin. It was reported that the risk of fistula thrombosis in patients with serum albumin levels equal to or below 3.0 g/dL was 2.7 times greater than in those with serum albumin levels above 3.0 g/dL [11]. In the present study, the serum albumin level was significantly lower in patients with vascular access failure, although serum albumin level was not associated with vascular access failure in multivariate analysis. How hypoalbuminaemia is associated with high clotting risk in dialysis patients is unclear, but some possible mechanisms could be suggested. A low serum albumin level increases plasma fibrinogen and lipoprotein (a) levels in dialysis patients despite a normal cholesterol level [24,25], which in turn may increase the risk for clotting. An inverse correlation was present between serum albumin and fibrinogen in our patients. In vitro and in vivo studies have shown that the addition of albumin blunted the stimulatory effect of free fatty acids which stimulated hepatic synthesis of fibrinogen. Decrease in serum albumin, therefore, may stimulate the production of fibrinogen in the liver [26]. The elevated plasma fibrinogen in turn, may contribute to the formation of thrombi in the vascular access.

In summary, we have prospectively evaluated the influence of plasma fibrinogen on vascular access failure in patients undergoing long-term haemodialysis. Our study showed that plasma fibrinogen is an independent risk factor for vascular access failure in haemodialysis patients.

Acknowledgements: This study was supported by a grant from the Ministry of Health and Welfare (97-0278, Park JS).

References
17. Canadian Erythropoietin Study Group. Association between recombinant human erythropoietin and quality of life and
Association of plasma fibrinogen with vascular access failure


Received for publication: 24.2.98
Accepted in revised form: 18.9.98