What are the Risk Factors of Arteriovenous Fistula Thrombosis in Hemodialysis Patients; is the Platelet Count Important?

Hemodiyaliz Hastalarında Arteriyovenöz Fistül Trombozunun Risk Faktörleri Nelerdir; Platelet Sayısı Önemli midir?

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Geliş Tarihi/*Received:* 24.11.2011
Kabul Tarihi/*Accepted:* 03.02.2012

This study was presented as a poster at 10th Bantao Congress, 13-15 October, 2011, Greece.

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ABSTRACT Objective: The aim of this study was to investigate factors associated with arteriovenous fistula thrombosis. **Material and Methods:** Clinical data from the last 5 years of 212 maintenance hemodialysis patients were reviewed retrospectively. Patients with clinical evidence of malignancy or procoagulant condition were excluded. This study group was comprised of 212 patients (M/F: 110/102), with a mean age of 52±16 years and the mean duration of hemodialysis was 62.3±30.1 months. Fistulography was performed in patients with arm pain or swelling, low blood flow rate during hemodialysis, and increased venous dialysis pressure. **Results:** Fistulography was performed on 116 patients (M/F: 49/67), thrombosis was observed in 65 patients (56%) and stenosis was observed in all remaining patients. Forty-six patients (70%) had both thrombosis and stenosis concurrently, those were evaluated in the thrombosis group. The frequency of hypertension (p=0.02), LDL cholesterol [91 (11-189); 76.5 (24-213) mg/dL p=0.005], total cholesterol [163 (89-300); 136 (64-299) mg/dL, p=0.000], triglyceride levels [151 (86-402); 127 (46-520) mg/dL, p=0.02] and platelet count [201 (110-380); 175 (60-130) K/mm^3, p=0.001] were higher in patients with arteriovenous fistula thrombosis than in patients with patent arteriovenous fistula. **Conclusion:** Presence of hypertension, lipid profile and higher platelet count are associated with arteriovenous fistula thrombosis.

Key Words: Arteriovenous fistula; cholesterol; renal dialysis; hypertension; platelet count

ÖZET Amaç: Bu çalışmanın amacı arteriovenöz fistül trombozu ile ilişkili faktörlerini incelemektir. **Gereç ve Yöntemler:** İdame hemodiyalizli 212 hastanın son 5 yıllık klinik verileri retrospektif olarak gözden geçirildi. Malignite veya koagülasyon bozukluğu bulguları olan hastalar çalışma dışı bırakıldı. Çalışma grubunu oluşturan bu 212 hastada (E/K:110/102), ortalama yaş 52±16 yıl, ortalama hemodiyaliz süresi 62,3±30,1 ay idi. Kolunda ağrı ve şişme olan, hemodiyaliz sırasında kan akım hızı düşük, venöz basıncı yüksek olan hastalara fistülografi uygulandı. **Bulgular:** Fistülografi 116 hastaya (E/K:49/67) uygulandı, 65 hastada tromboz (%56), diğerlerinde stenoz saptandı. Tromboz olan hastaların 46 sında (%70) aynı zamanda stenoz da vardı. Hipertansiyon sıklığı (p=0,02), LDL kolesterol [91 (11-189); 76,5 (24-213) mg/dL, p=0,005], total kolesterol [163 (89-300); 136 (64-299) mg/dL, p=0,000], trigliserid düzeyleri [151 (86-402); 127 (46-520) mg/dL, p=0,02] ve trombosit sayısı [201 (110-380); 175 (60-130) K/mm^3, p=0,001] arteriovenöz fistül trombozu olan hastalarda, patent arteriyovenöz fistülü olanlardan daha yüksekti. **Sonuç:** Hipertansiyon varlığı, lipid profili ve artmış trombosit sayısı arteriovenöz fistül trombozu ile ilişkilidir.

Anahtar Kelimeler: Arteriyovenöz fistül; kolesterol; böbrek diyalizi; hipertansiyon; trombosit sayma

Turkiye Klinikleri J Nephrol 2012;7(1):1-7

The incidence and prevalence of chronic kidney disease (CKD) are increasing due to the aging population and increase in co-morbid conditions such as diabetes and hypertension. Hemodialysis (HD) is the standard renal replacement therapy for 75.7% of patients with end-stage kidney disease in Turkey.[1] Effective hemodialysis is critically dependent on obtaining and maintaining repeated access to the circulation. The options for vascular access options are native arteriovenous fistula (AVF), synthetic arteriovenous graft or central venous catheter. An ideal access method delivers a flow rate adequate for the dialysis prescribed, has a long use-life and a low rate of complications, such as infection, stenosis, thrombosis, aneurysm and limb ischemia. Although no current type of vascular access fulfills all of these criteria, the native AVF has the lowest rate of complication. Studies have demonstrated that native access has the best four to five years patency rate and requires the fewest interventions compared with other access types.[2,3] Therefore, AVF is universally acknowledged as the optimal access option with the best long-term patency, lowest cost and lowest infection rate. The proportion of the native AVF in Turkey is 86%.[1] Failure of dialysis access can result from either inadequate blood flow due to stenosis of the venous outflow tract or complete or partial occlusion due to thrombosis. About 80-85% of arteriovenous access failure result from thrombosis, which is due to AVF stenosis occurring in more than 85% of cases.[3] Intimal hyperplasia of the draining vein has been identified as the most frequent culprit. On the other hand, procoagulant environment resulting from endothelial damage, inflammation, intrinsic deficiency of antithrombotic factors are suggested to be added to the mechanical obstruction.[4] In this study, we investigated the clinical and laboratory parameters associated with AVF thrombosis.

MATERIAL AND METHODS

Clinical data from the last 5 years on 212 maintenance HD patients, which had been on hemodialysis treatment for more than 12 months, were reviewed retrospectively. At the time of the study, each patient was undergoing bicarbonate HD 3 times weekly in sessions lasting 4-5 hours. Hemophane membranes (1.8 m^2) were used. During HD sessions the blood flow rate ranged from 250-350 ml/minute (median, 300 ml/minute) and mean Kt/V was kept at 1.4±0.2. None of the patients had clinical evidence of malignancy or procoagulant conditions. In each case, a venous blood sample was drawn before the first dialysis session of the week. As well, each patient's chart was reviewed and the laboratory parameters were determined once a month and the results of the last twelve months were averaged to obtain a mean value. The parameters studied were hemoglobin, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, intact parathyroid hormone (PTH), lipid profile (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and triglyceride), serum iron levels, iron binding capacity, saturation index and ferritin. All the patients were given 50-150 U/kg/week erythropoietin (EPD), according to saturation index, serum ferritin and hemoglobin level. The target hemoglobin level was 10-12 g/dL. Medical records were also reviewed to assess presence/absence of diabetes mellitus in each case. Hemoglobin levels were determined by spectrophotometer method (Cell DYN 3700 Abbott, Indianapolis, IL, USA) and intact PTH levels were measured by electrochemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN, USA). Serum levels of blood urea nitrogen, creatinine, calcium, phosphorus, albumin, and serum lipid profiles were assessed using standard laboratory methods (Roche Hitachi analyzer 902, Indianapolis, IN, USA).

The site of AVF was also recorded (radiocephalic, brachiocephalic, brachiobasilic). Fistulography was performed in patients with arm pain or swelling, low blood flow rate during hemodialysis, increased venous dialysis pressure. The laboratory and clinical parameters of patients with and without AVF thrombosis were compared.

STATISTICAL ANALYSIS

Statistical analysis was performed using the statistical package SPSS v 16.0. For each continuous variable, normality was checked by Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. Comparisons between groups were applied using one way ANOVA test for normally distributed data and Kruskal Wallis test were used for the data not normally distrubuted. Since analysis of variance was significant, comparisons were applied using the Post Hoc test and Mann-Whitney U test. The categorical variables between the groups were analyzed by using the Chi square test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Clinical records of 212 patients (Male/Female: 110/102) were evaluated. Clinical characteristics of the patients were shown in Table 1 and laboratory findings in Table 2. Patients were grouped according to presence of thrombosis or stenosis and the results were compared with patients with patent AVF. The mean age of the patients was 52±16 years, with a mean duration of HD 62.3±30.1 months (Table 1). The dose of EPO was adjusted to maintain hemoglobin levels between 10 and 12

TABLE 1: Clinical characteristics of the patients.

	Patent AVF	Thrombosis	Stenosis
No of cases	96 (45.3%)	65 (30.7%)	51 (24%)
Gender (M/F)	61/35	33/32	16/35
Age (years)	50.6±17.2	53.7±17.1	52.7±15.6
Time on dialysis (months)	61.16±31.9	65.12±27.1	61±30.6
ESRD etiology			
DM	24	17	15
HT	7	12	7
GN	9	6	6
Stone	15	5	7
PKD	2	2	2
Unknown	33	21	12
VUR	5	2	0
Amyloid	1	0	0
MM	0	0	1

AVF: Arteriovenous fistula; ESRD: End stage renal disease; DM: Diabetes mellitus; HT: hypertension; GN: Glomerulonephritis; PKD: Polycystic kidney disease; VUR: Vesicoureteral reflux; MM: Multiple myeloma.

TABLE 2: Laboratory Data of the patients with patent AVF, thrombosis and stenosis.

	Patent AVF n= 96	Thrombosis n= 65	Stenosis n= 51
Hemoglobin (g/dL)	10.5 (7.3 -13)	10.4 (8.2-13)	10.2 (7.3-13)
Platelet (K/mm^3)	175 (60-310)	201 (110-380)[a]	210 (109-486)
LDL-cholesterol (mg/dL)	76.5 (24-213)	91 (11-189)[b]	77 (31-161)
HDL-cholesterol (mg/dL)	33.5 (16-63)	34 (21-81)	31 (19-64)
Total cholesterol (mg/dL)	136 (64-299)	163 (89-300)[c]	152 (80-245)
Triglyceride (mg/dL)	127 (46-520)	163 (64-851)[d]	168 (70-624)*
CRP (mg/L)	8 (3-40)	8 (3-26)	9 (3-64)
Uric acid (mg/dL)	6.2 (2-6.5)	6.3 (4.8-9.5)	6.6 (3.6 -9.1)**
PTH (pg/mL)	317 (21-1977)	304 (2.7-1634)	324 (2.4-1625)
Calcium (mg/dL)	8.7 (6.9-10.5)	8.7 (6.7 -10.2)	8.6 (6.2 -10.2)
Phosphorus (mg/dL)	5.8 (3.3-9.7)	5.6 (3.4-8)	5.2(2.5-8)
Albumin (gr/dL)	3.6(2.8-4.5)	3.7 (3.1-4.6)	3.5 (2.8-4.3)
SI (%)	30 (15-74)	27 (9-77)	26 (15-69)
Ferritin (ng/ml)	480 (54-1800)	558 (146-1525)	477 (81-1453)

p<0.05 was considered statistically significant. Values were shown as median and range. Patent AVF were separately compared with thrombosis and stenosis. [a],p= 0.001; [b],p= 0.005; [c]p= 0.000; [d]p=0.001. *,p=0.000, **p=0.02.

AVF: Arteriovenous fistula; SI: Saturation index; CRP: C-reactive protein; PTH: Parathyroid hormone.

g/dL and the maximum dose was 150 U/kg/week. The only five of the patients were using aspirin regularly. Fistulography was performed in 116 patients (Male/Female: 49/67), thrombosis was observed in 65 patients (56%) and stenosis in 51 patients (44%) (Table 2). Forty-six patients (70%) who had both thrombosis and stenosis concurrently were evaluated in the thrombosis group. Age, gender, duration of HD and the site of AVF were not different in patients with and without AVF thrombosis. But, majority of the patients with stenosis were female (35/16). The frequency of hypertension was higher in patients with AVF thrombosis (p=0.02). Serum LDL cholesterol [91 (11-189); 76.5 (24-213) mg/dL, p=0.005], total cholesterol [163 (89-300); 136 (64-299) mg/dL, p=0.000], triglyceride levels [163 (64-851); 127 (46-520) mg/dL, p=0.001] and platelet count [201 (110-380); 175 (60-130) K/mm^3, p=0.001] levels were also significantly higher in patients with AVF thrombosis compared with patients with patent AVF (Table 2), (Figure 1, 2). Thrombotic group was further divided into two groups, patients who have pure thrombosis (n=19) and who have both thrombosis and stenosis (n=46). Those groups were separately compared with patent AVF group. In the pure thrombosis group serum total cholesterol (172 ± 37; 144 ± 42 mg/dL, p=0.04), triglyceride [151 (86-402); 127 (46-520) mg/dL, p=0.02] and platelet [205 (110-380); 175 (60-310) K/mm^3, p=0.02] were higher than patent AVF group. Serum LDL cholesterol levels were similar in the pure thrombosis group and in the patent AVF group [99 (11-149); 76.5 (24-213) mg/dL, p=0.06, respectively]. Serum triglyceride [168 (70-624); 127 (46-520) mg/dL, p=0.00] and uric acid [6.6 (3.6-9.1); 6.2 (2-6.5) mg/dL, p=0.04] were higher in the stenosis group than patent AVF group. Platelet count (210 (109-486); 175 (60-310) K/mm^3, p=0.153) and LDL cholesterol levels (77 (31-161); 76.5 (24-213) mg/dL, p=0.118) were not different between stenosis and patent AVF groups.

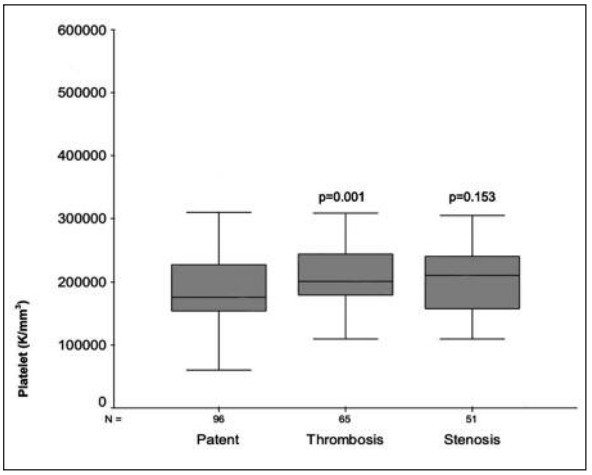

FIGURE 2: Platelet count in patients with patent and thrombotic - stenotic AVF. Platelet count levels were significantly higher in patients with AVF thrombosis compared with patients with patent AVF.
AVF: Arteriovenous fistula.

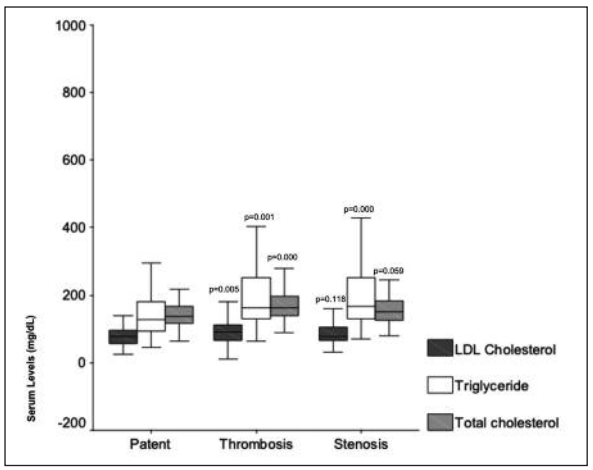

FIGURE 1: Serum levels of lipids in three arterivenous fistula groups. Comparisions were made between patent and thrombotic- stenotic arteriovenous fistulas.

DISCUSSION

Effective HD is dependent on a well functioning AVF. Failure of the AVF can result from either inadequate blood flow due to stenosis of the venous outflow tract or complete or partial occlusion due to thrombosis. According to previous reports, thrombosis is associated with underlying venous stenosis in approximately 85% of cases. In our study, stenosis was observed in 70% of patients with thrombosis. It is essential to perform fistulography for the diagnosis of stenosis and thrombosis.[3,5] The three most common abnormalities

observed are focal stenosis near the anastomosis or in the draining vein, the presence of large accessory veins or excessively deep fistulas.[6] There are also biochemical factors and clinical conditions that can influence AVF patency.

Controversial influences of diabetes, lipid profile, CRP, hyperparathyroidism, hematocrit (HCT) and platelet levels have been reported. We did not find any association between CRP, PTH, HCT, presence of diabetes and AVF thrombosis. In some studies the presence of diabetes mellitus, a mean weekly erythropoietin dose, serum levels of lipid profile, CRP, hyperparathyroidism, HCT and fibrinogen have been shown to be associated with AVF failure.[7-9] Actually, diabetic patients are supposed to have more AVF thrombosis than non-diabetics, because of greater prevalence of vascular calcification.[10] But in the same study, arterial and venous diameter and peak systolic velocity measurements were similar between patients with and without diabetes. Arterial and venous diameters are important for AVF creation. Most of the patients had poly tetra fluore thylene PTFE graft in the two previous studies which were showing increased incidence of vascular access failure in diabetics. Thus increased incidence of vascular failure in diabetic patients may depend on presence of PTFE graft.[11,12] On the other hand, Garrancho et al. evaluated 1254 patients and they identified diabetes as predictive factor for vascular access failure.[13] We considered, due to small sample size of our study population and only patients with native AVF were included we did not find any effect of diabetes on AVF thrombosis.

In the retrospective study of Kirkpantur et al., a lower LDL and HDL cholesterol and albumin levels, higher serum CRP levels were found in patients with AVF thrombosis.[9] However, Serati et al. showed that an LDL cholesterol value >130 mg/dL was a major prognostic factor for AVF thrombosis.[14] Furthermore, Grandaliano et al. and Song et al. both failed to demonstrate any effect of cholesterol on AVF failure.[7,8] In our study, higher levels of total cholesterol, LDL cholesterol and triglyceride were associated with AVF thrombosis. Dyslipidemia is very common in dialysis patients and is a traditional risk factor for cardiovascular disease, as well as diabetes and hypertension. Over 60% of dialysis patients have lipid abnormalities sufficient enough to require therapy. Deposition of lipid droplets within the hyperplastic intima is a key feature of atherosclerotic lesions. Additionally, small LDL cholesterol particles, which are increased in dialysis patients, are more atherogenic than other particles.[15] Furthermore, statins and homocysteine-lowering folic acid therapy are associated with prolonged arteriovenous fistula survival.[16] Two risk factors for atherosclerosis, higher frequency of hypertension and an abnormal lipid profile, may also impact AVF patency.

The reference interval for the platelet count is 150-450 K/mm^3. Although it was in normal range, higher platelet count was found to be associated with AVF thrombosis. It has been shown that an increased platelet count was associated with iron deficiency anemia in a group of healthy women.[17] On the other hand, in another study, the relative thrombocytosis (> 300 K/mm^3 platelet count) was observed in 15% of the study population and was associated with a 30% greater weekly dose of EPO. There was evidence of iron depletion in those CKD patients.[18] The level of thrombocytosis, caused by iron deficiency, may be a cause of AVF thrombosis. In our study neither serum iron level indexes nor hemoglobin levels were associated with AVF thrombosis. Grandaliano et al. found no difference in serum iron, ferritin and transferrin saturation between patients with and without AVF failure.[7] Thrombocytosis may not be prominent in our patients because of sufficient serum iron levels. Nevertheless, we did find that platelet count was associated with AVF thrombosis. The mechanisms through which higher platelets counts contribute to AVF thrombosis is uncertain. Oxidative stress, endothelial dysfunction, platelet activation might be some of the causes. Ando et al. previously showed that circulating platelet-derived microparticles were higher in uremic patients with thrombotic events than in those without thrombotic events and these particles did

not correlate with platelet count. They suggested that EPO had an effect on the particles.[19] In another study, a higher level of circulating activated platelets was associated with a shorter survival of vascular access in hemodialysis patients. Platelet count was similar between the control group and patients with recurrent vascular access failure and longer vascular access survival.[20] In a recent study, a human platelet antigen polymorphism was shown to be associated with susceptibility to thrombosis in hemodialysis patients. The human platelet antigen 4b allele was found to be significantly more frequent in thrombotic patients than non-thrombotic patients or the control group.[21]

In our study, due to varying monthly EPO doses, we could not evaluate the direct effect of EPO on AVF thrombosis. Although the platelet count did not reach a level indicative of thrombocytosis, platelets may cause thrombosis via the uremic milieu, circulating activated platelets or human platelet antigen polymorphism. Thrombosis can result from all of these conditions. Using antiplatelet drugs, such as aspirin, could prolong AVF survival. Hasegawa et al. showed that consistent aspirin use was significantly related to a lower risk of final AVF failure.[22]

Limitations of our study; since it was retrospective, we have not got information about APTT, INR or fibrinogen levels. We evaluated patients only with clinical symptom of arm swelling, pain, low flow rate, increased venous pressure during hemodialysis. Maybe we have overlooked some patients with trombosis due to absence of those symptoms.

In conclusion, presence of hypertension, an abnormal lipid profile and higher platelet count impact AVF patency. Lowering cholesterol levels and aspirin therapy may improve AVF availability. However, randomized trials are needed to verify those observations.

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