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CLINICAL STUDY

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Abstract

Background: Arteriovenous fistula (AVF) is the most important vascular access method for hemodialysis (HD). In this study, the relationship between AVF success and inflammation in patients who had HD due to end-stage renal failure (ESRF) was investigated. *Material and method*: In the study, a total of 658 patients, who started HD for ESRF, were evaluated retrospectively. A total of 386 patients were included in this study. The demographic data and C-reactive protein, albumin and fibrinogen levels were investigated in patients with recognized success AVF. *Results*: In total 311 patients with successful AVF and 75 unsuccessful AVFs were found. In unsuccessful AVF group the average low albumin level, high C-reactive protein and fibrinogen levels were found to be statistically meaningful when compared with successful AVF group ($p < 0.001$, $p < 0.001$, $p < 0.001$). *Conclusion*: As a result, we think that the evaluation of inflammation before creating AVF in HD patients is very important for increasing the success of AVF.

Introduction

Hemodialysis (HD) is the most common treatment method for renal replacement therapy in end-stage renal failure (ESRF) patients.[1] In HD patients, arteriovenous fistula (AVF) is the most important vascular access route. Vascular access problems are important precursors of mortality and morbidity in HD patients.[2–4] The most important reason for dysfunctions in AVFs in early periods is venous thrombosis due to stenosis developed in anastomosis location in the early periods. In many studies, clinic factors (diabetes mellitus, age, sex, smoking and drug use), biochemical factors (cytokine abnormalities, cholesterol, apolipoproteinemies, factors related to hemostasis) and vascular factors (vein diameter, reduced flow rate, intimal hyperplasia, and atherosclerosis) are found to be related to vascular intervention dysfunction. Also, in some studies point mutations are shown in proinflammatory cytokines related to endothelium dysfunction and vascular wall proliferation in proteins related to the coagulation system and it is stated that this situation is related to thrombosis and atherosclerosis.[4–7] It is shown that inflammation indicators have predictive value for mortality in HD and peritoneum dialysis patients.[8–10] Besides, it is found that inflammation and high serum C-reactive protein (CRP) levels, low serum albumin, low hemoglobin levels, increased

fibrinogen levels are related in HD patients.[9,11] But it is not investigated whether there is a relationship between AVF success and inflammation.

In this study, we aim to study the relationship between AVF success and CRP, albumin and fibrinogen as inflammation markers in patients who were diagnosed with ESRF and had AVF opened for HD in our center.

Material and method

This study was carried out on patients who had AVF opened by specialists who took part in the study, with at least 1 year of specialist experience, in Erzurum Regional Training and Research Hospital Cardiovascular Surgery Service between January 2005 and December 2009. A total of 658 (368 female, 290 male) patients who had AVF opened when going on to HD from pre-dialysis, HD and peritoneum dialysis were investigated for the study. 286 patients whose information on file were complete and had successful or unsuccessful AVFs were included in the study. HD and peritoneum dialysis were performed by HD and peritoneal catheters respectively until AVF maturation was developed and then these catheters were removed. Otherwise, AVF was performed for preparation of HD in pre-dialysis patients. As criteria for inclusion in the study, patients who had AVF opened for the first time and patients with at least 3 months of AVF use were included. Exception criteria were patients who had previous AVF opening, who had vena cava superior syndrome, who had

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incomplete file information, the condition of whom are not known or who couldn't be reached, who had vascular abnormalities hindering AVF success, who had systemic diseases other than diabetes mellitus (DM) and hypertension, hemiplegic patients, post organ transfer patients, who had malignity, who died in the first 3 months after AVF was opened, who had systemic coagulation disorder and whose CRP level was higher than 50 mg/L. Diabetic patients included had a good glycemic control with medical treatment and blood glucose levels of these patients were checked regularly during study. Before AVF was opened in patients, the area of AVF creation was clinically evaluated. All patients had Allen tests. The vascular diameters and blood flow rates of patients, who were clinically considered to have arterial or venous failure, were evaluated by arterial and venous Doppler ultrasonography. AVF was opened in the AVF area (wrist or antecubital region) with suitable arterial and venous vascular structure. After local anesthesia was applied to AVF area, following the skin incision, AVF anastomosis was not carried out in case of vascular abnormalities, insufficient vascular diameter; widespread atherosclerotic thickening in arterial system and AVF was opened in some other suitable region.

Patients starting HD after 4 weeks of waiting period from the first AVF opening and sufficient blood flow at the end of 3rd month were accepted as AVF success. Patients whose AVF was clogged after opening or developed insufficiency in the first 3 months and needed new vascular access routes were evaluated as unsuccessful AVF.

When it comes to demographic characteristics, all cases were evaluated in terms of age, sex and blood pressure. Blood samples were drawn from cases in the morning of the operation after 12 h of night hunger for measuring fasting blood glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, total protein, albumin, CRP, fibrinogen.

Serum total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, total protein, albumin CRP and fibrinogen levels were studied in the central biochemistry laboratory.

The serum CRP level was studied with Beckman Coulter device using CRP IMMAGE kit (Beckman Couter Ireland Inc.). The serum threshold value was accepted as 3.0 mg/L.

The serum albumin level was studied with coagulation Modular-P800 device by using ALB Plus kit (Roche Diagnostics GmbH, Mannheim, Germany). The normal levels were accepted as 3.5–5.2 g/dL.

Fibrinogen was studied on Dade Behring device by using Multifibren U kit (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). The normal values were accepted as 180–350 mg/dL.

Statistical analysis

The differences in average age, weight, total cholesterol, triglyceride LDL-cholesterol and HDL-cholesterol, triglyceride, albumin, CRP and fibrinogen averages were analyzed with student-t test and the differences in terms of sex, hypertension and DM rates were analyzed with χ^2 test. Pearson correlation test was applied to evaluate the correlation between CRP and other parameters. SPSS 11.5 package program was used in statistical analysis and $p < 0.05$ was accepted as meaningful.

Results

A total of 168 of 311 patients who had successful AVF were female and 143 were male and the average age of patients were 54.35 ± 20.4 years (age range 17–92 years). Forty-five of a total of 75 patients who had unsuccessful AVF were female and 30 were male and the average age of patients were 56.36 ± 15.6 years (age range 32–82 years). AVF success rate was found to be 80.56%. The demographic characteristics, AVF opening site and renal failure etiology of successful and unsuccessful AVF groups are presented in Table 1.

While no meaningful difference between average age sex, AVF opening site, catheter area information of successful and unsuccessful groups were not found ($p > 0.05$), DM was found to be statistically meaningfully high ($p < 0.001$) in terms of hypertension existence in the unsuccessful AVF group. The average systolic blood pressure, diastolic blood pressure, serum total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, total protein, albumin CRP and fibrinogen averages of successful and unsuccessful AVF groups and statistical evaluation results are presented in Table 2.

No statistically meaningful difference between the average values of successful and unsuccessful AVF groups, between HDL-cholesterol, LDL-cholesterol, triglyceride and total

Table 1. The demographic characteristics of groups.

Variables	Successful AVF ($n = 311$)	Unsuccessful AVF ($n = 75$)	p Value
Median age	54.35 ± 20.4	56.36 ± 15.6	0.492
Sex			0.562
Male	168 (54%)	45 (60%)	
Female	143 (46%)	30 (40%)	
Median weight (kg)	70 ± 5.4	72 ± 4.9	0.520
BMI (kg/m^2)	21.9 ± 4.6	22.6 ± 4.2	0.101
Diabetic nephropathy	134 (43%)	35 (46%)	0.121
Chronic glomerulonephritis	72 (23.2%)	12 (16%)	0.097
Hypertensive nephropathy	58 (18.7%)	18 (24%)	0.233
Chronic pyelonephritis	31 (9.9%)	6 (8%)	0.104
Obstructive nephropathy	16 (5.1%)	4 (5.3%)	0.088
COPD	77 (24.7%)	18 (24%)	0.309
Smoking	156 (50.1%)	41 (54.6%)	0.289
Median GFR	33 ± 17	38 ± 16	0.411
PAD	29 (9.3%)	8 (10.6%)	0.410
History of MI	14 (4.5%)	3 (4%)	0.250
BUN levels (mg/dL)	110 ± 33	118 ± 30	0.809
Creatinine levels (mg/dL)	4.1 ± 2.5	4.2 ± 2.6	0.597
Mean BP (mm Hg)	136 ± 37	131 ± 33	0.103

COPD, chronic obstructive pulmonary disease; BUN; blood urea nitrogen; GFR, glomerular filtration rate; BP: Blood pressure; PAD, Peripheral arterial disease; MI, Myocardial infarction.

Table 2. Between groups in fistula localization.

AVF opening site	Successful AVF ($n = 311$)	Unsuccessful AVF ($n = 75$)	p Value
Left radiocephalic	138 (44.4%)	27 (37%)	0.310
Left brachiocephalic	56 (18%)	18 (24%)	0.842
Right radiocephalic	77 (24.8)	17 (22.7%)	0.633
Right brachiocephalic	40 (12.9)	13 (17.3%)	0.421

Table 3. The factor affecting in terms of the fistula success.

	Successful AVF (n = 311)	Unsuccessful AVF (n = 75)	p-Value
Systolic blood pressure (mmHg)	124.5 ± 12	114.6 ± 14	**<0.05**
Diastolic blood pressure (mmHg)	76.8 ± 11	68.4 ± 8	**<0.05**
Total Cholesterol (mg/dL)	172.3 ± 44.9	183.5 ± 28.2	>0.05
HDL-cholesterol (mg/dL)	39.6 ± 11.8	42.8 ± 12.5	>0.05
LDL-cholesterol (mg/dL)	114.8 ± 28.3	118.7 ± 28.6	>0.05
Triglyceride (mg/dL)	153.8 ± 82.2	148.6 ± 74.8	>0.05
Total protein (g/dL)	7.33 ± 0.46	6.8 ± 1.02	>0.05
Albumin (g/dL)	3.96 ± 0.4	3.0 ± 0.8	**<0.001**
CRP (mg/dL)	4.6 ± 2.2	18.6 ± 4.3	**<0.001**
Fibrinogen (mg/dL)	348.9 ± 96.8	530.5 ± 172.4	**<0.001**

Notes: *p*-Values of <0.05 were considered significant. HDL, High-density lipoprotein; LDL, Low-density lipoprotein; CRP, C-Reactive protein.

protein levels were found ($p > 0.05$). The low levels of average serum protein and albumin, high CRP, high fibrinogen in unsuccessful AVF group were found to be statistically meaningful ($p < 0.001$, $p < 0.001$, $p < 0.001$) when compared with successful AVF group (Table 3).

While positive correlation between CRP and fibrinogen was found in successful and unsuccessful AVF groups ($r = 0.443$, $p < 0.05$), no correlation was found between other parameters (Table 3).

In successful AVF cases, serum CRP level was found to be high in 25.7%, fibrinogen level was high in 29.5% and albumin level was low in 32.4%. In unsuccessful AVF cases, serum CRP level was found to be high in 69.3%, fibrinogen level was high in 81.3% and albumin level was low in 90.6%.

Discussion

For patients with ESRF, the highest mortality reason is cardiovascular disease in dialysis patients regardless of primary renal disease, age, sex, race and nationality. The cardiovascular death rate in ESRF patients is higher than the general population in all age groups. This situation is especially obvious in young patients.[12] In ESRF patients, cardiovascular disease prevalence is high especially due to increased general atherosclerosis risk factors such as hypertension and DM.

In this study, AVF success was found to be 80.6%. American National Kidney Federation vascular intervention guide states that 1 and 2 year patency can be respectively 70% and 60% for all AVFs.[13] We think that the reason for high AVF success rate is the retrospective characteristic of it, which not all patients were reachable and AVF success was evaluated at the end of the 3rd month. We also think that opening the AVFs in a single center by experienced specialists is an important factor on success although route of dialysis of patients is not important for AVF success.

CRP is a major acute phase reactant which was defined a long time ago. CRF serum concentration increases in cases of inflammation, infection and tissue damage. CRP levels can increase up to 500 to 1000 times the normal level according to the severity of the inflammatory activity. This increase or decrease is due to the secretion or non-secretion of acute phase proteins by hepatocytes.[14,15] In this study, serum CRP level was found to be high in 25.7% of successful AVF

cases and in 69.3% of unsuccessful AVF cases. A positive correlation was found between unsuccessful AVF and serum CRP levels in this study. The physiological function of CRP is not totally explained but it can function as a cleaning factor for endotoxins and opsonized bacterial products. In HD patients, serum levels have increased 5 to 10 times when compared with healthy controls.[16] It is also shown that CRP levels increase meaningfully when compared with healthy control group in the early periods in both HD and peritoneal dialysis patients.[17] It shows direct correlation with plasma CRP concentration, coronary, cerebral and peripheral arterial atherosclerosis.[18,19] The relationship between AVF success and inflammation could not be discussed as there are not sufficient studies in literature.

Fibrinogen is an acute phase reactant like CRP. Its increased levels cause blood coagulation, platelet aggregation and vascular wall changes. It is shown that increased fibrinogen level is an independent cardiovascular risk factor. The relationship between B-fibrinogen G/A 455 polymorphism that is reported to influence plasma fibrinogen concentrations and cardiovascular disease development is disputed. It is possible to decrease the fibrinogen level by decreasing body weight, regular exercise, giving up tobacco use and benzo fibrate. No therapeutic agent that selectively affects fibrinogen levels has been found yet.[20] In this study, serum fibrinogen level was found to be high in 29.5% of successful AVF cases and 81.3% of unsuccessful AVF cases. As there is no study in literature that shows the relationship between AVF success and fibrinogen, our results could not be discussed.

Serum albumin level is a negative phase reactant and decreases in inflammation. Serum CRP and other acute phase reactants are found to be high in chronic renal failure patients and in low albumin levels. In chronic renal failure, serum albumin concentrations decrease. The reason for this is shown to be decreased albumin synthesis in uremia, continuous inflammation, insufficient protein and calorie intake, increased catabolic status.[8] In this study serum albumin level was found to be low in 32.4% of successful AVF cases and in 90.6% of unsuccessful AVF cases. Also, as there is no study in literature showing the relationship between AVF success and albumin, our results are open for discussion.

In this study, a positive correlation between CRP and fibrinogen in both successful and unsuccessful AVF groups was detected. The reason for this is fibrinogen being an acute phase reactant like CRP. Increased fibrinogen level can cause increased coagulation activity, platelet aggregation and vascular endothelial dysfunction and can play a role as an independent risk factor for cardiovascular disease.[20]

In this study, a negative relationship between increased average systolic and diastolic blood pressure and primary AVF success was found. Culp et al.[21] have reported that diastolic blood pressure before dialysis has a great importance in terms of fistula opening. It is proposed that diastolic blood pressure is more important than systolic blood pressure. In the patients who were included in our study, decreased diastolic blood pressure suitable with literature was detected in unsuccessful AVF group. Besides, changes in blood density affecting vascular wall and called Shear stress, changes in pathophysiologic condition which is inversely related with

high blood pressure and correct vascular diameter, affect AVF vein endothelium and cause the secretion of procoagulation and anti-inflammatory mediators. As a result of this, construction and intimal hyperplasia develops in the vein and AVF success is inversely affected.[22,23]

Morena et al.[24] have stated that due to mineral metabolism deterioration in HD patients and due to inflammation, thrombosis risk increases in the group where serum albumin, prealbumin, CRP, calcium, phosphorus, bone type alkaline phosphatase, osteoprotegerin, parathyroid hormone levels increase.

Wali et al.[25] have stated that AVF insufficiency appears as a result of platelet activation and intimal hyperplasia which is caused by the secretion of mediators because of primary and/or secondary defects in vascular endothelium due to mucoid or myxoid degeneration, mural calcification, inflammatory reaction or erythrocyte/macrophage infiltration on the vascular wall.

As a result, it is seen in this study that there is a negative relationship between AVF success and inflammation. We think that the evaluation of inflammation condition when opening AVF is an important factor to increase AVF success. Besides, we are of the opinion that prospective studies should be carried out in wider patient groups to verify this.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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