Native Arteriovenous Fistula in Hemodialysis Patients: The Impact of Clinical, Nutritional, Inflammatory, Atherosclerotic and Genetic Factors on Prognosis

Serkan Kahraman[1], Ender Özden[2], Barbaros Başeskioğlu[2], Gültekin Gençtoy[1], Mustafa Arici[1], İlhan Erkan[2], Mehmet Bakkaloğlu[2], Şali Çağlar[1]

Hacettepe University Faculty of Medicine, Department of Nephrology[1] and Department of Urology[2], Ankara

Introduction

AVF is the recommended vascular access for HD patients by the Dialysis Outcomes Quality Initiative (DOQI) guidelines (1). Numerous studies have established that an AVF provides the lowest complication rate and the longest functional survival (2, 3). However, only one third of HD patients have a functional AVF (4). Lack of protection of superficial, upper extremity veins results in primary loss of chance to have a native AVF. Maintenance of functional AVF has gained great concern in recent years in order to prevent secondary failures. Unfortunately, access related complications account for 16% to 25 % of hospital admissions in HD patients with a cost of over 1 billion $ annually (5, 6).

There are many studies about causes for primary surgical failure in AVF. Secondary failures are not rare but it usually does not attract adequate attention and care. Once the AVF has been placed, it is recommended that serial monitoring of the AVF should be done for long term effective function. Delays in preventing complications may lead to AVF dysfunction. However, little is known about the factors determining long term prognosis of an AVF. This study was designed to evaluate the impact clinical, metabolic, nutritional, genetic, inflammatory, and atherosclerotic factors on AVF survival.

Patients and Methods

One-hundred and eighteen patients (70 men and 48 women, mean age 49±30 years) undergoing maintenance HD three times a week with polysulfone dialyzers were participated in the study. Patients with vascular access other than radiocephalic, brachiocephalic or brachiobasilic autogenous AVF were not included to the study. All patients had been on bicarbonate hemodialysis for 57±53 (mean±SD) months. The mean duration of the dialysis procedure was 240 minutes (range 210 to 270 minutes). Mean blood flow rate was 250 mL/min (range, 200 to 280 mL/min). Dialysate fluid composition was sodium 140 mEq/L, potassium, 1-3 mEq/L, calcium, 3 mEq/L, bicarbonate, 33 mEq/L and acetate, 2 mEq/L. Etiology of renal disease was diabetic nephropathy in 24, glomerulonephritis in 38, nephrolithiasis and pyelonephritis in 15, nephrosclerosis in 22 and unknown and other etiologies in 19 patients. Patients with infectious and inflammatory diseases were excluded. Patients receiving antibiotics, corticosteroids and anti-inflammatory agents were not included to the study. Smoking status and type of anticoagulation was also recorded. Informed consent was obtained for additional blood sampling.

Clinical data for serum levels of C-Reactive protein (CRP), homocysteine, lipids (total cholesterol, LDL-cholesterol, triglyceride, and HDL-cholesterol), apolipoproteins (lipoprotein a, apolipoprotein A1 and apolipoprotein B100), albumin, prealbumin, calcium, phosphorus, parathyroid hormone (PTH) and hemoglobin were collected from medical records of preceding 6 months for each patient and mean value were used for statistical analysis. The body mass index (BMI) was calculated as dry weight in kilograms divided by the square of height in meters. In all subjects, an ultrasound high-resolution B-Mode imaging examination of the common carotid arteries (CCA) with scaning on the longitudinal axis until the bifurcation was performed using an instrument generating a wide band ultrasonic pulse with a middle frequency of 7.5 MHz (Toshiba SSA-270 A, Tokyo, Japan). For each carotid artery, two longitudinal measurements of the intima media thickness (IMT) were obtained and mean value was used for analysis. All examinations were carried out by the same experienced physician, who was unaware of patient history and laboratory findings. Blood pressure recordings were collected by 24-hour ambulatory blood pressure monitoring.

The polymorphism of the interleukin-10 (IL-10) gene promoter region at position –1082, -819 and-592, the tumor necrosis factor- α (TNF-α) gene promoter region at position –308 and –238 and the transforming growth factor- ß1 (TGF-ß1) gene exon 1 region at position –10 and –25 was assessed by the polymerase chain reaction with squence specific primers included in commercially available kits (cyclerplate system).

Number of successful surgical AVF procedures were recorded for all patients and called as “number of AVF”. This number included the last functional AVF and the number of all failed AVFs. In addition, time passed after the first use of surviving last functional AVF was calculated and signed as “survival of present AVF”. In patients with more than one surgical procedure, average life of failed AVFs were also determined and called as “survival of past AVF”. AVF procedures with primary surgical failure were not included.

Correspondence to: Serkan Kahraman, MD, Hacettepe Hastanesi, Nefroloji Bölümü, 06100-Sıhhıye, Ankara-TURKEY, ☎: +90-312- 324 3109, Fax: +90-312- 311 3958
marici@hacettepe.edu.tr

Statistical Analysis

Results were expressed as mean±SEM. Differences in continuous variables among groups were examined by ANOVA. Differences in noncontinuous variables among groups were determined by chi-squared analysis. To determine the correlations between variables Pearsons' test was used. All statistic analyses were conducted using the SPSS software program. A p value of less than 0.05 was considered to be significant.

Results

According to the number of AVF, there were 37 patients with one AVF, 38 patients with 2 AVFs, 19 patients with 3 AVFs and 24 patients with 4 and more AVFs. Table-1 shows clinical and serologic parameters of patients according to number of AVF.

Table-1. Clinical and metabolicparameters in patients (mean±SEM)

	Number of AVF				
Parameter	1 (n=37)	2 (n=38)	3 (n=19)	>4 (n=24)	P
Age (years)	55±10	44±2	43±4	42±2	>0.05
Gender (female/male)	15/22	17/21	5/14	11/13	>0.05
Duration of HD (m)	40±10	52±14	54±15	62±18	>0.05
Survival of last AVF (m)	32±6	37±7	33±11	23±5	>0.05
Average life of failed AVF (m)	42±8	48±9	40±13	32±7	>0.05
BMI (kg/m^2)	23±0.6	22±0.7	21±0.9	21±1.0	>0.05
Hemoglobine (g/dl)	10.7±0.3	10.1±0.2	10.4±0.6	10.3±0.4	>0.05
Ferritin (ng/ml)	336±51	418±55	429±138	524±117	>0.05
Calcium	9.1±0.1	9.3±0.1	8.8±0.2	9.5±0.2	>0.05
Phosphorus	4.3±0.2	5.2±0.3	4.7±0.4	4.1±0.2	>0.05
PTH	96±27	123±37	161±78	69±18	>0.05
Smoke	10/37	12/38	4/19	6/24	>0.05
Diabetes	7/37	9/38	3/19	5/24	>0.05
Heparin (LMW/standart)	11/37	12/38	5/19	6/24	>0.05
C-RP (mg/dl)	1.0±0.2	0.9±0.1	0.7±0.4	0.7±0.1	>0.05
Homocysteine (mg/dl)	23±1.1	22±1.3	26±2.7	20±1.2	>0.05
Total cholesterol (mg/dl)	168±7	146±10	163±16	139±9	>0.05
LDL-cholesterol (mg/dl)	89±5	77±7	90±13	72±8	>0.05
Triglyceride (mg/dl)	174±13	150±13	159±24	137±13	>0.05
HDL-cholesterol (mg/dl)	38±13	38±13	39±12	37±12	>0.05
Lipoprotein a (mg/dl)	27±3.8	25±4.8	24±6.7	24±5.6	>0.05
Apolipoprotein A1 (mg/dl)	104±2.7	102±3.1	105±7.0	101±5.5	>0.05
Apolipoprotein B100 (mg/dl)	78±4.0	74±4.2	75±6.1	80±5.1	>0.05
Albumin (g/dl)	4.1±0.1	4.1±0.2	3.9±0.2	3.9±0.1	>0.05
Prealbumin (mg/dl)	32±1.6	33±1.6	29±2.5	31±2.0	>0.05
CCA IMT (mm)	0.65±0.04	0.62±0.04	0.61±0.03	0.57±0.03	>0.05
24-hr Systolic BP (mmHg)	120±6	128±4	100±9	117±8	>0.05
24-hr Diastolic BP (mmHg)	75±2	84±3	73±5	71±6	>0.05
24-hr Pulse Pressure (mmHg)	45±4	44±2	40±8	46±3	>0.05

None of the parameters were significantly different among patient groups based on AVF number. AVF number and survival was found to be correlated with several clinical and metabolic parameters (Table 2). Clinical factors like presence of diabetes, smoking status and type of anticoagulation have no relation to AVF outcome.

Among genetic factors, IL-10 promoter 819 gene polymorphism has a significant effect on AVF survival. For the present AVF survival, patients with TT genotype were found to have longest AVF survival (CC:33±36, CT:61±53 and TT:80±64 months, $P<0.05$). For the survival of AVF in the past, low producers (T allele) have significantly longer AVF survival than high producers (low producers: 65±54 vs 33±36 months, $p<0.01$). IL-10 promoter 592 gene polymorphism was also found to have an effect on present AVF survival. High producers for IL-10 promoter 592 (C allele) have better present AVF survival (High producers: 24±17 vs low producers: 42±40 months, $p<0.05$). There were not any significant effect of TNF-α promotor 308 and 238 and TGF-β exon 1 10 and 25 gene polymorphisms on AVF prognosis.

Table 2. Correlations of AVF survival and number with other parameters

Correlation	r	p
BMI and AVF number	-0.261	0.018
BMI and present AVF survival	-0.254	0.021
Total cholesterol and past AVF survival	-0.249	0.029
LDL-cholesterol and past AVF survival	-0.245	0.032
Triglyceride and AVF number	-0.246	0.032
Feeritin and present AVF survival	0.342	0.002
Ferritin and past AVF survival	0.278	0.010
Lipoprotein a and past AVF survival	-0.223	0.044
Pulse pressure and past AVF survival	-0.376	0.011
CCA IMT and present AVF survival	-0.374	0.002
CCA IMT and past AVF survival	-0.342	0.002
Duration of HD and AVF number	0.411	0.000

Discussion

The number of patients on maintenance HD is steadily increasing in the world and one of the critical aspect in their management is the creation of a well functioning vascular access. A native AVF is stated as an optimal initial vascular access in HD patients with a placement of a radiocephalic anastomoses (7). As far as longer survival, a native AVF has an advantage with low rates of infectious complications compared to other routes of vascular accesses (8). In addition, among the vascular access types autogenous AVF has the most economic option for HD patients. Unfortunately, incidence of primary surgical failure is high ranging from 10% to 30% during the creation of native AVF (9). Many studies were carried out about the factors associated with primary AVF failure. Diabetic patients, elderly, women, patients with peripheral vascular disease and patients with premature access puncture have more chance for primary failure. After successful establishment of an AVF, there is an urgent and compelling need to reduce the rate of dysfunction and maintaining AVF patency for efficient HD. Survival of radiocephalic AVF are reported to be 53 % and 45 % for 5 and 10 years respectively (9,10). However, the impact of factors resulting in susceptibility to development of AVF dysfunction is presently under intense scrutiny and in particular, interest has focused on clinical, nutritional, atherosclerotic, inflammatory and genetic determinants. So far only limited information is available on the prognosis of native AVF.

In a recent study, Grandaliano and coworkers found that smoking, erythropoietin dose, elevated mean plasma PTH level and high titer of anti-cytomegalovirus antibody significantly increased the risk of AVF dysfunction (11). In analysis of more than 6400 HD patients, Pisoni and coworkers stated that AVF use was significantly associated with younger age, male gender, lower BMI, non-diabetic status, lack of peripheral vascular disease and absence angina (4). But they did not give any information about the survival of the AVF. Our study is the first report for the evaluation of association between AVF prognosis and clinical, nutritional, inflammatory, atherosclerotic and genetic factors. Our results did not show any effect of gender, smoking status, diabetes, uncontrolled blood pressure and type of anticoagulation. However, as expected serological risk markers for the development of atherosclerotic vascular disease and atherosclerosis itself have been found to be significantly correlated with AVF survival. In addition there may be some genetic determinants on AVF prognosis. Inconsistent with our findings, Obialo and coworkers (12) were found that survival rate of AVF was higher in younger, male and nondiabetic patients in an African American group of Hd patients.

In conclusion, autogenous AVF is considered the first choice vascular access in terms of lower morbidity, cost and complication, and higher survival rates compared to other vascular access types. In last years, attention has been focused on maintenance of functional AVF patency. According to the results of recent studies and our findings, some clinical factors may be responsible for long term failure of AVF, although underlying mechanisms remains to be clarified with larger prospective analyses. Today, for each individual center, monitoring and salvage of failing is important for achievement of successful AVF outcomes. While the protection against preventable causes of AVF dysfunctions are considered, methods for improvement of quality of AVF care should gain priority in HD units.

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