

Arterial Stiffness and its Related Factors in Patients on Hemodialysis

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ABSTRACT

Objective: To evaluate the prevalence of arterial stiffness in patients on hemodialysis and related factors that aggravate the condition.

Study Design: Prospective-cohort study.

Place and Duration of Study: Department of Nephrology, Firat University Hospital, Turkey, from August to October 2019.

Methodology: Central blood pressure (BP), augmentation index (Alx) and aortic pulse wave velocity score (PWVs) were assessed using the mobil-o-graph pulse wave velocity system. Increased arterial stiffness (AS) was defined by the aortic PWV of >10 m/s.

Results: The mean PWVs were 8.14 ± 2.39 m/s the mean Alx was 21.23 ± 11.58 m/s, and AS was 33.7% in hemodialysis patients. Systolic blood pressure, pulse rate, pulse pressure, central systolic blood pressure, older age, HD vintage, HT vintage, creatinine, CRP and neutrophil leukocyte ratio (NLR), were related factors with AS. Multivariate linear regression analysis showed that systolic blood pressure ($\beta=0.322$; 95% CI: 0.007-0.042; $p = 0.006$), and age of patients ($\beta=0.787$; 95% CI: 0.095-0.127; $p<0.001$) were independent determinants of PWVs.

Conclusion: The frequency of AS was 33.7% in hemodialysis patients without a history of cardiovascular disease. Increased age and systolic blood pressure were independent factors affecting PWV. Effective blood pressure control therapy can reduce AS in hemodialysis patients.

Key Words: Pulse wave velocity, Arterial stiffness, Cardiovascular disease, Systolic blood pressure, Hemodialysis.

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INTRODUCTION

Chronic kidney disease (CKD) is an important health problem today due to its high incidence and prevalence. Chronic renal failure is defined as a chronic and progressive metabolic-endocrine dysfunction that develops as a result of a decrease in glomerular filtration value and failure to adjust the fluid-solute balance of the kidney. The prevalence of chronic kidney disease is estimated to be between 8% and 16% worldwide.¹

Cardiovascular morbidity and mortality increase in end-stage renal disease (ESRD). ESRD is associated with increased mortality compared to the normal population, and more than half of deaths are due to cardiovascular disease (CVD). In ESRD patients, CVD increases 10-30-fold compared to the normal population.²

It is important to treat major risk factors (diabetes mellitus, hypertension and dyslipidemia) as well as non-traditional risk factors in order to reduce CVD mortality in patients with CKD. Endothelial dysfunction, vascular calcification and AS are non-traditional risk factors, closely associated with CVD. Arterio sclerosis is closely related to AS. As a result of atherosclerosis, it causes important clinical outcomes such as increased stiffness of the large arteries, increased systolic blood pressure and pulse pressure, left ventricular hypertrophy, and decreased coronary perfusion.³ Today, AS, which is a marker of arterial disease, can be measured with PWV, which is a non-invasive technique. Large artery stiffness can be evaluated with PWV method. The previous studies have shown that there is a relationship between PWV score (PWVs) and high cardiovascular risk.

It has been reported that AS and arterial calcification increase, so it may contribute to the development of CVD.⁴ The current study aimed to investigate the prevalence of AS and the factors related with AS in ESRD patients, treated with hemodialysis.

METHODOLOGY

This cross-sectional study was conducted in the Hemodialysis Unit of tertiary university hospital from August to October 2019.

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A total of 86 patients, with undergoing hemodialysis for ESRD, were included in the study. Patients, aged over 18 years, registered in the hemodialysis unit, having end-stage renal failure for at least one year, and undergoing hemodialysis treatment three times a week, were included in the study. Patients with instable hemodynamic parameters, chronic atrial fibrillation, severe aortic stenosis, peripheral artery disease, recent myocardial infarction, and cerebrovascular event within last three months, decompensated heart failure, acute infection, morbid obesity, and bilateral arteriovenous (AV) fistula, were excluded from the study.

The socio-demographic characteristics of the participants were obtained with the questionnaire form prepared by scanning the literature data. Their demographic characteristics, included age, gender, marital status, educational level, comorbid diseases (hypertension and diabetes mellitus), smoking habits, duration of HT and hemodialysis. The heights of the patients were measured with a standing and 0.1 cm sensitive accurate wall mounted height meter. The dry weight of the patients were measured with sensitive digital scale. Body mass index (BMI) was calculated using the conventional Quetelet formula (kg/m^2).

Blood samples were drawn in the fasting condition from all patients. All blood samples were collected before the hemodialysis period. Hemogram, blood urea nitrogen (BUN), creatinine (Cr), parathyroid hormone (PTH), lipid profile, C-reactive protein (CRP), Calcium (Ca) and Phosphate (P) levels were evaluated in blood samples. The neutrophil-lymphocyte ratio was calculated by dividing the neutrophil counts of all patients by lymphocyte counts.

For determination of central BP, PWV and augmentation index (Alx), the mobil-o-graph (Stolberg, Germany) was used. It is non-invasive gold standard commercially available brachial-cuff-based oscillometric device for the assessment of central vascular pressures and aortic PWV score. Its BP detection unit has been validated in accordance with the European Society of Hypertension international protocols. Simultaneous brachial BP, PWV, and Alx measurements are provided by the oscillometric mobil-o-graph arteriograph device. The derived PWV is an indirect estimate of large-artery stiffness based on mathematical models incorporating several parameters derived from pulse wave analysis and wave-separation analysis as previously published.⁵ The first valid oscillometric measurement was used in the analysis. Brachial artery systolic and diastolic BP were measured at the non-AV fistula arm of HD patients using a validated aneroid sphygmomanometer to compare mobil-o-device's systolic and diastolic blood pressure measurements. Pulse rate was measured simultaneously with AS measurements. Pulse pressure was estimated as the difference between systolic and diastolic blood pressures. Before starting the measurements, the patients were informed about the mobil-o-graph device and the measurement. The patients were asked not to move or speak during the measurement. All measurements were performed before hemodialysis, in a quiet room at a stable temperature ($20 \pm 2^\circ\text{C}$), and after resting the patients in supine

position for at least 10 minutes. All measurements were made from the non-fistula arms of the patients. The arm circumference of the participants was measured and size appropriate cuff was determined. Increased AS was defined by the aortic PWV of >10 m/s proposed in the 2018 ESC Guidelines. According to the guideline, PWV scores above the threshold are associated with increased cardiovascular risk.⁶

Statistical analysis of the datas was performed by IBM SPSS 22 statistics package programme. The distribution of continuous data was analysed using the Shapiro-Wilk test. Descriptive data are given as mean \pm SD for continuous variables with normal distribution, median (quartile 1-quartile 3) for continuous data with non-normal distribution, and number (n) and percentage (%) for categorical variables. For comparison of two independent groups, Student-t-test was used for normal distributed continuous data, Mann-Whitney U-test for non-normal distributed continuous data. Pearson Chi-square test was used to analyse categorical data, in relation between of two continuous data. Considering the distribution of continuous data, Pearson correlation analysis or Spearman correlation analysis was used to examine the relationship between continuous variables. Multivariate linear regression analyses were performed to determine predictors of arterial stiffness parameters. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 86 hemodialysis patients were included in the study. The mean age was 53.80 ± 16.98 years; and 66.3% ($n=57$) of the participants were males. In the study cohort 62.8% ($n=54$) had hypertension and 29.1% ($n=25$) had diabetes mellitus; 16.3% ($n=14$) of patients declared smoking. The mean PWV score of the patients were 8.14 ± 2.39 m/s and the mean Alx score was 21.23 ± 11.58 m/s. The rate of patients with AS (PWV >10 m/s) were 33.7% ($n=29$). The age was significantly higher in the AS group ($p < 0.001$). Arterial stiffness was significantly higher in married ($p=0.001$), hypertensive ($p=0.024$) and diabetic patients ($p=0.022$). The relationship between AS and socio-demographic characteristics of the participants is presented in Table I.

Systolic blood pressure ($p=0.006$), pulse pressure ($p < 0.001$), creatinine ($p < 0.001$), ferritin ($p=0.029$), and HT vintage ($p=0.011$) were significantly higher in AS. Comparison of AS with blood pressure and biochemical parameters of patients is shown in Table II.

Bivariate correlation analysis demonstrated a significant association between PWV and patient age, systolic blood pressure, pulse, pulse pressure, central systolic BP, HD vintage, HT vintage, creatinine, Crp and NLR (Table III).

Multivariate linear regression analysis showed that systolic blood pressure ($\beta=0.322$; 95% CI: 0.007-0.042; $p=0.006$) and age of patients ($\beta=0.787$; 95% CI: 0.095-0.127; $p < 0.001$) were independent determinants of PWV (Table IV).

Table I: Baseline characteristics of patients and relation with arterial stiffness.

Characteristics	PWV ≤10 (m/s) n (%)	PWV >10 (m/s) n (%)	Total (n=86) n (%)	p-value
Age (year)	46.23±14.44	68.69±10.59	53.80 ± 16.98	<0.001
Gender				
Female	18 (31.6)	11 (37.9)	29 (33.7)	0.556
Male	39 (68.4)	18 (62.1)	57 (66.3)	
Marital status				
Single	23 (40.4)	2 (6.9)	25 (29.1)	0.001
Married	34 (59.6)	27 (93.1)	61 (70.9)	
Educational status				
Below high school	36 (63.2)	24 (82.8)	60 (69.8)	0.061
High school and above	21 (36.8)	5 (17.2)	26 (30.2)	
Income perception				
Insufficient	28 (49.1)	13 (44.8)	41 (47.7)	0.706
Sufficient	29 (50.9)	16 (55.2)	45 (52.3)	
Hypertension diseases				
Have not	26 (45.6)	6 (20.7)	32 (37.2)	0.024
Have	31 (54.4)	23 (79.3)	54 (62.8)	
Hypertension drug use status				
Does not use	35 (61.4)	17 (58.6)	52 (60.5)	0.803
Use	22 (38.6)	12 (41.4)	34 (39.5)	
Diabetes mellitus diseases				
Have not	45 (78.9)	16 (55.2)	61 (70.9)	0.022
Have	12 (21.1)	13 (44.8)	25 (29.1)	
Tobacco use				
Does not use	45 (78.9)	27 (93.1)	72 (83.7)	0.093
Use	12 (21.1)	2 (6.9)	14 (16.3)	
Aortic pulse wave velocity (PWV) and augmentation index (Alx) scores				
PWV (m/s) [mean±sd]	8.14±2.39			
Alx (%) [mean±sd]	21.23±11.58			
PWV (m/s)		n (%)		
No arterial stiffness (PWV ≤10 m/s)		57 (66.3)		
Arterial stiffness (PWV >10 m/s)		29 (33.7)		
Total		86 (100.0)		

Table II: Comparison of blood pressure and biochemical parameters in arterial stiffness and non-stiffness groups.

Variables	No arterial stiffness (n=57)	Arterial stiffness (n=29)	p-value
BMI (kg/m ²)	23.54±4.94	24.94±5.83	0.248
Brachial BP			
Systolic BP (mmHg)	117.51±28.48	140.76±37.81	0.006
Diastolic BP (mmHg)	78.56±16.91	77.45±18.61	0.781
Pulse Pressure (mmHg)	40.42±13.38	63.31±24.87	<0.001
Central BP			
Systolic BP (mmHg)	121.89±19.08	133.45±28.07	0.027
Diastolic BP (mmHg)	78.89±14.38	80.00±16.34	0.748
BUN (mg/dl)	147.02±43.57	141.64±34.10	0.571
Creatinine (mg/dl)	8.96±2.97	7.24±1.28	<0.001
Calcium (mg/dl)	8.64±0.84	8.70±0.88	0.742
Phosphate (mg/dl)	5.22±1.36	4.78±1.21	0.147
PTH (pg/ml)	434.00 (260.90-617.00)	363.70 (165.95-603.15)	0.313
T. Cholesterol (mg/dl)	163.15±42.71	172.22±35.38	0.343
Triglycerides (mg/dl)	173.87±80.57	199.33±116.80	0.314
HDL (mg/dl)	33.00 (26.00-41.40)	31.90 (25.70-41.10)	0.828
LDL (mg/dl)	88.43±35.32	98.41±30.43	0.213
Uric acid (mg/dl)	6.20±1.36	5.88±1.01	0.287
Ca×PO ₄	45.18±12.23	41.47±11.50	0.187
NLR	2.95±1.19	3.48±1.24	0.059
Crp (mg/dl)	5.30 (3.13-12.10)	8.58 (3.33-18.28)	0.115
Ferritin (µg/L)	423.00 (239.00-1010.00)	679.00 (434.78-1142.98)	0.029
HD vintage (year)	5.00 (2.00-7.50)	4.00 (1.00-6.00)	0.115
HT vintage (year)	4.00 (0.00-12.50)	10.00 (4.50-20.00)	0.011

Table III: Correlation between PWV score and continuous variables.

Variables	PWV		Variables	PWV	
	r	p		r	p
Systolic BP	0.432	<0.001	T. Cholestrole	0.091	0.417
Diastolic BP	0.077	0.480	HDL	0.129	0.247

Pulse/min	-0.278	0.009	LDL	0.130	0.245
Pulse Pressure	0.575	<0.001	Triglycerids	0.004	0.971
AlX	0.021	0.849	Calcium	0.041	0.713
Central SBP	0.339	0.001	Phosphate	-0.110	0.322
Central DBP	0.105	0.337	PTH	-0.092	0.407
Age	0.800	<0.001	Ferritin	0.170	0.124
HD vintage (year)	-0.248	0.021	Crp	0.277	0.011
HT vintage (year)	0.319	0.003	BMI	0.181	0.095
BUN	-0.082	0.459	Ca*PO ₄	-0.092	0.406
Creatinine	-0.401	<0.001	NLR	0.300	0.006
Uric acid	-0.162	0.145			

Table IV: Multivariate linear regression analysis to determine independent predictors of PWV.

Variables	PWV (m/s) $R^2=0.856$, $p<0.001$		
	Coefficient	95% CI	p-value
Systolic BP	0.322	0.007-0.042	0.006
Pulse	0.092	-0.001-0.033	0.064
Pulse pressure	0.092	-0.013-0.033	0.369
Central SBP	0.050	-0.008-0.019	0.454
Age	0.787	0.095-0.127	<0.001
HD vintage (year)	-0.008	-0.052-0.044	0.867
HT vintage (year)	0.094	-0.001-0.056	0.057
Creatinine	-0.026	-0.117-0.070	0.621
Crp	0.087	0.000-0.009	0.069
NLR	-0.001	-0.196-0.190	0.977

DISCUSSION

The current study was found the mean PWV score of 8.14 ± 2.39 m/s. AS prevalence was found 33.7% in study population. In three different studies previously reported, the mean PWC scores was 10.5, 9.4 and 8.80, respectively.⁷⁻⁹ The mean PWV score obtained in the current study was similar to the literature data; which suggested that the study measurements were reliable. According to current study, 33.7% of hemodialysis patients had AS. Thanakitcharu *et al.* reported the prevalence of AS in 59% of patients with chronic renal failure,¹⁰ and Utescu *et al.* reported prevalence of AS in 43% among hemodialysis patients.⁹ The prevalence of AS in current study was found to be lower than previous studies among hemodialysis patients. Patients with known cardiovascular disease were excluded from current study, so AS prevalence may be lower than literature data.

The most of previous studies reported that there was a positive relation between AS and all-cause or cardiovascular mortality.¹¹⁻¹⁵ Therefore, it is important to determine the factors affecting AS. Several estimated associated factors of AS were confirmed by the present study. Some factors found to be significantly associated with AS included aging, diabetes mellitus, hypertension, pulse pressure, serum creatinine, ferritin and duration of hypertension. In similar studies among hemodialysis patients, factors affecting AS support this study findings.^{9,10} Age, diabetes mellitus, hypertension, and the duration of hypertension are data expected to affect vascular stiffness. In clinical practice, these factors are reported as non-modifiable risk factors in the European Guidelines on cardiovascular disease prevention.¹⁵ The current study data showed that high serum creatinine, ferritin and pulse pressure were associated with AS. These

factors are important because these are modifiable factors, which can reduce AS by fight against these factors. Ha *et al.* reported that ferritin levels were independently correlated with AS.¹⁶ Lin *et al.* reported that serum ferritin associated with the progressive AS, especially when serum ferritin >500 ng/mL in hemodialysis patients.¹⁷ The current study results showed that ferritin level is important in reducing AS. In patients with hemodialysis, especially keeping ferritin levels below 500 ng/dl may contribute to reducing AS. A recent study, which was conducted with 1,290 untreated patients by Mourad *et al.*, showed that plasma creatinine level is associated with arterial stiffness.¹⁸ Kharlamova *et al.* reported that creatinine levels were independently correlated with arterial stiffness.¹⁹ The data obtained in this study were similar with the literature. In this context, the present researchers could reduce AS by controlling serum creatinine with effective hemodialysis programmes.

The predictivity of the PVW score for cardiovascular events had evaluated in a meta-analysis study by Ben-Shlomo *et al.* As a result of that study, it was reported that the PVW score could be useful in better determining the population with high risk of cardiovascular disease and in the management of aggressive risk factors.²⁰ In another study, Vlachopoulos *et al.* reported that the high PWV score is an important determinant of cardiovascular events and deaths from all causes. An increase in aortic PWV score of 1 m/s or of one SD has been associated with a 10% to 40% increase in the risk of cardiovascular events and all-cause death.³ In this study, systolic blood pressure, pulse rate, pulse pressure, central systolic blood pressure, age, duration of hemodialysis, duration of HT, creatinine, CRP and NLR found to be associated with PWV. In multivariate linear regression analysis model, age and systolic blood pressure were significantly related

with PWV independent of other factors. In many studies, age has been reported as a risk factor for AS and high PWV score.⁸⁻¹⁰ Age is also a non-modifiable risk factor for cardiovascular disease.¹⁵ The effect of age factor on PVW and arterial stiffness was an expected finding.

The most important finding obtained in this study is the determination of high blood pressure as an independent factor on PWV and AS. In many studies, the relationship between high blood pressure and AS was similar to this data.^{7,9,10,21} High blood pressure is a modifiable risk factor for AS. Laurent *et al.* reported that AS was an independent risk factor for cardiovascular mortality.¹¹ This data suggests that AS, risks of cardiovascular disease and cardiovascular mortality may be reduced by effective blood pressure control. Other modifiable risk factors affecting PWV score in this study were pulse pressure, pulse rate, central systolic pressure, creatinine, CRP and NLR. In the literature, creatinine, pulse pressure, central systolic blood pressure and heart rate were reported to be associated with PWV.^{9,10,22} It has been reported in many studies that the increase in neutrophil-leukocyte ratio associated with systemic inflammation is positively correlated with the increase in the PWV score.^{23,24} Similar to the literature, NLR and CRP, which is an indicator of inflammation, were associated with PWV score in this study. The findings of this study were supported by literature data. In future studies, it may be focused on modifiable factors affecting AS and PWV, because the patients can be protected from cardiovascular morbidity and mortality by reducing modifiable risk factors.

There are several potential limitations of our study. First, because of the cross-sectional design of this study, the data do not directly indicate a cause-effect relationship. The small number of patients may be insufficient to determine the factors affecting AS and PWV score. Another limitation of the study was that some data (duration of HT and DM, duration of hemodialysis, smoking, etc.) were obtained, based on patient declaration.

CONCLUSION

The prevalence of AS in hemodialysis patients was 33.7% in this study. Systolic blood pressure, pulse rate, pulse pressure, central systolic blood pressure, age, duration of hemodialysis, duration of HT, creatinine, CRP and NLR found to be associated with PWV. PWV-related factors except age, HT duration, and HD duration were found to be modifiable factors. Age and blood pressure were found to be related to PWV, independent of other factors. The data of this study once again highlighted the importance of preventing modifiable risk factors in reducing cardiovascular mortality and morbidity.

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

ETHICAL APPROVAL:

The study protocol was approved by the Ethics Committee of Firat University (Number:15-17, Date: 17/10/2019).

PATIENTS' CONSENT:

Written informed consents were obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

AUTHORS' CONTRIBUTION:

BY: Data collection, design, compiling, and discussion, conceived the project, and authored the manuscript.

MD: Contributed to collecting and analysing data, and discussion.

EO: Contributed to collecting data and discussion.

MOK: Contributed to collecting data, statistics and analysing data.

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