

THE EFFECT OF ARTERIAL STIFFNESS ON DISEASE PROGRESSION AND MORTALITY IN CHRONIC KIDNEY PATIENTS

KRONİK BÖBREK HASTALIĞINDA ARTERİYEL SERTLİĞİN BÖBREK PROGRESYONU VE MORTALİTE ÜZERİNE ETKİSİ

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Cite this article as: Erkus E, Karakose S, Ozkan Kurtgoz P, Gencer V, Guney I. The effect of arterial stiffness on disease progression and mortality in chronic kidney patients. J Ist Faculty Med 2021;84(2):214-20. doi:10.26650/IUITFD.2020.0060

ABSTRACT

Objective: Pulse wave velocity (PWV) is frequently used for arterial stiffness assessment in chronic renal disease (CRD). There are very few studies in the literature about the relationship between arterial stiffness and renal progression leading to mortality in CRD. Herein, we searched the relationship between arterial stiffness, and progression of kidney disease, leading to mortality in CRD patients.

Methods: 194 stage 3-5 CRD patients were included in the study. The patients were followed at least four years. The primary endpoints were initiation a renal replacement treatment and death. PWV was measured using the Mobil-O-Graph NG arteriography device.

Results: The study was completed with 194 patients within four years. During this period, out of 194 patients, 89 needed a renal replacement treatment (72 hemodialysis patients, 17 renal transplantation) and 15 died. Ninety of them are still being followed as predialysis CKD patient in the nephrology outpatient clinic. Increased PWV was detected as an independent predictive marker of mortality.

Conclusion: Our study demonstrated that PWV might be an independent predictor of mortality. In this sense, monitoring the PWV and taking measures in this direction can reduce the effect of arterial stiffness on mortality.

Keywords: Arterial stiffness, mortality, chronic renal disease

ÖZET

Amaç: Nabız dalga hızı (NDH), vasküler kalsifikasyon tanısında kullanılan elektron ışını bilgisayarlı tomografi (EIBT) ile korelasyon gösterir ve kronik böbrek hastalığında (KBH) arteriyel sertlik değerlendirmesi için sıklıkla kullanılır. Literatürde KBH' da arteriyel sertlik ile böbrek progresyonu ve mortalite arasındaki ilişki hakkında çok az çalışma vardır. Bu çalışmada KBH'da arteriyel sertlik ile böbrek hastalığının progresyonu ve mortalite arasındaki ilişkiyi araştırdık.

Gereç ve Yöntem: Aralık 2014-Haziran 2015 tarihleri arasında nefroloji polikliniğine başvuran evre 3-5 kronik böbrek hastaları çalışmaya alındı. Hastalar en az dört yıl takip edildi. Birincil sonuçları bir renal replasman tedavisi başlanması (renal transplantasyon, hemodiyaliz veya periton diyalizi) ve ölümdür. Nabız dalga hızı (NDH) Mobil-O-Graph NG (Stemberg Germany Stolberg Germany) arteriograf cihazı kullanılarak ölçüldü.

Bulgular: Çalışma 4 yıl boyunca düzenli kontrole gelen 194 hasta ile tamamlandı. Bu süre zarfında 194 hastanın 89'unda renal replasman tedavisi (72 hemodiyaliz, 17 renal transplantasyon) gerekti ve 15'i öldü. Doksan hasta nefroloji polikliniğinde prediyaliz KBH'sı olarak izlenmektedir. Artan NDH, mortalitenin bağımsız bir prediktif belirteci olarak tespit edildi.

Sonuç: Bu çalışmada, NDH'deki artışın mortalitenin bağımsız bir belirteci olduğunu bulduk. Bu anlamda, NDH'nin izlenmesinin ve bu yönde önlemler alınmasının arteriyel sertliğin mortalite üzerindeki etkisini azaltabileceğini gösterdik.

Anahtar Kelimeler: Arteriyel sertlik, mortalite, kronik böbrek hastalığı

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Submitted/Başvuru: 14.05.2020 • **Revision Requested/Revizyon Talebi:** 20.05.2020 •

Last Revision Received/Son Revizyon: 12.08.2020 • **Accepted/Kabul:** 09.09.2020 • **Published Online/Online Yayın:** 05.03.2021



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INTRODUCTION

Chronic renal disease (CRD) is a significant cause of morbidity and mortality and its prevalence varies between 11-13% worldwide (1). Arterial stiffness demonstrates resistance to the expansion of the vessel wall which is a flexible tissue. The arterial system, which has the ability to expand, contains the blood transmitted by the systole of the heart and thus ensuring the blood reaches the tissues with a smooth flow. Arterial elasticity plays a crucial role in cardiovascular physiology in terms of sustained oxygen and nutrient requirements to the tissues.

It is known that cardiovascular problems are more common in individuals with CRD and causes the reduction of life expectancy (2). Early and accelerated atherosclerosis is a substantial cause of increased cardiovascular mortality in this group of patients (3). Increased arterial stiffness occurs before atherosclerosis and is considered a risk factor for atherosclerosis (4). Even mild renal dysfunction is considered a medical condition leading to an increased cardiovascular risk (2). Increased inflammatory status starting from the early stages of CRD accelerates the coagulation cascade and atherosclerosis by causing platelet activation (3). This increased inflammatory process in CRD contributes to the process of atherosclerosis and endothelial dysfunction and plays an important role in the increase in cardiovascular mortality (4).

Pulse wave velocity (PWV) measurement is considered to be the most common, simple, reproducible, and noninvasive stiffness assessment method (5). PWV is also frequently used to detect the arterial stiffness in patients with renal insufficiency (6). There are few studies in the literature on the effect of arterial stiffness on renal progression and mortality in CRD.

The aim of this study was to determine the relationship between arterial stiffness and progression of chronic renal disease and mortality in patients with CRD.

MATERIALS AND METHODS

This was a prospective observational study conducted at the University of Health Sciences, Konya Research, and Training Hospital. CRD patients (Stage 3-5) who were admitted to the nephrology outpatient clinic between December 2014-June 2015 were included in the study. At the first admission, the patients who were over 18 years old, not on a renal replacement treatment, without a history of cardiovascular disease or any signs of active infection were included in the study.

Age, gender, height, weight, waist circumference, body mass index, blood pressure, and smoking status of the patients were recorded at the beginning of the study. Blood pressure values of all patients were measured and

recorded using a calibrated sphygmomanometer with an appropriate size cuff. Guidelines of the European Society of Hypertension were applied during clinical blood pressure measurements (7). Body mass index (BMI) was calculated by dividing weight by the square of the height. Waist and hip circumference were measured according to the recommendations of World Health Organization for obesity (8). Serum urea, creatinine, hemoglobin, sodium, potassium, phosphorus, calcium, albumin, parathormone (PTH), ferritin, total cholesterol, triglyceride, HDL, LDL, CRP, uric acid, creatine and protein in spot urine and venous blood gas values were recorded from routine laboratory tests. The eGFR was calculated using MDRD (Modification of Diet in Renal Disease) formula (9).

PWV was measured using Mobil-O-Graph NG (Stemberg Germany Stolberg Germany) arteriography device. This device allows the measurement of all arterial stiffness parameters from the upper extremity through the brachial artery by the oscillometric method. The measurements were made after resting for at least five minutes in a room away from external stimuli, which was reserved for the study. In the last hour before the procedure, patients were asked not to take stimulants such as tobacco and coffee.

The patients were followed at least four years. The primary endpoints were renal replacement treatment (renal transplantation, hemodialysis or peritoneal dialysis) and death. We investigated the relationship between PWV and poor renal outcomes.

Ethical issues

The research followed the Tenets of the Declaration of Helsinki. Informed consent was obtained, and the work was accepted by the University of Health Sciences, Konya Research, and Training Hospital ethics committee. The local ethics committee approved the study protocol (approval no: 48929119/774/28-25). This research has been supported by the University of Health Sciences, Konya Research, and Training Hospital.

Statistical analysis

The analysis of the study was performed by using SPSS 22.0 (IBM) software. The Kolmogorov-Smirnov test was used to determine whether the data was normally distributed or not. The results are given as mean with standard deviation for normal distribution and as median (minimum-maximum) for skewed distribution. In pairwise comparisons, the T-test was used for normal distributions and the Mann Whitney-U test was performed for skewed distributions. The independent predictors of end-stage renal disease (ESRD) and mortality were determined by performing Cox-regression (Backward Stepwise) analysis. The independent predictors were those with $P < 0.05$ in binary comparisons. Type-I error value was taken as 5% in all analyzes and P values less than 0.05 were accepted as statistically significant.

RESULTS

The study was completed with 194 patients as 39 patients did not come to regular control within four years. During this period, out of 194 patients, 89 needed renal replacement treatment (72 hemodialyses, 17 renal transplan-

tation) and 15 died. Ninety patients were followed in the nephrology polyclinic as predialysis CRD (Table 1). The underlying etiologies of chronic renal diseases of the patients were as follows; hypertension (HT; 38 patients, 19.6%), glomerulonephritis (GN;20 patients, 10.3%), diabetes mellitus (DM;58 patients, 29.9%), Polycystic kid-

Table 1: The demographic and laboratory results

Variables	non-ESRD (n=90)	ESRD (n=89)	non-mortality (n=179)	Mortality (n=15)
Age (year)	57.5 (23-83)	57 (19-81)	57 (19-83)	64 (37-82)^B
Gender (M/F)	36 (40%)/54 (60%)	49 (55.1%)/40 (44.9%)^A	94 (52.5%)/85 (47.5%)	6 (40%)/9 (60%)
Smoking (Yes /No)	7 (7.8%)/83 (92.2%)	13 (14.6%)/76 (85.4%)	20 (11.2%)/159 (88.8%)	1 (6.7%)/14 (93.3%)
Follow up time (month)	49 (25-52)	19 (1-50)^A	45 (1-52)	23 (1-46)^B
BMI (kg/m ²)	30.4 (19.1-49.8)	28.5 (13.5-53.1)	29.3 (13.5-53.1)	30 (19.2-51.0)
Waist circumference (cm)	98.9±14.9	96.4±15.8	97.7±15.4	101.3±18.4
SBP (mmHg)	130 (105-172)	142 (82-209)^A	136.5 (82-149)	151 (126-176)^B
DBP (mmHg)	87 (47-117)	94 (52-141)^A	90 (47-141)	90 (66-107)
DM (Yes/No)	17 (18.9%)/73 (81.1%)	30 (33.7%)/59 (66.3%)^A	47 (26.3%)/132 (73.7%)	11 (73.3%)/4 (26.7%)^B
Baseline eGFR (ml/min/1.73 m²)	44.4 (15.6-60.1)	22.3 (11.6-48.8)^A	34.3 (11.6-60.0)	35.9 (18.1-56.4)
Albumin (g/dl)	4.1 (1.6-4.7)	3.9 (1.8-4.5)^A	4.0 (1.6-4.7)	3.6 (2.9-4.2)^B
Hb (g/dl)	13.3±1.9	12.1±1.8^A	12.7±2.0	12.4±1.6
Uric acid (mg/dl)	7 (2.8-11.1)	7 (3.9-10.9)	7.0 (2.8-11.1)	6.3 (4.9-12.4)
Potassium (mEq/L)	4.7 (3-6.5)	4.7 (3.6-7.2)	4.7 (3-7.2)	5 (3.3-6)^B
Calcium (mg/dl)	9.3 (7.5-10.6)	8.7 (4.5-9.9)^A	9.0 (4.5-10.6)	9 (8.5-10.1)
Phosphorus (mg/dl)	3.4 (1.9-4.9)	3.8 (2.2-13.7)^A	3.5 (1.9-13.7)	3.8 (2.6-5)
PTH (ng/L)	113.3 (10.3-799)	219.8 (40-785)^A	155.4 (10.3-799)	110.7 (20.8-489)
Total cholesterol (mg/dl)	204 (120-318)	210 (94-415)	205 (94-415)	201 (162-377)
LDL (mg/dl)	127±37.8	135 (48-278)	132.1±41.5	129.2±43.1
HDL (mg/dl)	41 (25-74)	38 (22-93)	40 (22-93)	47.5 (29-62)^B
Triglycerides (mg/dl)	150 (42-679)	159 (40-634)	153 (40-679)	143 (67-458)
CRP (mg/l)	3.54 (3.28-201)	3.54 (3-201)	3.44 (3.28-201)	6.01 (3.28-28.2)
PWV (m/s)	8.2±1.8	8.6±1.9	8.39±1.82	9.94±2.13^B
Pulsepressure (mmHg)	44.5 (28-93)	48.5 (23-94)	47 (23-94)	56 (36-89)^B
Proteinuria (g/day)	0.71 (0.07-12.72)	2.94 (0.43-13.92)^A	1.42 (0.07-13.92)	1.84 (0.11-6.62)

^Ap<0.05 as compared with non-ESRD ^Bp<0.05 as compared with non-Mortality; LDL:low density lipoprotein; HDL:High density lipoprotein; BMI:Body mass index; SBP:Systolic blood pressure; DBP:Diastolic blood pressure; DM:Diabetes Mellitus; Hb:Hemoglobin; PTH:Parathormone; CRP:C-reactive protein; PWV:Pulse wave velocity

ney disease (PCKD; 20 patients, 10.3%), Amyloidosis (4 patients, 2.1%), Chronic tubulointerstitial nephritis (CTIN; 8 patients, 4.1%), urological problems (9 patients, 4.6%) and idiopathic (37 patients, 19.1%).

In our study, male gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), DM, baseline eGFR, Hgb, albumin, phosphorus, calcium, PTH, and 24-hour proteinuria were significantly different in patients that progressed to ESRD (Table 1). In the Cox-Regression analysis for these parameters, male gender, low eGFR, and Hgb, an increase in DBP, phosphorus, and proteinuria were found to be independent predictors of ESRD (Table 2).

Our study showed that age, DM, albumin, potassium, HDL cholesterol, PWV, SBP, and pulse pressure were statistically and significantly different for mortality in chronic renal disease. The presence of DM, hypoalbuminemia, increase in HDL, and PWV were found to be independent indices of mortality in Cox-Regression analysis for these parameters (Table 3). Each unit increase in PWV raised the mortality rate approximately 1.5 times.

DISCUSSION

In this study, we found that an increase in PWV was an independent marker of mortality in CRD. We found that each unit increase in PWV raised the mortality rate approximately 1.5 times. Baumann M et al. showed that an

Table 2: COX-Regression analysis for ESRD

Variable	Model 1			Model 10		
	p	HR	(95%CI)	p	HR	(95%CI)
Gender (male)	0.006	2.333	(1.281-4.250)	<0.001	2.576	(1.545-4.296)
Baseline eGFR	<0.001	0.900	(0.872-0.929)	<0.001	0.905	(0.880-0.930)
Hemoglobine	0.0054	0.853	(0.726-1.003)	0.023	0.846	(0.733-0.977)
Phosphorus	0.098	1.206	(0.966-1.504)	0.032	1.221	(1.018-1.466)
DBP	0.115	1.020	(0.995-1.046)	0.037	1.019	(1.001-1.037)
Proteinuria	0.001	1.270	(1.105-1.461)	<0.001	1.246	(1.158-1.341)
Calcium	0.717	1.091	(0.682-1.744)			
DM	0.729	1.117	(0.597-2.089)			
Albümin	0.860	0.932	(0.424-2.048)			
BMI	0.397	0.978	(0.928-1.030)			
PTH	0.895	1.000	(0.998-1.002)			
PWV	0.349	0.908	(0.743-1.111)			
SBP	0.926	1.001	(0.982-1.020)			
Smoking	0.473	1.328	(0.612-2.878)			

Table 3: COX-Regression analysis for mortality

Variables	Model 1			Model 5		
	p	HR	(95%CI)	p	HR	(95%CI)
PWV	0.480	1.674	(0.400-6.996)	0.016	1.467	(1.074-2.004)
DM	0.045	0.235	(0.570-0.967)	0.051	0.281	(0.780-1.006)
Albumin	0.002	0.241	(0.097-0.597)	0.004	0.302	(0.133-0.683)
HDL	0.008	1.058	(1.015-1.103)	0.012	1.057	(1.012-1.103)
Age	0.771	0.969	(0.783-1.199)			
Potassium	0.186	1.866	(0.741-4.703)			
SBP	0.981	0.999	(0.947-1.054)			
PulsePressure	0.917	1.003	(0.948-1.061)			

increased PWV was an independent marker of mortality after a study with 135 CRD patients and 42 month follow-up period. They reported that the mortality increased in patients with $PWV \geq 10$ m/s. They also found that an increase of 10 m/s raised the mortality 5.1 times but PWV was not significant for the progression to ESRD (10). In our study, we found that a PWV increase was not a significant marker for predicting the progression of the disease. Similarly, Jacques Blacher et al. reported that the increase in PWV was an independent predictor of mortality in both groups (with and without ESRD) of patients after a 78 ± 46 month follow-up period. They observed a 34% crude and 14% corrected increase in both cardiovascular and total mortality for each 1 meter / second increment in PWV (11).

Chen et al. conducted a study with 145 stage 3-5 CRD patients and reported that the increment of PWV was a determinant of progression of CRD to ESRD and mortality (12). On the other hand, in the Nephro Test study, with 186 stage 2-5 CRD patients and a 3.1-year follow-up period, no correlation was found between PWV and CRD progression (13). In our study, there was not a significant correlation between a PWV increase and progression to ESRD in CRD patients who were followed for four years. In our study, we considered those who had 25 ml/dak /1.73 m² or more decreases in eGFR compared to baseline value was meaningful for evaluating the progression to ESRD. However, Ford et al. reported that aortic stiffness had a predictive value to predict the CRD progression (14).

These different results in the studies might be attributed to differences in patient numbers, follow-up times, etiologies of CRD, and comorbidities.

Observational studies show that patients with CRD and normal blood pressure maintain glomerular filtration rate (GFR) better than hypertensive patients (15). In our study, systolic and diastolic blood pressure differed significantly between the end-stage renal failure and predialysis groups. In addition, there was a significant difference in SBPs between predialysis patients, and those resulted in mortality. Likewise, in a study by Ford et al, SBP showed a significant difference between the groups (14).

High pulse and systolic blood pressures suggest that arterial stiffness, cardiovascular events, and mortality may be higher in patients with CRD. Therefore, it can be thought that the cardiovascular event and mortality can be reduced by the treatment regimens applied to decrease the pulse pressure and systolic blood pressure.

Anemia might be a risk factor for the progression of renal disease to ESRD. Mohanram A et al. conducted a study with 1500 diabetic CRD patients with four years of follow up time and found that the risk of progressing to ESRD

was approximately two times higher in patients with low Hb values compared to patients with Hb values above 13.8 g/dL (16). In our study, low hemoglobin levels were also associated with renal progression. Anemia treatment in chronic kidney patients will not only reduce renal progression but also benefit cardiac dysfunction and increase exercise tolerance, improve signs and symptoms of the central nervous system, appetite, and sexual function.

In a prospective study (145 stage 3-5 CRD patients and with 15 month follow up time) by Tsai YC et al. showed that PWV, hypertension, low eGFR, and high phosphate levels were associated with renal disease progression (12). Similarly, in our study, hypertension, high phosphate level, and PWV increase were found to be associated with progression. Calcium phosphorus accumulation in the kidney interstitium can initiate an inflammatory reaction that causes interstitial fibrosis and tubular atrophy, thereby causing renal progression. There are several important methods in the treatment of hyperphosphatemia, which has such a negative effect on renal progression. Primarily, regulating diet and using phosphorus binders in predialysis patients and additionally, effective dialysis treatment for hemodialysis patients are important ways to control the phosphorus level.

Ford et al. reported that PWV, systolic blood pressure, and protein to creatinine ratio were associated with renal progression (14). A significant correlation was also found between progression and proteinuria and PWV according to our results. Matsushita et al. reported that decreased eGFR and albuminuria in chronic renal disease correlated with increased risk of cardiovascular events and all-causes of mortality (17). The Nord-Trondelag Health Study revealed that evaluation of proteinuria with eGFR is more significant in assessing the risk of progression to ESRD than eGFR alone. Out of 65589 adults who participating in the study, 124 patients progressed to ESRD after 10 years of follow-up. Both eGFR and proteinuria were independently associated with progression to ESRD (18). In our study, proteinuria and initial eGFR were found to be independent risk factors for the progression of chronic renal disease to ESRD.

Regardless of the primary event, proteinuria itself and its results like hypervolemia, and hyperlipidemia, negatively affect the course of kidney disease. Reducing proteinuria and albuminuria is important for preventing renal progression and increased mortality.

Various studies have shown that non-diabetic kidney disease progresses more rapidly in men (19-21). Proteinuria, severe hypertension, and smoking have not been shown to be a sex-independent risk factor for chronic renal disease progression in the literature. On the other hand, our study showed that male gender was an independent risk factor for the progression of CRD to ESRD.

Men and women with extremely high HDL cholesterol in the general population have paradoxically high all-cause mortality. In two prospective studies, the relationship between HDL cholesterol concentrations and all-cause mortality was U-shaped for both men and women, and excessively high and low concentrations were associated with a high risk of all-cause mortality (22). In a study conducted in the general population with a 326016 person-year follow-up, a U-shaped relationship with all-cause mortality was reported. Low and high HDL cholesterol concentration has been found to be associated with mortality (23). In our study, we found an independent relationship between high HDL cholesterol concentration and mortality. This finding seems to be supported by other studies.

Interestingly, in a prospective study, an independent relationship was detected between PWV and serum oxalic acid, glucose, and triglyceride in hemodialysis patients (24). In the future, conducting studies showing whether there is a relationship between cholesterol, HDL, LDL, triglyceride, and PWV in predialysis CRD patients will contribute to the literature.

CONCLUSIONS

In this study, we found that an increase in PWV was an independent predictor of mortality. We found that each unit increase in PWV raised the mortality approximately 1.5 times. We found that high HDL cholesterol has an independent relationship with mortality in CRD patients. In this sense, we have demonstrated that monitoring PWV which is a non-invasive measure and taking measures in this direction can reduce the effect of arterial stiffness which has an independent effect on mortality. This study will shed light in terms of future studies and measures.

Limitations of the study: The limitations of our study are that it is a single-center study, there are patients who have left the follow-up for different reasons during the four-year follow-up period and the PWVs of the patients were not measured again after four years. If patients had control PWV measurements at the end of four years, it would add value to the study.

Peer Review: Externally peer-reviewed.

Ethics Committee Approval: This study was approved by the Ethical Committee of the University of Health Sciences Konya Research, and Training Hospital (No:48929119/774/28-25).

Informed Consent: Written consent was obtained from the participants.

Author Contributions: Conception/Design of Study- E.E., İ.G.; Data Acquisition- E.E., P.Ö.K., V.G.; Data Analysis/Interpretation- İ.G., S.K.; Drafting Manuscript- E.E., S.K., P.Ö.K.; Critical Revision

of Manuscript- İ.G., V.G.; Final Approval and Accountability- E.E., S.K., P.Ö.K., V.G., İ.G.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: This study was supported by the University of Health Sciences, Konya Training and Research Hospital.

Hakem Değerlendirmesi: Dış bağımsız.

Etik Komite Onayı: Bu çalışma için etik komite onayı Sağlık Bilimleri Üniversitesi, Konya Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan alınmıştır (Sayı:48929119/774/28-25).

Bilgilendirilmiş Onam: Katılımcılardan bilgilendirilmiş onam alınmıştır.

Yazar Katkıları: Çalışma Konsepti/Tasarım- E.E., İ.G.; Veri Toplama- E.E., P.Ö.K., V.G.; Veri Analizi/Yorumlama- İ.G., S.K.; Yazı Taslağı- E.E., S.K., P.Ö.K.; İçeriğin Eleştirel İncelemesi- İ.G., V.G.; Son Onay ve Sorumluluk- E.E., S.K., P.Ö.K., V.G., İ.G.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Bu çalışma Sağlık Bilimleri Üniversitesi, Konya Eğitim ve Araştırma Hastanesi tarafından desteklenmiştir.

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