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Original Article

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Evaluation of Cardiovascular Status with Non-Invasive Markers in Patients with Diabetic and Non-Diabetic Chronic Kidney Disease

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Abstract

Objective: Chronic kidney disease (CKD) and diabetes mellitus (DM) both have an increased risk of cardiovascular disease (CVD). Based on estimated glomerular filtration rate values, both CVD and CKD have powerful and independent relationships even after adjusting for known CVD risk factors, history of CVD events, and proteinuria. However, there are limited data about the individual effects of the underlying etiology of CKD on CVD. This study aims to evaluate the cardiovascular status (CVS) of patients with diabetic and non-diabetic stage 3, 4, and 5 CKD with non-invasive methods.

Materials and Methods: A total of 187 patients who had stage 3-5 CKD were grouped on the basis of whether they had DM or not. The non-invasive cardiovascular markers such as pulse wave velocity, carotid intima media thickness, central systolic and diastolic pressures, and central pulse pressures were evaluated in these patients.

Results: A total of 187 patients with CKD were recruited for this study. Of them, 46 (25%) had diabetic CKD (mean age, 57.7±9.2 years) and 141 (75%) had non-diabetic CKD (mean age, 56.8±12.4 years). Clinical systolic blood pressure, clinical pulse pressure, central systolic blood pressure, central pulse pressure, cardiac output, and pulse wave velocity were significantly higher in patients with CKD who had DM.

Conclusion: The impaired renal function and DM have additive effects on the development of peripheral arterial calcification. The CVS of patients with CKD and DM is worse than that of patients with CKD who were not diabetic; therefore, extra effort must be given for diabetic CKD patients.

Keywords: Chronic kidney disease, diabetes mellitus, pulse wave velocity

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INTRODUCTION

Chronic kidney disease (CKD) is defined as having abnormalities in kidney structure and function that have been continuing for more than three months (1). Diabetes mellitus (DM) is the most common cause of CKD, and the prevalence of CKD increases day by day owing to the increase in the frequency of DM (2-4). Acute coronary syndrome, stroke, heart failure, and sudden cardiac death occur at a younger age in patients with CKD, and this implies that CKD accelerates the risk of CVD (5).

The traditional risk factors like hypertension, smoking, and hyperlipidemia and non-traditional risk factors that are specific to renal dysfunction such as electrolyte imbalance, malnutrition, anemia, and mineral and bone disorder are related to high CVD prevalence among patients with CKD (6). However, there are limited data about the individual effects of the underlying etiology of CKD on CVD. Although there are studies that report the cardiovascular complications of DM in patients with CKD (7-9), the impact of DM on CVD is generally neglected once CKD is diagnosed. The significance of CVD in

patients with CKD is critical as the population of patients with CKD who have DM is increasing; therefore, it is important to understand precisely how the presence of DM affects CVD in the CKD patient population. This study aims to evaluate the cardiovascular status (CVS) of patients with stage 3, 4, and 5 CKD with and without DM via non-invasive methods.

MATERIALS AND METHODS

This study was conducted between January 2017 and March 2018. The study protocol was approved by the Ethics Committee of Necmettin Erbakan University Meram School of Medicine (Approval Date: December 02, 2016; Approval Number: 2016/736), and the patients gave written informed consent. A total of 187 patients with stage 3-5 CKD were enrolled in the study. We excluded patients with peripheral arterial disease, type 1 DM, history of myocardial infarction, coronary revascularization (either by percutaneous coronary intervention or bypass), and malignancy. The final 187 patients were grouped on the basis of whether or not they had DM.

Demographic and clinical data obtained from the files of the patients and anthropometric data including the height, weight, and waist-to-hip ratio were measured by a physician. After an overnight fast, blood samples were collected in the morning to measure the serum hemoglobin A1c, fasting plasma glucose, urea, creatinine, calcium, phosphorus, uric acid, bicarbonate, parathormone, C-reactive protein (CRP), hemogram, and lipid profiles. The eGFR was calculated using the Modification of Diet in Renal Disease Study formula (CKD stage 3, eGFR=30-59 mL/min/1.73 m^2; CKD stage 4, eGFR=15-29 mL/min/1.73 m^2; and CKD stage 5, eGFR <15 mL/min/1.73 m^2) (10). Weight and height were measured and body mass index (BMI) was calculated by dividing the weight by the square of height (kg/m^2). Body surface area was calculated by using Mosteller RD formula (11).

All patients were examined after at least five minutes of rest and then as an indicator of arterial stiffness, pulse wave velocity (PWV) was calculated by using an automatic wave form analyzer (Mobil-O-Graph NG; IEM GmbH, Stolberg, Germany) arteriograph device (12). The same device was used to detect the cardiac output, augmentation index (AIx; @75), total peripheral resistance, and central systolic and diastolic blood pressures. The central blood pressures, AIx, cardiac output, total peripheral resistance, and PWV measurements were made as described before by Afsar et al. (13). Cardiac index was calculated by dividing the cardiac output by the body surface area. Clinical blood pressure measurements were made by a specialist clinician after PWV measurement. European Society of Hypertension guidelines were applied during clinical blood pressure measurements (14).

High-resolution B-Mode ultrasonography with a 12-MHz linear probe (Hitachi EUB 7000 HV, Tokyo, Japan) was used for measuring the carotid intima media thickness (CIMT). The mean CIMT was calculated from at least three different arterial intimal wall thickness measurements of the carotid artery on both sides.

Statistical Analysis

The statistical analysis was performed with the Statistical Package for the Social Sciences 16.0 version (SPSS Inc., Chicago, IL, USA). Normal distributions of the quantitative variables were analyzed by Kolmogorov-Smirnov test. Parametric tests were applied when variables distributed normally, and nonparametric tests were applied when variables did not distribute normally. Parametric test results were given as means plus standard deviations. Nonparametric test results were given as means and minimum-maximum ranges. Differences between groups were analyzed by student t test or Mann-Whitney U test when appropriate. Frequencies were analyzed by $\chi 2$. Correlations between variables were performed using Spearman's rho correlation coefficient. A probability value of 0.05 was considered to be statistically significant.

RESULTS

This study included 187 patients with CKD. Of these patients, 46 (25%) had diabetic CKD (mean age, 57.7±9.2 years), and 141 (75%) had non-diabetic CKD (mean age, 56.8±12.4 years). There was no difference in diabetic and non-diabetic CKD groups in terms of age and sex distribution (p=0.118 and p=0.843, respectively). Four (8.7%) of the 46 patients with diabetic CKD and 22 (15.6%) of 141 patients with non-diabetic CKD were smokers. There was no significant difference between the two groups in terms of smoking (p=0.328).

There were no statistically significant difference the two groups with regard to BUN, creatinine, eGFR, uric acid, sodium, calcium, phosphorus, total cholesterol, low-density lipoprotein and high-density lipoprotein-cholesterol, triglyceride, parathormon, CRP, hemoglobin, accounts of lymphocyte, platelet, and monocyte (p>0.05). Mean BMI and BSA, glucose, potassium, bicarbonate, spot urine protein/creatinine ratio, account of neutrophil, and neutrophil/lymphocyte ratio were significantly higher in diabetic patients with CKD (p<0.05). In contrast, mean platelet volume was significantly lower in these patients (p=0.045) (Table 1).

Clinical systolic blood pressure, clinical pulse pressure, cardiac output, central systolic blood pressure, central pulse pressure, and PWV were significantly higher in diabetic patients compared with the non-diabetic patients (p<0.05). There was no statistically significant difference the two groups in terms of other parameters (p>0.05) (Table 2).

Main Points

- Other than CKD complications there are factors that might be controlled and thus, a positive contribution can be made to the patient survey.
- Herein, with non-invasive and reproducible methods, we showed that diabetic CKD patients had worser cardiovascular status when compared to same stages of CKD patients without diabetes mellitus.
- Taking care of blood sugar control even after the development of chronic kidney disease can have a mortality-reducing effect.

Table 1. Demographic and laboratory characteristics of patients according to diabetes status

Characteristics	Non-diabetic group (n=141)	Diabetic group (n=46)	p
Age (mean±SD) (years)	56.8±12.4	57.7±9.2	0.118
Sex (female/male) (n)	62/79	21/25	0.843
Smoker/nonsmoker (n)	22/119	4/42	0.328
BMI (kg/m^2) (mean±SD)	28.5±5.6	34.3±7.4	0.001
BSA (m^2) (mean±SD)	1.9±0.2	2±0.2	0.001
BUN (mg/dL)	73 (28-256)	76 (32-242)	0.626
Creatinine (mg/dL)	2.1 (1.2-4.8)	2.2 (1.2-5.2)	0.754
eGFR (mL/min/1.73 m^2)	31 (15-59)	30 (15-59)	0.630
Uric acid (mg/dL)	7.2±1.8	6.8±1.4	0.244
Sodium (mmol/L)	137 (127-142)	136 (129-141)	0.088
Potassium (mmol/L)	4.7±0.5	4.9±0.6	0.006
Calcium (mmol/L)	9.1±0.75	9.0±0.7	0.598
Phosphorus (mmol/L)	3.4 (2.1-7.7)	3.6 (2.6-5.4)	0.092
Bicarbonate (mmol/L)	20.7±3.7	23.1±3.0	0.007
Spot urine protein/creatinine	0.9 (0.1-7.9)	2.6 (0.2-10)	0.001
Glucose (mg/dL)	94 (70-110)	152 (81-473)	0.001
Total cholesterol (mmol/L)	205.6±51.7	214.0±49.3	0.114
LDL (mmol/L)	130.5±40.0	135.5±39.2	0.470
HDL (mmol/L)	38 (22-93)	37 (25-62)	0.824
Triglycerides (mmol/L)	145 (40-1190)	166 (61-694)	0.598
Parathormone (pg/mL)	105 (10-1850)	133 (19-441)	0.511
CRP (mg/L)	3.4 (3.2-16)	4.3 (3-22)	0.116
Hemoglobin (g/dL)	13.1±2.2	12.5±1.7	0.084
Neutrophil (×10^3/µl)	4.585±1870.2	5.481±1622.1	0.004
Lymphocytes (×10^3/µl)	1.986±600.0	2.050±681.9	0.547
Platelet (×10^3/µl)	239.0±71.6	260.7±88.9	0.139
Monocyte (×10^3/µl)	0.538±0.171	0.514±0.157	0.405
Neutrophil/Lymphocyte	2.5±1.4	3.1±1.8	0.029
MPV (fl)	10.5±0.9	10.1±1.0	0.045

BMI: body surface index: BSA: body surface area; BUN: blood urea nitrogen; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; CRP: C-reactive protein; MPV: mean platelet volume

Table 2. Hemodynamic characteristics of the patients according to diabetes status

Characteristics	Non-Diabetic (n=141)	Diabetic (n=46)	p
Clinical SBP (mm Hg)	135.2±17.8	151.2±21.3	0.001
Clinical DBP (mm Hg)	89.4±13.1	93.0±14.0	0.114
Clinical pulse pressure (mm Hg)	45.6±13.3	58.2±15.6	0.001
Cardiac output (L/min)	4.3±0.7	4.8±1.0	0.001
Cardiac index	2.4±0.6	2.4±0.6	0.929
TPR (mm Hg/mL)	1.4±0.2	1.4±0.3	0.274
Central SBP (mm Hg)	126.8±16.8	137.9±19.1	0.001
Central DBP (mm Hg)	90.7±13.3	94.8±14.7	0.083
Central pulse pressure (mm Hg)	36.1±11.5	43.1±13.1	0.001
PWV (m/sn)	7.9±1.7	8.8±1.8	0.003
CIMT (mm)	0.7 (0.4-1.4)	0.8 (0.5-1.1)	0.061
Augmentation index (@75)	24.8±15.1	26.3±13.1	0.565

SBP: systolic blood pressure; DBP: diastolic blood pressure; TPR: total peripheral resistance; PWV: pulse wave velocity; CIMT: carotid intima media thickness.

DISCUSSION

It is a known fact that cardiovascular mortality in patients with DM and end-stage renal disease (ESRD) is higher than in patients with ESRD without DM (15, 16). However, there are limited data about the difference between the CVS of patients with diabetic CKD and those with non-diabetic CKD. In the present study, patients with CKD were evaluated with non-invasive cardiovascular markers such as PWV, CIMT, and central blood pressure measurements. This study, via non-invasive, inexpensive, and repeatable markers, showed that impaired renal function and DM have additive effects on the development of peripheral arterial calcification. Choi et al. (17) conducted a study in the same group of patients and showed with an expensive and deleterious method that diabetic CKD patients have a greater extent of coronary calcification and atherosclerosis.

The clinical and central systolic blood pressures were significantly higher in diabetic CKD patients. In the light of the latest literature, especially central blood pressure correlated with cardiovascular events (18). Safar et al. (19) also reported that only central pressure remained predictive in patients with renal failure after adjusting the co-founders. Roman et al. (20) showed that individuals with central pulse pressures ≥50 mm Hg are at greatest risk of future cardiovascular events. Although the central pulse pressures were below 50 mm Hg in this study, the difference between the two groups was statistically significant. If we had more patients who had higher stages of CKD or longer duration of DM, then the central pulse pressures might have been higher. The cardiac output of the diabetic CKD patients was significantly different than that of the non-diabetic CKD patients, but the cardiac index was not statistically different; this state was probably due to the larger body surface area of diabetic patients.

AIx (@75) is a widely used index of wave reflection that can be determined non-invasively from either central or peripheral arterial waveforms (21). After adjusting for other CVS risk factors, it was demonstrated that higher AIx was related to adverse CVS events and all-cause mortality (22, 23). The AIx's (@75) of the patients in this study were not statistically significantly different between the groups. In addition, total peripheral resistance was similar in both the groups.

Arterial stiffness is strongly associated with cardiovascular events (24, 25). PWV is a non-invasive and easy method to evaluate the arterial stiffness. Although the well-known cardiovascular risk factors such as hyperlipidemia, smoking, and male sex were not different between the two groups, the PWV of diabetic CKD patients was significantly higher than that of the non-diabetic CKD patients. Matsuda et al. (26) showed that arterial stiffness increased in a stepwise manner in non-diabetic CKD patients as the stage of renal disease increased. The author of Atherosclerotic Risk Community study notified that the carotid arteries of patients with non-insulin-dependent DM or borderline glucose intolerance is stiffer than patients with normal glucose tolerance, and the decreased elasticity was independent of arterial wall thickness (27). The CIMT was not different in diabetic and non-diabetic CKD group, but PWV was higher in the diabetic CKD group in this study. These data are compatible with the ARIC study. However, this study showed that not only CKD but also DM is specifically important for arterial stiffness. This study also supports the previous data and emphasizes the adverse effects of DM on arteries.

CONCLUSION

CKD and DM have a synergistic effect on the development of peripheral arterial calcification. The CVS of diabetic CKD patients is poorer than that of non-diabetic CKD patients. Therefore, special attention should be paid to the treatment of diabetic CKD patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Necmettin Erbakan University Meram School of Medicine (Approval Date: December 02, 2016; Approval Number: 2016/736).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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