Investigation of the relationship between glomerular filtration rate and aortic propagation velocity, epicardial fat thickness, and carotid intima-media thickness in chronic kidney disease patients

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Abstract

Background: Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in chronic kidney disease (CKD) patients. Aortic propagation velocity (APV), epicardial fat thickness (EFT), and carotid intima-media thickness (CIMT) measurements could provide additional information on assessing renal decline in CKD patients. The study aimed to evaluate EFT, AVP, and CIMT in CKD patients and then investigate the association among those parameters. Methods and Results: A total of 170 CKD consecutive subjects were enrolled in the study. Patients were divided into five groups according to their GFR values. Each patient underwent complete transthoracic echocardiography examination. APV, EFT and CIMT were measured for analyses. A multivariate linear regression model was used for analysis to determine the independent predictors of GFR. The lowest APV was observed in stage IV-V, and the highest APV was observed in stage I-II ($p<0.001$). Stage IV-V patients had the highest EFT, and stage I-II patients had the lowest EFT ($p<0.001$). Moreover, the lowest CIMT was observed in stage III, and the highest APV was observed in stage V ($p<0.001$). GFR was significantly and positively correlated with APV and negatively correlated with EFT and CIMT. In multivariate analyses, APV (OR: 0.289, $p<0.001$), EFT (OR: -0.135, $p<0.001$) and CIMT (OR: -0.388, $p<0.001$) were independent predictors of GFR. Conclusion: We found that APV decreased, and EFT and CIMT increased as CKD progress. The present study suggests that APV, EFT, and CIMT might be incorporated with the examination of CKD patients in daily practice.

Introduction

Patients with chronic kidney diseases (CKD) have increased morbidity and mortality compared to the general population. Cardiovascular disease (CVD) is the primary cause of mortality and morbidity in CKD patients. Early vascular aging and arterial stiffness are the most specific changes in arteries in CKD patients, and it can also be seen in the early stages of CKD (1). Many reasons have been asserted for decreased vascular compliance and increased arterial stiffness, including activation of the renin-angiotensin system, vascular calcification, and endothelial dysfunction in CKD patients (2).

Arterial stiffness has been recognized as a vascular biomarker, and it describes the arterial pressure response to stroke volume changes (3). Besides, arterial stiffness is also closely related to the propagation velocity

of the pressure. Carotid-to-femoral pulse wave velocity (PWV), accepted as a marker of arterial stiffening, is known to be a strong predictor of morbidity and mortality in CKD patients (4). Arterial stiffness is most prominently observed in the aorta and becomes progressively worse as CKD progresses (5). Aortic propagation velocity (APV) reflects the presence of aortic stiffness and is measured with an echocardiographic method. The measurement of APV is based on the propagation velocity of the descending thoracic aorta. Gunes et al. was used the APV to evaluate aortic stiffness in coronary artery disease (CAD) patients and showed that it is related to carotid and coronary atherosclerosis (6).

Epicardial adipose tissue (EAT) is found between the pericardial visceral layer and myocardium. EAT direct contact with the surface of the myocardium and coronary vessels (7). EAT secrets adipocytokines which have cardioprotective effects (8). The pathological increase in EAT correlated with cardiovascular disease risk (9). Many studies proposed that there was a significant relationship between the CKD and epicardial fat thickness (EFT). Previously increased EFT has been noted in hemodialysis patients (10). Increased EFT is accepted as a cardiovascular risk factor in CKD patients. Nakanishi et al. evaluated EAT volume by computed tomography and showed that CKD patients had more EAT compared to patients without CKD (11). Moreover, Increased EFT has been associated with a worse cardiovascular prognosis in CKD patients (12).

The accumulation of lipids in the arterial wall causes thickening of the intima-media layers and atherosclerotic plaque formation (13). Carotid intima-media thickness (CIMT) is accepted as a marker of subclinical atherosclerosis and is associated with the presence of CAD (14). CKD patients could have subclinical atherosclerosis in the arterial wall. The prominence in the carotid artery wall and outward remodeling was reported in CKD patients (15). CIMT is associated with cardiovascular events and mortality in CKD patients (16). Zuo et al. presented that hypertensive patients with CKD had increased CIMT compared to non-CKD hypertensive patients (17). Another study described that there was a negative correlation between CIMT and estimated glomerular filtration rate (GFR) (16).

APV, EFT, and CIMT measurements could provide additional information on assessing renal decline in CKD patients. We hypothesized that APV, EFT, and CIMT might be related to CKD stages. The study aimed to evaluate EFT, AVP, and CIMT in CKD patients and then investigate the association among those parameters.

Methods

This study included a total of 170 cross-sectionally chosen CKD patients older than 18 years belonging to our clinic between September 2016 to July 2017. The definition and the diagnostic criteria for chronic kidney disease were proposed in the K/DOQI guidelines: estimated glomerular filtration rate (GFR ml/min/1.73 m^2) calculated by the MDRD formula (18). Patients were divided into five groups according to their GFR values (Stage-I=76 (GFR>90), Stage-II=39 (GFR=60-89), Stage-III=25 (GFR=30-59), Stage-IV=15 (GFR=15-29), Stage-V=15 (GFR<15)). Patients with the following conditions were excluded from the study: uncontrolled hypertension, left ventricular systolic dysfunction, valvular pathology, any effusion, aortic aneurysms, acute coronary syndromes, chronic lung disease, hepatic dysfunction, known malignancy, systemic infection or inflammatory disorders, and dialysis application. Informed consent was obtained from all patients before the study. This study was performed according to the principles stated in the Declaration of Helsinki and was approved by the local ethics committee of the Van Training and Research Hospital.

Physical examinations, including anthropometric measurements, history, and basic laboratory tests, were performed. After an overnight fast of at least 8 hours, blood samples were taken from the antecubital vein with an atraumatic puncture and sent to the laboratory for analysis. Routine electrocardiography (ECG) was recorded in each patient. Each patient underwent complete transthoracic echocardiography following the American Society of Echocardiography guidelines. The transthoracic echocardiography was performed at rest, with the patient in the left lateral decubitus position, using an echocardiographic device (Vivid S6, General Electric, Horton, Norway) with a 3.0-MHz transducer. Two experienced cardiologists blinded to clinical data performed the echocardiography. Echocardiographic images were also recorded, and offline

measurements were performed.

Color M-mode Doppler recordings were obtained from the suprasternal window in the supine position. The cursor was placed parallel to the main direction of flow in the descending aorta. The Nyquist limit was adapted to 30–50 cm/s, switching to the M-mode with a recorder sweep rate of 200 mm/s. If the slope of the flame was unclear, baseline shifting was used to change the aliasing velocity until a clear delineation of the velocity slope was obtained (Figure 1). AVP was then calculated by dividing the distance between the points corresponding to the beginning and end of the propagation slope by the duration between the corresponding time points. Thus, AVP corresponds to the velocity at which the flow is propagating down the artery. The mean of at least three measurements was recorded as the AVP.

The EFT was measured on the free wall of the right ventricle from the parasternal long-axis view, using the aortic annulus as an anatomic reference. The thickness of the free right ventricular wall was measured at the end-systolic period. When space was found without an echogenic view between visceral pericardium and myocardium, it was estimated as epicardial fat. To measure EFT, the thickest area was chosen to measure, preferably the right supraventricular area (Figure 2). The average value of the three cardiac cycles was noted.

Carotid arteries were evaluated using a Logiq 7 (General Electronic, Waukesha, WI, USA) with a 7.5-MHz transducer. All examinations were performed by two experienced radiologists who were blinded to the patients' clinical information. Measurements were performed for the right and left carotid arteries and involved primary transverse and longitudinal scanning of the common carotid artery, bifurcation, and internal carotid. The patient was lying in a supine position with their head directed away from the side of interest and neck slightly extended. The CIMT was measured on the far wall, 1 cm from the bifurcation of the common carotid artery, as the distance between the lumen intima interface and the media-adventitia interface. The CIMT was measured from the frozen frame of a suitable longitudinal image. At least three measurements were performed on both sides, and the average measurement was taken as the CIMT. All measurements were made at a plaque-free site.

Statistical analyses

Data were analyzed with SPSS software version 25.0 for Windows (SPSS Inc, Chicago, Illinois). The Kolmogorov-Smirnov test was used to test whether the data were distributed normally. Continuous normally distributed variables are expressed by their mean and standard deviation. In multiple comparisons, one-way analysis of variance (ANOVA) test followed by the Tukey post hoc test was used for normally distributed continuous data. Nominal parameters were compared using Chi-square test. Pearson's correlation test was used for correlation analysis. A multivariate linear regression model was used for analysis to determine the independent predictors of GFR. Statistical significance was defined as $p<.05$.

Results

The clinical and demographic characteristics of the patients are shown in Table 1. Patients were classified into five groups according to the GFR levels (stage I-V). Patients in stage II-III-V were older than stage I and IV. Body mass index and gender were similar between the CKD groups. While DM and smoking were similar in the groups, CAD was mostly observed in stage V. Stage IV patients had a significantly higher rate of hypertension and hyperlipidemia. In hematology analysis, white blood cell count and hemoglobin were the lowest in stage IV-V. In the biochemical analysis, the highest creatinine value was observed in stage IV-V. Stage IV patients had the lowest C-reactive protein value.

In the echocardiographic analysis, the left ventricular ejection fraction was similar in the CKD stages. The lowest APV was observed in stage IV-V, and the highest APV was observed in stage I-II ($p<0.001$) (Figure 3A). Stage IV-V patients had the highest EFT, and stage I-II patients had the lowest EFT ($p<0.001$) (Figure-3B). Moreover, the lowest CIMT was observed in stage III, and the highest APV was observed in stage V ($p<0.001$) (Figure 3C).

The correlation among the GFR, APV, EFT, and CIMT is shown in table 2. GFR was significantly and

positively correlated with APV and negatively correlated with EFT and CIMT (Figure 4-6). APV was significantly and negatively correlated with EFT (r=-0.401 p<0.001) and CIMT (r=-0.628 p<0.001). EFT values had a significantly positive correlation with CIMT (r=0.522 p<0.001).

Multivariate linear regression analyses of the association between the GFR and multiple parameters are listed in table 3. In multivariate analyses, APV (OR: 0.289, p<0.001), EFT (OR: -0.135, p<0.001) and CIMT (OR: -0.388, p<0.001) were independent predictors of GFR.

Discussion

In this study, we have investigated APV, EFT, and CIMT levels in CKD stages. The key findings of this study are as follows. First, stage IV-V patients had the lowest APV and highest EFT and CIMT. Second, GFR was correlated negatively with APV and positively with EFT and CIMT. Third, APV was significantly and negatively correlated with EFT and CIMT in CKD patients. Last but not least, APV, EFT, and CIMT were independently associated with GFR levels in CKD patients.

APV is an aortic stiffness parameter that can be measured during a routine echocardiographic examination. APV is correlated with aortic strain and aortic distensibility in patients with CAD (19). Arterial stiffness is one of the early signs of cardiovascular dysfunction in CKD patients (20). A decrease in propagation velocity can be observed with arterial stiffening in CKD patients. PWV, a marker of arterial stiffness, is an independent predictor of all-cause mortality and cardiovascular mortality in end-stage renal failure patients (21). It was reported that GFR is negatively correlated with arterial stiffness, and increased PWV could predict the presence of CKD (17). Reduced arterial stiffness improved life expectancy in end-stage renal failure patients regardless of blood pressure status (22). In this study, we showed that stage IV-V patients had the lowest APV. This result is compatible with the work by Wang et al., who found that arterial stiffness gradually increased over time as CKD progress. Moreover, our finding shows that arterial stiffness increases gradually as GFR decreases. APV was significantly and positively correlated with GFR levels that show the potential damage of both structure and function of large vessels in patients with CKD. Due to the negative correlation among the APV, EFT, and CIMT levels in CKD patients, APV can be considered as a surrogate marker in subclinical atherosclerosis.

EAT contributes to cardiac function through paracrine and vasocrine secretion of pro-inflammatory and pro-atherogenic cytokines into the myocardial structures. EAT has its protective effects in healthy people, such as mechanical protection, regulation of coronary flow, and energy supplementation of fatty acids. The pathological increase in EFT is associated with increased cardiovascular disease in CKD patients (9). The reason for the increase in EFT is not fully understood in CKD patients. It has been suggested that increased inflammation plays a role in the increase of EFT in these patients (23). Aydın et al. reported that hemodialysis was an independent predictor of increased EFT (24). Patients with essential HT and microalbuminuria had higher EFT compared to HT patients with normoalbuminuria (25). Another study proposed that EFT was an independent predictor of albuminuria in type 2 DM patients (26). Cordeiro et al. evaluated the EFT in 227 non-dialysis CKD patients and reported that EFT correlated with cardiovascular disease severity. Moreover, the authors found that increased EFT was related to poor cardiovascular prognosis (12). A meta-analysis, including the results of 17 studies, suggested that EFT and epicardial fatty volume were increased in CKD patients compared to the control group subjects (27). Sheng et al. evaluated epicardial fatty volume by computed tomography in 120 CKD patients and 30 healthy subjects. They found that stage IV-V patients had higher epicardial fatty volumes compared to the controls (28). Despite this, Ozkurt et al. showed that EFT was similar in CKD patients and control subjects (29). In this study, we found that stage IV-V patients had the highest EFT. This result is supported by a meta-analysis by Song et al. (27). Besides, we reported that EFT was correlated negatively with APV. The result is similar to work done by Turan et al. (30).

CIMT is considered a marker of subclinical atherosclerosis. The increased CIMT has been previously reported in CKD patients. The increased CIMT was associated with low-grade systemic inflammation in CKD patients (31). Higher CIMT was associated with progressively decreasing GFR. Moreover, in CKD patients, GFR

could predict the increase in CIMT (16). CIMT is associated with a high mortality rate in CKD patients (32). A previous study showed that CIMT was significantly higher in hemodialysis patients compared to the control subjects (24). CIMT is independently associated with microalbuminuria in type 2 DM patients (33). Patel et al. investigated CIMT in 62 CKD patients and 50 controls. They found that CIMT was significantly higher in CKD patients compared to the controls. Furthermore, the authors showed that dialysis patients had higher CIMT compared to stage III and V (31). Another study indicated that HT patients with CKD had significantly higher CIMT compared to HT patients without CKD (17). In contrast, Margekar et al. found no significant differences in CIMT in different stages of CKD (34). In this study, we showed that CIMT is significantly and negatively correlated with GFR. This finding is consistent with previous findings in the literature (16). Similar to the results of this study, Patel et al. observed the highest CIMT in stage V patients (31).

Limitations

There were a few limitations in this study. This was a single-center study based on a relatively small group of patients. The sample size may not be large enough to generalize the results. Patients on hemodialysis were also excluded; therefore, the validity of the results for different populations is potentially limited. We could not confirm EFT measured by magnetic resonance and computed tomography imaging methods. Another limitation was that the association with APV and PWV was not evaluated. A large randomized clinical trial is needed to provide strength to present study findings.

Conclusion

In conclusion, in this study, we found that generally, APV decreased, and EFT and CIMT increased as CKD progress. Our findings suggest that increased EFT and CIMT, and decreased APV are closely associated with reduced GFR in CKD patients. APV, EFT, and CIMT might be used for risk assessment in various stages of CKD. The present study suggests that APV, EFT, and CIMT might be incorporated with the examination of CKD patients in daily practice.

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Ethical approval: All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Figure Legends

Figure-1. Aortic velocity propagation (AVP) in a patient with stage-V (AVP=38.2 cm/s) (Figure-1A), and in a patient with stage-III (AVP=57.3 cm/s) (Figure-1B).

Figure-2. Measurement of Epicardial fat thickness in a patient with stage-V (Figure-2A) and a patient with stage-I (Figure-2B). Epicardial fat thickness (EFT) perpendicular to the right ventricular free wall (arrow).

Figure-3. Aortic propagation velocity (A), Epicardial fat thickness (B), and Carotid intima-media thickness (C) values in chronic kidney disease stages.

Figure-4. Correlation analyzes between the glomerular filtration rate and Aortic propagation velocity ($r=0.587$, $p<0.001$).

Figure-5. Correlation analyzes between the glomerular filtration rate and Epicardial fat thickness (r=-0.453, p<0.001).

Figure-6. Correlation analyzes between the glomerular filtration rate and Carotid intima-media thickness (r=-0.640, p<0.001).

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