Type II Diabetes as the Main Risk Factor of Arterial Stiffness in Chronic Kidney Disease Patients

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ABSTRACT

Chronic kidney disease (CKD) is frequently linked to an increased risk of cardiovascular disease. Diabetes, hypertension, dyslipidemia, and obesity are all traditional risk factors of cardiovascular disease in CKD. However, the contribution of each of the traditional risk factors to arterial stiffness is unknown. This was a correlational study with a cross-sectional design. This study included forty CKD patients from Universitas Airlangga Hospital Surabaya, between December 2019 until March 2020. Serum samples were used to measure laboratory parameters, and Doppler ultrasound was used to assess carotid-femoral Pulse Wave Velocity (cfPWV). Spearman's analysis was conducted to determine correlations between cf-PWV and e-GFR, HBA1C, serum creatinine, and cystatin-C. Mann-Whitney test was performed to determine the association between type II diabetes with cf-PWV. Significant results were continued with linear regression analysis model. There were significant correlations between cf-PWV and e-GFR, HBA1C, serum creatinine, and cystatin-C. HBA1C showed the most significant positive correlation with a moderate correlation coefficient ($p = 0.000$; $r = 0.581$). Patients with type II diabetes was associated with increased cf-PWV. Linear regression model also revealed that HBA1C and history of diabetes were significant predictors of increased cf-PWV in CKD patients ($\beta = 0.400$; $p = 0.011$ and $\beta = 0.537$; $p = 0.000$, respectively). We found a positive correlation between HBA1C and cf-PWV and association between type II diabetes and increased cf-PWV. This proved that type II diabetes, especially with high HBA1C, acted as a significant risk factor for predicting increased arterial stiffness in CKD patients.

CCS CONCEPTS

• **Applied computing**; • **Life and medical sciences**; • **Consumer health**;

KEYWORDS

Type II diabetes, cf-PWV, arterial stiffness, chronic kidney disease, cardiovascular disease

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1 INTRODUCTION

Chronic kidney disease (CKD) affects up to 15% of adults globally and may be linked to an increased risk of cardiovascular disease (CVD) [1]. Chronic kidney disease causes end-stage renal failure, reduces kidney function, and is linked to comorbidities including cardiovascular disease [2, 3]. Along with traditional risk factors, CVD can be caused by non-traditional risk factors in patients with CKD. Compared to the general population, traditional risk factors such as diabetes, hypertension, dyslipidemia, and obesity play a significant role. In patients with CKD, there is a bidirectional relationship between oxidative stress and inflammation [4, 5].

Diabetes prevalence has been growing globally in recent years [6]. Diabetes is a well-established risk factor for CVD, kidney failure, and death from any cause [7]. When diabetes is combined

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with arterial stiffness, the risk of CVD and all-cause death increases substantially [8]. Fasting blood glucose (FBG) levels have been implicated as a risk factor for arterial stiffness. Patients with prediabetes and diabetes have a faster pulse wave velocity (PWV) than normal FBG [9]. Blood glucose control and measuring arterial stiffness are critical for CKD patients, even at physiological HBA1C values [10].

In diabetics, arterial stiffness is linked to oxidative stress via NOS release and oxidative damage to endothelial cell proteins, lipids, and DNA. Inflammation can enhance arterial stiffness by lowering nitric oxide bioavailability and raising endothelin-1. Conversely, oxidative stress and inflammation can promote vascular stiffening by promoting vascular smooth muscle cell hyperplasia and collagen synthesis [11]. It has long been recognized that oxidative stress and inflammation can affect arterial stiffness, particularly in patients with CKD. However, the contribution of each of the traditional risk factors, especially type II diabetes, to arterial stiffness is unknown.

2 MATERIAL AND METHODS

2.1 Study design and participants

This was a cross-sectional study conducted on forty CKD subjects at Universitas Airlangga Hospital in Surabaya, Indonesia, between December 2019 and March 2020. Participants had to meet the following criteria: (1) male or female with CKD based on The Kidney Disease Improving Global Outcomes (KDIGO) criteria [12]; (2) be over the age of 21, and (3) be willing to participate in research and sign an informed consent form. Participants were excluded if they had any of the following: (1) acute coronary syndromes; (2) acute heart failure; (3) severe infections; (4) cancer; or (5) arrhythmia. The Ethical Committee of Universitas Airlangga Hospital approved this study with certificate number 189 / KEH / 2019.

2.2 Data collection

The following methods were used to collect data: history taking (history of hypertension, diabetes, dyslipidemia, and smoking), physical examination (blood pressure, body mass index, waist circumference), blood collection (lipid profile, renal function test, HBA1C), and Doppler Ultrasound of carotid and femoral artery.

2.3 Carotid-Femoral Pulse Wave Velocity (cf-PWV)

B-mode imaging was used to determine the position of the common carotid artery in the supine position up to the supraclavicular level (1-2 cm from bifurcation). Electrocardiography (GE Vivid 5, GE Healthcare, United States of America) was then performed concurrently with Doppler wave identification. The femoral artery was also examined. Using a digital caliper, time was measured from the R waves in the QRS complex to the Doppler wave foot. Using a measuring tape, the common carotid and femoral arteries were measured (d).

2.4 Statistical Analysis

Descriptive data were presented as the mean and standard deviation. Normality test was performed by Shapiro-Wilk test. Spearman correlations were used to determine the relationship between continuous variables. Mann-Whitney test was used to determine the association between history of diabetes and cf-PWV. Variables that showed significant correlation/association with cf-PWV were analyzed further with linear regression test. When using a two-tailed analysis, P = 0.05 was considered statistically significant. All analysis was conducted with SPSS version 23 (IBM SPSS, Inc.).

3 RESULTS

3.1 Characteristics of Study Subjects

Table 1 summarizes the characteristics of the study subjects. The age of the subjects ranged from 31 to 71 years old. Male patients (60%) were predominant than females (40%). The most prevalent cardiovascular risk factors identified in the study participants were hypertension (92.5%), diabetes (67.5%), and dyslipidemia (57.5%). Obesity was identified as a risk factor for cardiovascular disease in this study. The majority of study participants were overweight or obese, with a BMI of greater than 25 kg/m^2.

Additionally, we discovered additional cardiovascular risk factors in the study subjects, including an increase in total cholesterol levels (204.72 ± 50.47 mg / dL), Low Density Lipoprotein (LDL) (122.87 ± 41.72 mg / dL), serum creatinine (7.24 ± 6.93 mg / dL), serum cystatin-C (3.91 ± 2.69 mg / L), and HBA1C (6.72 ± 1.56 %) and decrease in High Density Lipoprotein (HDL) (43.18 ± 14.22 mg / dL) and e-GFR (28.98 ± 30.33 mL / min / 1.73m2).

Continous data were presented as mean ± SD

All study subjects had varying stages of CKD. 42.5% of subjects had stage 5 CKD and had received dialysis, while only 7.5% had stage 1 CKD. The remainder of the patients had varying degrees of stage 2-5 CKD. All subjects were treated identically during the collection, sampling, and examination of primary data.

3.2 Results of the Carotid-Femoral Pulse Wave Velocity (cf-PWV) Measurement

The results of the cf-PWV test in the study subjects are summarized in Table 2. The Shapiro-Wilk test revealed that the data had an abnormal distribution ($p < 0.05$); thus, the Spearman test was used to determine the correlation between the study subjects' characteristics and cf-PWV.

There were significant positive correlations between e-GFR and HBA1C and cf-PWV ($r = 0.431$; $p = 0.005$ and $r = 0.581$; $p = 0.000$, respectively). Serum creatinine and cystatin-C also had significant negative correlations with cf-PWV ($r = -0.490$; $p = 0.001$ and $r = 0.439$; $p = 0.005$, respectively) (Table 3).

* = data with significant correlation ($p < 0.05$)

For categorical data, we performed analysis to determine the associations between hypertension, type II diabetes mellitus, dyslipidemia, and smoking. We found that type II diabetes was associated with increased cf-PWV ($p = 0.000$) (Table 4). Linear regression confirmed that HBA1C and type II diabetes were predictive factors of increased cf-PWV ($p = 0.011$ and 0.000, respectively).

* = data with significant association ($p < 0.05$)

* = data with significant association ($p < 0.05$)

4 DISCUSSION

This study enrolled forty patients with chronic kidney disease, most of whom were male. Sex hormones contribute to CKD progression,

Table 1: Characteristics of the participants

Variables	Value (n = 40)
Gender, male (%)	24 (60)
Age (years)	56.55 ± 8.1
Hypertension n (%)	37 (92.5)
Type II diabetes mellitus n (%)	27 (67.5)
Dyslipidemia n (%)	23 (57.5)
Smoking n (%)	6 (15)
Systolic Blood Pressure (mmHg)	139.43 ± 21.24
Diastolic Blood Pressure (mmHg)	78.63 ± 12.39
Body Mass Index (kg/m^2)	26.02 ± 4.31
Waist circumference (cm)	95.22 ± 12.66
Total cholesterol (mg/dL)	204.72 ± 50.47
Low Density Lipoprotein (mg/dL)	122.87 ± 41.72
High Density Lipoprotein (mg/dL)	43.18 ± 14.22
Serum creatinine (mg/dL)	7.24 ± 6.93
e-GFR ($mL/min/1.73m^2$)	28.98 ± 30.33
Serum cystatin-C (mg/L)	3.91 ± 2.69
HBA1C (%)	6.72 ± 1.56

Table 2: The study subjects' cf-PWV test results

	Min	Max	Mean	Standard deviation
cf-PWV (m/s)	5.41	29.21	12.42	5.46

Table 3: Correlation analysis between characteristics of study subjects and cf-PWV

Variables	r	p-value
Age	0.207	0.200
Systolic Blood Pressure	-0.291	0.069
Diastolic Blood Pressure	-0.133	0.412
Waist circumference	-0.071	0.665
Body Mass Index	-0.067	0.683
Total cholesterol	0.110	0.501
Low Density Lipoprotein	0.126	0.437
High Density Lipoprotein	0.168	0.299
Serum creatinine	-0.490	0.001*
e-GFR	0.431	0.005*
Serum cystatin-C	-0.439	0.005*
HBA1C	0.581	0.000*

Table 4: Associations between characteristics of study subjects and cf-PWV

Characteristics	p-value
Hypertension	0.401
Type II diabetes mellitus	0.000*
Dyslipidemia	0.871
Smoking	0.985

Table 5: Linear regression between HBA1C and type II diabetes with cf-PWV

Variables	Beta	p-value
HBA1C	0.400	0.011*
Type II diabetes mellitus	0.537	0.000*

with estrogen acting as a renoprotective factor by inhibiting oxidative stress. Male gender is associated with a more rapid progression of chronic kidney disease [13]. Other risk factors for CKD development include hypertension, hyperglycemia, albuminuria, dyslipidemia, BMI, lifestyle, and renal structure [13–15]. Most participants were over 50. Chronic kidney disease is considered to increase with age [16]. The high prevalence of CKD in older persons reflects the impact of risk factors such diabetes and hypertension [17].

Muntner P et al. estimate that up to 86% of patients with chronic renal disease have hypertension. Hypertension is a modifiable risk factor for cardiovascular disease and is linked to CKD [18]. Uncontrolled hypertension has several adverse effects on kidney function, including glomerular sclerosis and arteriolar nephrosclerosis, which can damage the kidneys [19]. Diabetes mellitus is the second risk factor. Glycosylation end products and reactive oxygen species all contribute to diabetic kidney damage. The kidneys are damaged by many cytokines, growth factors, and hormones, leading to diabetic nephropathy [20]. Along with the two risk factors mentioned previously, the subjects of this study discovered that 57.5 % of subjects had dyslipidemia. Proteinuria is associated with high cholesterol and triglycerides levels. While lipoprotein lipase and LDL receptors are downregulated in CKD, an increase in triglycerides is caused by a slowdown in the catabolism of triglyceride-rich lipoproteins [21].

The average BMI of the subjects in this study was 26.02 ± 4.31, with a BMI of over 25 (kg/m^2) is considered overweight and over 30 (kg/m^2) is considered obese. Hypertension, diabetes, and low HDL all influence the link between obesity and CKD [22]. Biological processes that link obesity with CKD include hormonal variables, inflammation, oxidative stress, and endothelial dysfunction [23]. In this study's subjects, smoking was a minor risk factor. Only 15% of study participants have a history of smoking. Inflammatory responses, immune system regulation, vasopressin-mediated antidiuresis and insulin resistance are all affected by cigarette smoke exposure [24].

The results of the cf-PWV examination varied between 5.41 and 29.21 m/s for the subjects in this study. The standard noninvasive technique for assessing arterial stiffness is pulse wave velocity measurement in the carotid-femoral artery segment [25, 26]. The cf-PWV should be 10 m/s or higher to predict an increased risk of cardiovascular mortality. The link between higher cf-PWV and cardiovascular mortality and incidence [27]. Chronic kidney disease is a risk factor for increased arterial stiffness as measured by cf-PWV and progresses more rapidly than normal renal function subjects [28]. Additionally, cf-PWV is a marker of arterial disease progression in patients with CKD [29].

The presence of cf-PWV was weakly negatively correlated with the progression of kidney disease as measured by serum creatinine and cystatin-C, but positively correlated with glycemic status as measured by HbA1c in this study. Temmar et al. also state that arterial stiffness and vascular calcification manifest earlier in patients with CKD [30]. However, as CKD progresses, only vascular calcification worsens [31]. Increased arterial stiffness is more closely associated with age, systolic blood pressure, diabetes, and vascular calcification in adult patients with chronic kidney disease than uremic toxicity [32].

There is a definite link between hyperglycemia, oxidative stress, inflammation, and type 2 diabetes mellitus development and progression [33]. Arterial stiffness and diabetes are two serious health problems that have been linked [34]. According to Tougaard et al., cfPWV was associated with an increased risk of renal complications, cardiovascular events, and mortality in diabetes individuals [35]. Oxidative stress has been linked to vascular stiffness in diabetics. Alterations in vascular function may be caused by increased oxidative stress and decreased anti-oxidant defense mechanisms [36, 37]. Arteriosclerosis is immediately associated with structural changes in the tunica media, including elastin fragmentation and calcification. Nonetheless, it is influenced by changes in the intima layer's cellular and molecular composition. By increasing the hemodynamic stresses in the vascular lining, particularly the low-impedance and high-flow vessel linings, arteriosclerosis can cause end-organ damage [28].

This study's limitations include subject diversity in terms of CKD development from early stages to end-stage renal disease. Another constraint is the control group's absence from the healthy population.

5 CONCLUSION

According to the results of this study, there was a positive correlation between HBA1C and cf-PWV in patients with CKD. While further studies are required to examine the clinical value of these results, type II diabetes could serve as a predictor of increased arterial stiffness. Thus, HBA1C testing should be regarded standard in CKD patients as a predictor of cardiovascular disease. Additional research with control is needed to determine the effect of type II diabetes and other parameters as the risk factor of arterial stiffness as measured by cfPWV that represent the risk of cardiovascular disease in CKD patients.

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