

Correlations between Total Antioxidant Capacity and 8-Hydroxydeoxyguanosine with carotid-femoral pulse wave velocity in chronic kidney disease

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RESEARCH ARTICLE

Correlations between Total Antioxidant Capacity and 8-Hydroxydeoxyguanosine with Carotid-Femoral Pulse Wave Velocity in Chronic Kidney DiseaseMochamad Yusuf Alsagaff^{1,*}, Budi Susetyo Pikir¹, Mochammad Thaha², Hendri Susilo¹²⁷Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya 60132, Indonesia ⁴⁵⁶Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Jl. Mayjen Prof. Dr. Moestopo No.47, Surabaya 60132, Indonesia ⁴

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Abstract

BACKGROUND: Chronic kidney disease (CKD) is often associated with an increased risk of cardiovascular disease. Cardiovascular disease in CKD can be affected by oxidative stress and inflammation. The oxidative stress can affect arterial stiffness, especially in patients with CKD, which will increase the risk of cardiovascular disease. This study aimed to explain the correlation between total antioxidant capacity (TAC) and 8-hydroxydeoxyguanosine (8-OHdG) with carotid-femoral pulse wave velocity (cf-PWV) in patients with CKD.

METHODS: Forty-three CKD patients was included in this cross-sectional study. TAC was measured from serum samples by colorimetric method and 8-OHdG was measured from urine by enzyme-linked immunoassay method. cf-PWV was measured by Doppler ultrasound as a diagnostic tool for arterial stiffness.

RESULTS: Significant correlations were found between age, estimated glomerular filtration rate (e-GFR), Hemoglobin A1C (HbA1C), serum creatinine, cystatin-C, and severity of CKD with urinary 8-OHdG levels. Serum creatinine, cystatin-C, severity of CKD, age, high-density lipoprotein (HDL), e-GFR, and HbA1C also had significant correlations with serum TAC levels. Other significant correlations between e-GFR, HbA1C, serum creatinine, cystatin-C, and severity of CKD with cf-PWV were also obtained. A significant negative correlation was obtained between serum TAC and cf-PWV with moderate levels of correlation coefficient ($r=-0.504$).

CONCLUSION: There was a negative correlation between TAC and cf-PWV, but there was no significant correlation between 8-OHdG and cf-PWV in patients with CKD.

KEYWORDS: chronic kidney disease, total antioxidant capacity, 8-hydroxydeoxyguanosine, carotid-femoral pulse wave velocity

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Introduction

³¹Chronic kidney disease (CKD) is a global health problem worldwide, in which the prevalence is estimated at up to 15% in the adult population.(1) In countries with low and moderate incomes, CKD has the prevalence of 14.3% and 36.1% in the general population and high-risk populations, respectively. In these countries, people have low awareness of CKD (6-10%).(2) The majority of patients with CKD have a higher risk of cardiovascular disease and death.

This risk increases with the progression of CKD, marked by decreased glomerular filtration rate and increased proteinuria.(3,4)

³⁹In addition to traditional risk factors such as diabetes and hypertension, cardiovascular disease in CKD can also be caused by non-traditional risk factors, such as oxidative stress and chronic inflammation. This is the impact of an increase in reactive oxygen species and a decrease in antioxidant levels.(5,6) In patients with advanced CKD, increased oxidative stress is associated with increased complications, such as hypertension, atherosclerosis,

inflammation, and anemia.(7) Some strategies performed to assess the balance of free radicals and antioxidants are the measurement of total antioxidant capacity (TAC) and 8-Hydroxydeoxyguanosine (8-OHdG).(8,9)

Arterial stiffness is supposed to be associated with oxidative stress through the mechanism of the release of nitric oxide synthase (NOS) and due to oxidative damage to proteins, lipids, and endothelial vascular cell DNA. (10) Inflammation can also cause an increase in arterial stiffness as inflammatory cytokines play a role in decreasing the relaxation of smooth muscle cells by reducing the bioavailability of nitric oxide (NO) and increasing endothelin-1 vasoconstrictor levels.(11) On the other hand, oxidative stress and inflammation can also cause the stiffening of the structure of blood vessels by stimulating the hyperplasia of vascular smooth muscle cells and increasing collagen synthesis.(12) Several methods have been performed to assess arterial stiffness, including pulse wave velocity (PWV).(13)

Oxidative stress is a non-traditional risk factor of CKD. The increase of oxidative stress explains the high incidence of cardiovascular disease in CKD, in which it also becomes a new target in therapeutic interventions. Oxidative stress has been known to affect arterial stiffness, especially in patients with CKD, and can be measured by several methods, such as malondialdehyde (MDA), superoxide dismutase (SOD), catalase, alkenals, TAC, 8-OHdG, etc. Each method has limitations and benefits, for example, MDA and alkenals have many confounding factors, *i.e.*, sugars, amino acid, bilirubin, albumin, and hemolysis. While SOD and catalase are only able to detect enzymatic antioxidants. Total antioxidant capacity has the benefits of measuring both enzymatic and non-enzymatic antioxidant activities. The 8-OHdG also has the benefit of measuring urinary oxidative stress and being a predictive factor for cardiovascular disease.(14,15)

However, until now, the correlation between TAC and 8-OHdG levels as the marker of oxidative stress with carotid-femoral PWV (cf-PWV) as the marker of arterial stiffness in patients with CKD is still unknown. Therefore, we performed this study to determine the correlation between TAC and 8-OHdG with arterial stiffness in CKD patients through the cf-PWV examination.

Methods

A cross-sectional study with 43 CKD patients at Universitas Airlangga Hospital, Surabaya, Indonesia, was conducted in

December 2019-March 2020. This study was approved by the Ethical Committee of Universitas Airlangga Hospital (Certificate No.: 189/KEH/2019).

The inclusion criteria for the participants were: patients with CKD undergoing routine treatment at Universitas Airlangga Hospital, and over 21 years old. The exclusion criteria for the participants were patients with: acute coronary syndromes (such as ST-elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina), acute heart failure, severe infections (sepsis), cancer, and arrhythmia. The sample was collected by consecutive sampling technique.

Data Collection

Data were collected through history taking, blood pressure and anthropometry measurement, blood and urine sampling, and Doppler ultrasound. History taking was assessed by interview. Systolic and diastolic blood pressure were measured by Riester Empire N Floor Mercury Sphygmomanometer (Medaval, Dublin, Ireland). Anthropometry test was performed to measure weight, height, and abdominal circumference. Blood serum was measured for total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins (HDL), creatinine, cystatin-C, Hemoglobin A1C (HbA1C), and TAC. Urine sampling was measured for 8-OHdG.

Oxidative Stress Markers

TAC was measured on the serum with the colorimetric method using Total Antioxidant Capacity Assay Kit (Cat No. PK-CA577-K274, Promokine, Heidelberg, Germany) according to the manufacturer's procedure. The absorbance of the sample was read at 570 nm using colorimeter Advia® 1800 Clinical Chemistry System (Siemens Healthineers, Erlangen, Germany) by comparing the result with the standard. The 8-OHdG was measured on urine using the enzyme-linked immunoassay method with 8-OHdG ELISA Kit (Cat. No. E-EL-0028, Elabscience, Houston, TX, USA) according to the manual instruction. The samples were measured by ELISA reader Humareader (Human Diagnostic Worldwide, Wiesbaden, Germany). The concentration of urinary 8-OHdG was then determined by comparing the optical density (OD) of the samples to the standard curve.

cf-PWV

In the supine position, the common carotid artery was determined by B-mode as high as supraclavicular (1-2 cm from bifurcation). Simultaneous Doppler wave identification was carried out by GE Vivid 5 echocardiography machine

(GE Healthcare, Chicago, IL, USA) synchronized with electrocardiography. This examination was also carried out on the common femoral artery. To find the transit time (t), time measurements were taken from the R waves in the QRS complex to the Doppler wave foot using a digital caliper. Distance between the common carotid artery to the common femoral artery (d) was determined using a measuring tape. cfPWV was obtained by dividing the distance (d) by transit time difference (Δt).

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Statistical Analysis

Data were presented as the mean \pm SD. Spearman tests were performed to assess the correlation between variables. $p < 0.05$ following a two-tailed analysis was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 23 (IBM Corporation, Armonk, New York, USA).

Results

Characteristics of Study Subjects

The characteristics of the study subjects are shown in Table 1. The age range of the study subjects was 31-71 years. Male patients (58%) outnumbered females (42%). The most common cardiovascular risk factors found in the study

subjects were hypertension (90.7%) followed by diabetes mellitus (69.8%) and dyslipidemia (58.1%). The mean body mass index (BMI) of the subjects of this study was 26.51 ± 4.63 , in which obesity ($BMI \geq 30 \text{ kg/m}^2$) is one of the cardiovascular risk factors. It was found that most of the study subjects were overweight and obese, with a BMI of more than 25 kg/m^2 .

In the study subjects we also found other cardiovascular risk factors including increase in total cholesterol levels ($205.86 \pm 52.54 \text{ mg/dL}$), LDL ($123.42 \pm 45.19 \text{ mg/dL}$), creatinine ($6.91 \pm 6.79 \text{ mg/dL}$), cystatin-C ($3.80 \pm 2.63 \text{ mg/L}$), and HbA1c ($6.81 \pm 1.69\%$) and decrease in HDL ($43.88 \pm 14.79 \text{ mg/dL}$) and e-GFR ($28.56 \pm 29.28 \text{ mL/min/1.73m}^2$).

All study subjects were patients with CKD at all stages. From all study subjects, 39.5% were patients with stage 5 CKD who had undergone dialysis, while only 6.96% were patients with stage 1 CKD. The rest of the patients had stage 2-5 CKD with varying percentages. All subjects were given the same treatment in terms of basic data collection, sampling, and examination.

Measurement Results of Serum TAC and urinary 8-OHdG levels

From the present study, the mean level \pm SD of TAC was $1.89 \pm 0.32 \text{ mmol/L}$ with range 1.39-2.50 mmol/L, while

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Table 1. Characteristics of the study subjects (n=43).

Characteristics	n (%)	Mean \pm SD
Male/Female		
Male	25 (58.1)	
Female	18 (41.2)	
Age (years)		56.91 \pm 8.04
History of hypertension	39 (90.7)	
History of diabetes mellitus	30 (69.8)	
Dyslipidemia	25 (58.1)	
Smoking	11 (25.6)	
SBP (mmHg)		139.33 \pm 22.92
DBP (mmHg)		81.05 \pm 13.21
BMI (kg/m ²)		26.51 \pm 4.63
Abdominal circumference (cm)		96.73 \pm 13.58
Total cholesterol (mg/dL)		205.86 \pm 52.54
LDL (mg/dL)		123.42 \pm 45.19
HDL (mg/dL)		43.88 \pm 14.79
Creatinine (mg/dL)		6.91 \pm 6.79
e-GFR (mL/min/1.73m ²)		28.56 \pm 29.28
Cystatin-C (mg/L)		3.80 \pm 2.63
HbA1C (%)		6.81 \pm 1.69
Hemoglobin (g/dL)		12.12 \pm 1.68

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; e-GFR: estimated glomerular filtration rate; HbA1C: Hemoglobin A1C.

13 the mean level of urinary 8-OHdG from the samples was 8.65 ± 11.16 ng/mL with range 0.18-53.60 ng/mL. Kolmogorov Smirnov normality test showed that the data of the two variables were not normally distributed ($p < 0.05$). Spearman correlation test was conducted to determine the correlation between the basic characteristics of the participants with the two variables. In the present study, we found a negative correlation between urinary 8-OHdG and serum TAC ($r = -0.494$, $p = 0.001$).

Table 2 shows the results of the correlation test. Significant positive correlations were obtained between age, e-GFR, and HbA1C with urinary 8-OHdG levels. There were also significant negative correlations between serum creatinine, cystatin-C, and severity of CKD with urinary 8-OHdG levels. Significant positive correlations were obtained between serum creatinine, cystatin-C, and severity of CKD with serum TAC levels. In addition, significant negative correlations were also found between age, HDL, e-GFR, and HbA1C with serum TAC levels.

The cf-PWV Results

The mean \pm SD of the cf-PWV test in the study subjects was 16.46 ± 8.57 m/s with range 6.15-40.60 m/s. Kolmogorov Smirnov test on the cf-PWV variable showed that the data had an abnormal distribution ($p < 0.05$); thus, the Spearman test was performed to determine the correlation between the characteristics of the study subjects with cf-PWV.

Significant positive correlations were obtained between e-GFR and HbA1C with cf-PWV. There were also significant negative correlations between serum creatinine, cystatin-C, and severity of CKD with cf-PWV (Table 3).

Correlation between TAC and 8-OHdG with cf-PWV

Spearman correlation test was performed to determine the correlation between urinary 8-OHdG and serum TAC with cf-PWV. A significant negative correlation was obtained between serum TAC and cf-PWV with moderate levels of correlation coefficient ($p = 0.001$, $r = -0.504$), whereas there was no significant association between 8-OHdG with cf-PWV ($p = 0.073$, $r = 0.276$). This shows that the lower the TAC level was, the higher the cf-PWV was.

Based on the scatter plot graph in Figure 1, visible data plot points form a straight-line pattern from the bottom right to the top left. This shows a linear and negative relationship between the TAC variable (X-axis) with the cf-PWV variable (Y-axis). This negative relationship means that the higher the TAC value is, the lower the cf-PWV value is.

Discussion

This study involved 43 CKD patients, which were dominated by male patients. Sex hormones play a role in the progression of CKD in which estrogen acts as renoprotective factors by inhibiting oxidative stress. Male gender is associated with worse CKD progression. (16) Other than sex hormones, the progression of CKD can also be influenced by several other risk factors, *i.e.*, hypertension, hyperglycemia, albuminuria, dyslipidemia, body mass index, lifestyle, and kidney structure. (16-18) Most of the subjects were more than 50 years old. It is said that the prevalence of CKD increases with age. (19) The high prevalence of CKD in older people reflects the

Table 2. Correlations between characteristics of the study subjects with urinary 8-OHdG levels and serum TAC.

Characteristics of The Study Subjects	8-OHdG		TAC	
	Correlation Coefficient (r)	Significance (p)	Correlation Coefficient (r)	Significance (p)
Age	0.431	0.004*	-0.432	0.004*
SBP	-0.237	0.126	0.119	0.448
DBP	-0.226	0.145	0.233	0.133
BMI	0.134	0.391	-0.057	0.719
Abdominal circumference	0.063	0.688	0.042	0.788
Total cholesterol	0.139	0.374	-0.043	0.787
LDL	0.085	0.589	-0.094	0.547
HDL	0.082	0.601	-0.306	0.046*
Creatinine	-0.537	0.000*	0.801	0.000*
e-GFR	0.517	0.000*	-0.789	0.000*
Cystatin-C	-0.56	0.000*	0.749	0.000*
Severe CKD (eGFR <30 mL/min/1.73m ²)	-0.399	0.008*	0.568	0.000*
HbA1C	0.485	0.001*	-0.336	0.028*

*Significant correlation, tested with Spearman test.

Table 3. Correlation test between characteristics of the study subjects and cf-PWV.

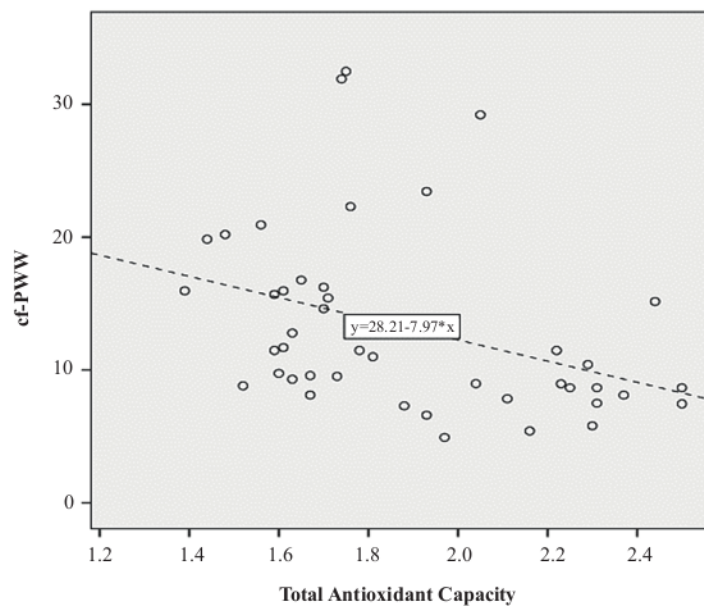
Characteristics of The Study Subjects	Correlation Coefficient (r)	Significance (p)
cf-PWV		
Age	0.287	0.062
SBP	0.217	0.162
DBP	0.058	0.712
Abdominal circumference	-0.017	0.915
BMI	-0.007	0.963
Total cholesterol	-0.029	0.856
LDL	-0.044	0.779
HDL	0.13	0.406
Creatinine	-0.451	0.002*
e-GFR	0.41	0.006*
Cystatin-C	-0.376	0.013*
Severe CKD (eGFR <30 mL/min/1.73m ²)	-0.341	0.025*
HbA1C	0.417	0.005*

cf-PWV: carotid-femoral pulse wave velocity; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; e-GFR: estimated glomerular filtration rate; CKD: chronic kidney disease; HbA1C: Hemoglobin A1C.

influence of different risk factors for CKD, such as diabetes and hypertension in older people.(20)

Significant positive correlations were obtained between serum creatinine, cystatin-C, and severity of CKD with serum TAC levels. Prior study stated that the increase in TAC in uremic patients tends to depend on the increase in uric acid levels.(21) Meanwhile in another study, it was mentioned that uric acid in circulation is a major antioxidant

and can help protect against oxidative damage by free radicals.(22) In addition, this study also found significant negative correlations between age, HDL, and HbA1C with serum TAC levels. The decrease of TAC in the elderly is associated with the decrease in antioxidant capacity and the increase in oxidative stress with age.(23) Also, the condition of dyslipidemia and chronic hyperglycemia will increase oxidative stress by stimulating the release of reactive

**Figure 1. Scatterplot showing the correlation between TAC with cf-PWV.**

oxygen species.(24) This study found that urinary 8-OHdG was independently correlated with serum TAC. Decreased TAC levels, which reflect to increased oxidative stress, may be the reason of increased urinary 8-OHdG in CKD patients. In the level of nucleic acid, 8-OHdG is a marker that indicates DNA damage due to oxidative stress. In this study, significant positive correlations were obtained between age, e-GFR, and HbA1c with urinary 8-OHdG levels. This is consistent with previous study which states that urinary 8-OHdG levels have a significant positive correlation with HbA1C.(25) Correspondingly, the increase of 8-OHdG and various other oxidative stress markers were also found to increase with age.(26) In this study, the level of urinary 8-OHdG was significantly higher in the lower CKD stadiums or pre-dialysis conditions. This is in line with the previous study which also found a significant increase in oxidative markers as well as a deficit of antioxidant defense in pre-dialysis populations.(27)

The mechanism underlying arterial stiffness in patients with CKD is a complex process. It involves vascular calcification, which is associated with chronic kidney disease-mineral and bone disorder (CKD-MBD). (28) CKD-MBD is a complex entity consisting of several abnormalities in mineralization, including hyperphosphatemia, hypercalcemia, hypocalcemia, and hyperparathyroidism.(29) Deposition of calcium salts on tunica intima turns to be a part of atherosclerosis, whereas deposition of calcium salts on tunica media leads to arteriosclerosis. Both conditions occur in CKD, in which arteriosclerosis plays the most crucial role in arterial stiffness progression.(30)

In this study, a negative correlation was obtained between TAC and cf-PWV. The decrease in TAC is associated with conditions with decreased antioxidant defense mechanisms, thereby increasing oxidative stress. The decrease of TAC and arterial elasticity in 133 patients with essential hypertension, while arterial stiffness increased in elderly patients with hypertension. The decrease of antioxidant capacity contributes to vascular damage and decreased arterial elasticity in elderly patients with essential hypertension.(31) Previous study showed that strength training programs significantly affected the oxidative stress parameters, which were positively correlated with arterial stiffness. Therefore, this finding has significant implications for cardiovascular fitness after high-intensity strength training.(32)

Increased oxidative stress and decreased ability of defense mechanisms to fight oxidative stress and inflammation can contribute to changes in vascular

function.(33) Increased arterial stiffness with arteriosclerosis can result in end-organ damage by increasing hemodynamic pressure in the lining of blood vessels, especially in the parts with low impedance and high flow.(30)

The measurement of urinary 8-OHdG in the present study subjects had no significant correlation with cf-PWV. As far as the authors know, there have been no studies linking urinary 8-OHdG with cf-PWV in patients with CKD. There was a significant correlation between serum 8-OHdG and arterial stiffness measured by ba-PWV in patients with stage 2-5 CKD.(34) Another study did not find any significant correlation between urinary 8-OHdG and cf-PWV in type 2 DM patients without hypertension, but there was a significant correlation in type 2 DM patients with hypertension.(35) The patients are influenced by several comorbidities such as diabetes mellitus, dyslipidemia, and hypertension, all of which are related to oxidative stress.(7,36) CKD itself is a condition of oxidative stress independently of the underlying conditions.(37) Hemodialysis has also been shown to play a role in increasing oxidative stress.(38) In addition, several comorbidities in research subjects with varying distribution can contribute to the progression of arterial stiffness (39), so measurement of 8-OHdG urine is not the only oxidative stress parameter that plays a role in the progression of arterial stiffness. The 8-OHdG is a product from the interaction between guanine in DNA and free radicals. It is usually detected in the urine or serum of the patients and, the elevated levels of 8-OHdG have been generally acknowledged as a biomarker for oxidative damage in atherosclerosis. However, its role in the arterial stiffness is still controversial and needs further research.(40)

More evidence shows that oxidative stress is considered as an important cardiovascular risk factor in patients with CKD. Cardiovascular disease is a significant etiology of morbidity and mortality in CKD patients. Biomarker examination can be used in clinical practice to monitor the oxidative imbalance of CKD patients. It is crucial to provide optimal intervention strategies to reduce oxidative stress in CKD patients.

The limitation of this study includes the high variability of the study population related to the distribution of chronic kidney disease from the early stages to end-stage renal disease. Another limitation includes the absence of the control group from the healthy population. Further research on the role of various other oxidative stress parameters on arterial stiffness as measured by cf-PWV needs to be conducted, as well as the research on the role of antioxidants in improving arterial stiffness and prospectively reducing the risk of cardiovascular disease.

Conclusion

There was a negative correlation between TAC and cf-PWV in patients with CKD. TAC measurement can be considered as a routine examination in CKD patients as a predictor of the risk of cardiovascular disease. In this research, there was no significant correlation between 8-OHdG and cf-PWV in patients with CKD. Even though 8-OHdG is widely known as the biomarker of arteriosclerosis, its role in the arterial stiffness still needs further research.

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