RESEARCH ARTICLE

The role of oxidative stress markers in Indonesian chronic kidney disease patients: a cross sectional study [version 1; peer review: awaiting peer review]

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Abstract

Background: Several aspects of chronic kidney disease (CKD) such as the incidence rate and mortality rate are concerning. Oxidative stress contributes to progression and mortality in patients with CKD; however, a specific correlation between several markers of oxidative stress and the estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) in the Indonesian population has not been sufficiently described yet.
Methods: This study was an analytic observational study with a sample of 56 patients with CKD in Universitas Airlangga Hospital, Surabaya, Indonesia, from December 2019 – March 2020. The markers for oxidative stress investigated were urinary 8-hydroxy-2 deoxyguanosine (8-OHdG), serum symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA). The correlations between each variable of oxidative stress and CKD were analyzed using Pearson analysis.
Results: There was a positive correlation between 8-OHdG and eGFR (p=0.00, r=0.51); however, there was a negative correlation between 8-OHdG and ACR (p=0.025, r=-0.30). SDMA and eGFR showed a negative correlation (p=0.00, r=-0.648), while SDMA and ACR showed a positive

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correlation (p=0.03, r=0.349). ADMA showed a negative correlation with eGFR (p=0.00, r=-0.476). There were significantly decreased 8-OHdG but increased ADMA and SDMA as the CKD stage progressed (p=0.001, p=0.00, and p = 0.00, respectively). Higher urine 8-OHdG was detected in patients without history of hemodialysis, whereas ADMA and SDMA showed higher value in patients with hemodialysis (p=0.00, p=0.00, and p=0.004, respectively), patients with history of diabetes mellitus (DM) had higher mean 8-OHdG (p 0.000) yet lower serum ADMA and SDMA (p=0.004 and p=0.003, respectively).
Conclusions: In patients with CKD in Indonesia, the markers for oxidative stress 8-OHdG, SDMA, and ADMA are correlated with eGFR and ACR levels. There were also significant difference in 8-OHdG, SDMA, and ADMA levels among CKD stages, between dialysis vs non dialysis, and DM vs non DM patients.

Keywords
oxidative stress, chronic kidney disease, 8-OHG, SDMA, ADMA, health risk

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Introduction

Chronic kidney disease (CKD) is one of the diseases with the highest incidence and mortality rates among noncommunicable diseases. There were 697.5 million cases of all-stage CKD, and 1–2 million people died from CKD in 2017.[1] A study in Korea found that the mortality rate of patients with CKD was 134 per 1000 patients annually and higher than that for patients with diabetes mellitus (DM) or hypertension without CKD, which was only 34 per 1000 patients annually.[2] This result showed that CKD is a health burden with a high cost for the health care system in both developed and developing countries, including Indonesia. According to the results of Basic Health Research in 2018, 0.38% or 739,208 Indonesian citizens suffer from CKD.[3] This number is increased compared to the result of Basic Health Research in 2017, which found that the prevalence of CKD at the time was 0.2%.[4]

Oxidative stress contributes greatly to the progression and mortality of patients with CKD. In a previous study, 8-Hydroxy 2-deoxyguanosine (8-OHdG) was found to have correlations with an increased risk of death in patients with CKD with different levels of the estimated glomerular filtration rate (eGFR).[5] Asymmetric dimethylarginine (ADMA), which inhibits nitric oxide both *in vivo* and *in vitro*, is a strong predictor of progression in patients with CKD stage 3–4 (eGFR between 25–40 mL/min/1.73 m2).[6] An increased level of symmetric dimethylarginine (SDMA), which also has a similar function as ADMA, is closely correlated with an increased risk of death in patients with CKD.[7] Several studies have shown that there is a correlation between the levels of oxidative stress markers and CKD in general; however, studies in the Indonesian population that showed the relationship between these variables are still very limited. Therefore, we decided to study the correlation between 8-OHdG, SDMA, and ADMA with the level of severity of CKD as measured by albumin-creatinine ratio (ACR) and eGFR.

Methods

Participants

This study was an analytic observational study with a cross-sectional design. This study used the consecutive sampling technique. The sample contained 56 patients with CKD in the Nephrology Outpatient Clinic, Universitas Airlangga Hospital, Surabaya, Indonesia who met the inclusion criteria from December 2019 to March 2020.[60] The inclusion criteria of this study selected patients with CKD of all stages who were under medical care in Universitas Airlangga Hospital aged 21 years and older. The exclusion criteria of the samples in the study removed patients with a history of acute coronary syndrome, acute heart failure, severe infection, cancer, and arrhythmia.

Written informed consent to be a study subject was obtained from the patients according to the Declaration of Helsinki. This study received approval from the ethical committee of Universitas Airlangga Hospital (certification number: 189/KEH/2019).

Data collection

Data was obtained through history taking, anthropometric and vital sign examinations, and blood and urine sampling from the patients. History taking was carried out by directly interviewing the patients: Basic identity, duration of kidney disease, duration of dialysis, history of hypertension, history of diabetes mellitus, history of smoking and history of cardiovascular disease were all taken into consideration. Anthropometric examination was carried out to measure height, body weight, and abdominal circumference. Vital sign examination of blood pressure was carried out using a mercury sphygmomanometer (Big Ben stand model, Riester, Germany). eGFR measurement was carried out using the CKD-EPI Creatinine Equation (2009) to estimate the glomerular filtration rate (GFR).[8] A 6-cc blood sample was drawn from the patients, the serum was separated, and urine samples were also obtained for laboratory marker examination in a private laboratory.

Laboratory examination

Measurement of 8-OHdG, ADMA, and SDMA levels was carried out with the enzyme-linked immunoassay (ELISA) method using a Human 8-OHdG ELISA Kit (Cat. No E-EL-0028, Elabscience, USA), Human ADMA ELISA Kit (Cat. No E-EL-0042, Elabscience, USA), and Human SDMA ELISA Kit (Cat. No E-EL-H5659, Civic Bioscience, Canada), respectively. HbA1c levels were measured using high-performance liquid chromatography using an HbA1c HPLC assay (Cat. No A1C31-H100, Eagle Bioscience, USA). Lipid profile [total, low-density lipoproteins (LDL), and high-density lipoproteins (HDL) cholesterol], albumin, and serum creatinine were performed in fasting patients and conducted in Prodia laboratory, Surabaya, Indonesia.

Urine samples were taken from patients with all CKD stages, including patients who had undergone chronic dialysis (5D) after dialysis. Each patient was given a urine sample tube to take home in order to collect the urine. The urine samples were checked for 8-OHdG by ELISA using the Human 8-OHdG ELISA Kit (Cat. No E-EL-0028, Elabscience, USA), the albumin was measured with a calorimetry method[9] using an Albumin (BCG) Assay Kit (Colorimetric) (Cat. No

ab235628, Abcam, UK) through the utilization of bromocresol purple that forms a colored complex specifically according to the manufacturer's instruction, and urine creatinine was measured with a colorimetry method using a creatinine assay kit (Cat. No MAK080, Sigma Aldrich, USA). From the albumin and urine creatinine levels, we calculated the albumin-creatinine ratio (ACR).

Statistical analysis

Numerical data are presented as the mean ± SD. Data normality tests were carried out using the Shapiro–Wilk test. Pearson correlation tests were used to analyze the correlation between each variable. Kruskal Wallis followed by Mann Whitney post hoc test was conducted to determine the differences of 8-OHdG level in each CKD stage. One-way ANOVA followed by post-hoc LSD test was performed to determine the differences of SDMA and ADMA levels in each CKD stage. The Mann Whitney test was used to analyze the differences in 8-OHdG and SDMA levels between dialysis vs non dialysis patients and DM vs non-DM patients. Independent t-test was performed to determine the association in ADMA levels between dialysis vs non dialysis patients and DM vs non-DM patients. A p value of <0.05 showed a significant test result. All statistical analysis was performed using SPSS application version 23 (IBM Corporation, Armonk, New York, USA).

Results

The characteristics of the study samples are presented in Table 1. The age range of the patients enrolled was between 31–71 years old, with a majority of subjects being male (55.4%) compared to female (44.6%). The sample was dominated by patients with CKD stage 5 (42.9%), in which 3.6% were predialysis and 39.3% were on dialysis. The majority of the study subjects had comorbid hypertension (89.3%). The majority of the patients had diabetic kidney disease (75%), while the cause of the other cases (25%) was not known. Anthropometric examination showed that the majority of the patients were categorized as obese (57%). Lipid profile tests also showed dyslipidemia in the majority of the samples with an increase in total cholesterol level and LDL cholesterol level, while a decrease in HDL cholesterol level. The oxidative stress marker examination found varied results.

As shown in Table 2, we found a significant positive correlation between 8-OHdG and eGFRR (p=0.00, r=0.51); however, there was a negative correlation between 8-OHdG and ACR (p=0.025, 5=-0.30). SDMA and eGFR showed a negative correlation (p=0.00, r=-0.648), while SDMA and ACR showed a positive correlation (p=0.03, r=0.349). Meanwhile, ADMA showed a negative correlation with eGFR (p=0.00, r=-0.476), whereas ADMA and ACR were not significantly correlated. From Table 3, it can be inferred that there were significant differences of 8-OHdG, ADMA, and SDMA levels among CKD stages. As can be seen, urinary 8-OHdG significantly declined as the CKD progressed (p=0.001), with the lowest level in stage V. On the contrary, both ADMA and SDMA showed significant increase as the CKD got more advanced (p=0.000 and p=0.000 respectively), with the highest levels in stage V.

8-OHdG, ADMA, and SDMA were also evaluated among patients with previous history of hemodialysis and diabetes mellitus (Table 4). All of the stress oxidative markers tested above showed different results when being compared between patients with a history of hemodialysis and patients without (8-OHdG p=0.000; ADMA p=0.000; SDMA=0.000). Higher urinary 8-OHdG was detected in patients without history of hemodialysis, whereas ADMA and SDMA showed higher value in patients with hemodialysis. Patients with history of diabetes mellitus also had higher mean 8-OHdG (p=0.000) yet lower serum ADMA and SDMA (p=0.004 and p=0.003, respectively).

Discussion

Sample characteristics

Gender and age

According to the results of the study, the number of male patients (31/56, 55%) was slightly greater than that of female patients (25/56, 45%); however, there was no significant difference between gender and the prevalence of CKD. We also found that the average age of the patients was 57.02±7.59, which is in accordance with the increasing prevalence of CKD with age. Increasing age will affect the anatomy, physiology and cytology of the kidneys. The changes that occur, including a reduced number of nephrons due to chronic glomerulonecrosis, cause disturbances of physiological processes of the kidneys, characterized by a decrease in GFR as age increases.[10]

CKD stage and history of hemodialysis

This study involved patients from all CKD stages.[1–5] According to this study, the majority of patients were in stage 5 (42.8%), followed with stage 3 and 4 (23.2% for both), stage 2 (7.1%), and the least were stage 1 (3.6%). The number of patients with a history of hemodialysis was 22 (39%). Hemodialysis is an artificial process as a substitute of the kidney,

Table 1. Characteristics of the study samples from all chronic kidney disease (CKD) stages.

Characteristics		Total	CKD Stage 1	CKD Stage 2	CKD Stage 3	CKD Stage 4	CKD Stage 5
Samples	n (%)	56 (100)	2 (3.6)[a]	4 (7.1)[a]	13 (23.2)[a]	13 (23.2)[a]	24 (42.8)[a]
Gender							
Male	n (%)	31 (55.4)[a]	0 (0)[a]	4 (7.1)[a]	7 (12.5)[a]	6 (10.7)[a]	14 (25)[a]
Female	n (%)	25 (44.6)[a]	2 (3.6)[a]	0 (0)[a]	6 (10.7)[a]	7 (12.5)[a]	10 (17.8)[a]
Age	years	57.02±7.59	56.00+8.49	58.25+7.85	58.31+4.87	59.15+4.88	55.04±9.69
History of Hypertension	n (%)	50 (89.3)[a]	1 (50)[b]	4 (100)[b]	9 (69.2)[b]	13 (100)[b]	23 (95.8)[b]
History of Diabetes Mellitus	n (%)	42 (75)[a]	2 (100)[b]	4 (100)[b]	11 (84.6)[b]	12 (92.3)[b]	13 (54.2)[b]
History of Smoking	n (%)	10 (17.9)[a]	0 (0)[b]	1 (25)[b]	1 (7.6)[b]	2 (15.4)[b]	6 (25)[b]
History of Hemodialysis	n (%)	22 (39.3)[a]	0 (0)[b]	0 (0)[b]	0 (0)[b]	0 (0)[b]	22 (91.7)[b]
Body Mass Index	cm/m^2	26.08±4.65	24.50±4.24	25.55±2.58	26.88±5.22	26.92±4.30	25.40±4.97
Abdominal Circumference	cm	91.84±17.79	88.50±13.44	86.00±1.41	91.08±20.46	96.42±13.10	90.51±20.00
Systolic Blood Pressure	mmHg	138.93±22.31	124.00±22.63	127.50±1.00	127.00±17.85	130.15±19.96	153.29±20.31
Diastolic Blood Pressure	mmHg	78.32±12.61	77.50±0.71	80.00±10.46	77.38±13.25	70.77±12.23	82.71±11.95
HbA1c	%	6.85±1.67	10.65±1.77	7.63±0.92	6.92±1.12	6.73±1.39	6.44±1.24
Total Cholesterol	mg/dL	216.55±66.02	225.50±12.02	192.00±48.35	250.52±80.78	213.62±57.36	203.04±63.46
HDL-Cholesterol	mg/dL	44,41±15.70	57.50±12.02	49.25±11.70	47.85±11.13	50.31±16.72	37.46±16.10
LDL-Cholesterol	mg/dL	126.39±52.73	142.00±4.24	113.00±34.77	166.00±66.34	126.77±52.61	105.67±36.91

[a]Percentage of total samples.
[b]Percentage of total samples in each stage.

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Table 2. Correlation between 8-hydroxy-2 deoxyguanosine (8-OHdG), serum symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) with estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR).

	eGFR		ACR	
	Correlation coefficient (r)	Significance (*p value*)	Correlation coefficient (r)	Significance (*p value*)
8-OHdG	0.51	0.00*	-0.30	0.025*
SDMA	-0.648	0.00*	0.349	0.03*
ADMA	-0.476	0.00*	0.147	0.278

*Statistically significant (p<0.05).

Table 3. Examination of stress oxidative markers as the chronic kidney disease (CKD) progresses.

	CKD Stage I	CKD Stage II	CKD Stage III	CKD Stage IV	CKD Stage V	p-value
8-hydroxy-2 deoxyguanosine	23.49±5.18	18.13±12.67	14.81±14.76	7.31±5.80	3.11±2.06	0.001[a]
Asymmetric dimethylarginine	75.50±10.61	81.50±5.20	83.00±14.62	93.85±16.76	106.83±15.22	0.000[b]
Serum symmetric dimethylarginine	100.50±27.58	142.50±25.33	240.85±90.30	357.00±155.51	929.29±436.47	0.000[b]

[a]Kruskal Wallis followed with Mann Whitney.
[b]ANOVA followed with LSD.

Table 4. Stress oxidative markers in patients with history of hemodialysis and diabetes mellitus.

	History of hemodialysis			History of diabetes mellitus		
	Yes	No	p-value	Yes	No	p-value
8-hydroxy-2 deoxyguanosine	2.78±1.62	12.37±11.54	0.000[x]	10.62±10.92	2.54±2.76	0.000[x]
Asymmetric dimethylarginine	108.14±15.24	87.09±14.97	0.000[y]	91.74±16.65	106.21±18.86	0.004[y]
Serum symmetric dimethylarginine	975.73±425.41	275.88±143.30	0.000[x]	407.93±292.12	979.50±560.99	0.003[x]

[x]Mann Whitney.
[y]Independent t-test.

removing wastes and excess water from the blood, mainly in patients with impaired renal function.[11] Most guidelines recommend dialysis in CKD patients with a GFR < 15 ml/min/1.73 m^2, while the role of hemodialysis in CKD patients with GFR above 15 ml/min/1.73 m^2 is uncertain.[12]

History of hypertension and diabetes mellitus

The majority of the patients had a history of hypertension (89.3%), with an average systolic blood pressure of 138.93±22.31 mmHg and diastolic blood pressure of 78.32±12.61 mmHg. From these results, we can see that the great majority of CKD patients suffer from hypertension, which is both a cause and an effect of the disease.[13] Moreover, we also found a large number of patients had a history of diabetes mellitus (75%) with an average HbA1c level of 6.85±1.67%. This is in accordance with a study by Sinusi and Hargono (2021) according to data from the Indonesian Family Life Survey 5 (IFLS-5), which showed that hypertension and diabetes mellitus are the primary risk factors for CKD.[14] Uncontrolled hypertension is a risk factor of arteriolar nephrosclerosis, a vascular injury in the preglomerular arterioles that leads to glomerular ischemia,[15] whereas a high level of blood glucose will impair the insulin signaling pathway in the glomerulus of the kidneys, which leads to proapoptotic environment.[16] Diabetic kidney disease (DKD) is

the most common cause of the end-stage renal disease (ESRD). The prevalence of DKD remains high despite rigorous treatments such as hyperglycemic management, blood pressure control, and the use of renin-angiotensin system blockades.[17] In DKD, increased proximal tubular reabsorption of glucose via sodium–glucose cotransporter 2 reduces distal supply of solutes, notably sodium chloride, to the macula densa. The consequent decrease in tubuloglomerular feedback may widen the afferent arteriole, increasing glomerular perfusion, whereas increased local angiotensin II production causes vasoconstriction at the efferent arteriole. These will lead to high intraglomerular pressure and glomerular hyperfiltration.[18,19]

Obesity and lipid profile

From anthropometric examination, it was found that the majority of patients were categorized as obese (57%), with an average body mass index (BMI) of 26.08±4.65 and average abdominal circumference of 91.84±17.79 cm. This corresponds to a previous study that showed that there is an association between obesity and high blood pressure.[20–22] The results of the lipid profile test of the patients also showed dyslipidemia in the majority of samples with increased total cholesterol levels (216.55±66.02 mg/dL) and LDL cholesterol (126.39±52.73 mg/dL) and decreased HDL cholesterol levels (44.41±15.70 mg/dL). Dyslipidemia is a common finding in patients with kidney disease, in which the abnormal lipid profile varies, such as high triglycerides and total cholesterol, increased LDL followed by low, normal, or increased HDL.[23]

Correlation between oxidative stress markers and CKD

8-OHdG and chronic kidney disease

One of the risk factors for kidney damage is oxidative stress.[24] One of the markers of oxidative stress found to be increased in patients with CKD is a product of nucleic acid oxidation, which is 8-OHdG.[25] 8-OHdG or 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) are free radicals commonly found due to oxidative injury and often become markers of oxidative stress or carcinogenesis.[26] This biomarker is also helpful in detecting the presence of microvascular and macrovascular complications.[27] 8-OHdG is excreted in the plasma and urine; therefore, can be easily measured.[28]

In patients with CKD, there is an increased level of oxidative stress biomarkers, including 8-OHdG.[29] In this study, there was a significant positive correlation between 8-OHdG and eGFR (p=0.00, r=0.51; moderate correlation); however, there was a negative correlation between 8-OHdG and ACR (p=0.025, r=-0.030; very weak correlation). This is in accordance with a previous study that also showed that increased levels of 8-OHdG were directly proportional to increased eGFR and inversely correlated with ACR.[30] Another study by Dincer *et al* (2008) also showed an increased level of this biomarker in patients with proteinuria.[31]

In this study, there was a significant decline in 8-OHdG level among CKD stages (p=0.001). This is different from previous studies, which showed an increased level of oxidative stress biomarker, including 8-OHdG along with CKD progression.[29,32] In contrast with SDMA and ADMA, which were measured from serum, 8-OHdG was measured from urine. A possible explanation was because renal function has a direct effect on the ability to filter and eliminate solutes like oxidant stress biomarkers. As a result, those with poor kidney function may have been the least able to filter biomarkers at the glomerular level and/or produce oxidative stress analytes into the urine. Low urine concentrations would arise from these abnormalities. In epidemiologic literature, this is referred to as reverse causation, because kidney function may alter the exposure measurements of interest.[30] We also found a significantly lower 8-OHdG level in dialysis vs non dialysis patients (p=0.000). This is in line with a study by Navarro *et al* (2019), which stated that the membrane and dialysate cause inflammation and a significant rise in ROS generation when dialysis is first started. The levels of Oxidized LDL have been found to be higher after dialysis. However, post-dialysis, xanthine oxidase activity and 8-OHdG levels are significantly lower, implying that oxidative stress indicators are efficiently filtered during the dialysis process, suggesting that dialysis could reduce oxidative stress markers[33] We also found a significantly higher 8-OHdG level in DM vs non-DM patients (p=0.000). A study conducted by Liu *et al* (2016) found significantly increased 8-OHdG in patients with type two DM with and without complications compared to healthy control. Increased levels of 8-OHdG as an oxidative stress marker are likely to cause strand breakage and oxidative base alterations, and numerous signaling pathways may potentially play a role in glucotoxicity's negative effects on cellular activities.[34]

ADMA and chronic kidney disease

ADMA is a potent endogenous nitric oxide synthase (NOS) inhibitor. This substance can accumulate and cause endothelial disorders, increased blood pressure, and proteinuria which contribute to the progression of cardiovascular diseases leading to kidney dysfunction.[35] Over synthesis of ADMA causes increased blood pressure, extracellular matrix

synthesis, and decimation of peritubular capillaries, which may result in chronic kidney failure.[36] Previous studies showed that there was an increase in ADMA levels due to inhibition of nitric oxide (NO) discharge in patients with CKD accompanied by decreased endothelial function. ADMA competes with L-arginine to inhibit NOS, which causes endothelial dysfunction.[37] Several functions of NO in the body are the regulation of vascular tone and blood pressure; therefore, if there is an inhibition of NOS, the regulation of both of these systems will also be compromised.[38] A previous study showed proof of the impact of increased ADMA levels on the cardiovascular risk of patients with CKD, which was a significant positive correlation between increased ADMA levels and carotid intima-media thickness; therefore, this biomarker can also detect atherosclerosis in patients with CKD.[39]

This study showed that there was a negative correlation between ADMA and eGFR (p=0.00, r=-0.476; moderate correlation). This is in accordance with other studies that also found that increased plasma ADMA concentration has a significant negative correlation with a decrease in eGFR; however, the exact mechanism is still unclear.[40] In this study, we found that significantly increased ADMA level was found in late CKD stage and in dialysis compared to non-dialysis patients (p=0.000 for both). As stated by previous studies, increased levels of ADMA are associated with the progression of CKD, especially in those who received routine hemodialysis.[41–43] Vallance *et al*. also found that hemodialysis patients with ESRD had higher ADMA levels than controls. ADMA appears to predict cardiovascular outcome and mortality in ESRD dialysis patients.[44] However, there are other independent factors that should be taken into consideration, including age, sex, and smoking history.[45] Another factor that should not be overlooked is genetic factors. Previous studies have shown that increased ADMA levels are also associated with certain genetic variations, primarily the G-449 allele in the DDAH2 gene.[46] We also found a significantly increased ADMA level in DM patients compared to non DM (p=0.004). In type 2 DM, ADMA may play a key role in increasing vascular damage and is a strong determinant of insulin resistance.[47]

This study also showed that there was no significant correlation between ADMA and ACR (p=0.278). This result contradicts previous studies that found that there is an association between ADMA level and ACR. Several mechanisms by which this association occurs are inflammatory processes, vascular disorders such as endothelial dysfunction or atherosclerosis, and other processes, namely, collagen production and glycation processes in the renal microcirculation.[48,49] However, these associations cannot be separated from other factors, such as distinct individual demographic characteristics, hemodynamics and metabolic factors.[50] The level of albumin in the urine also showed an interaction between ADMA and kidney structures. Increased ACR indicates the occurrence of endothelial dysfunction, which can develop into hypertension.[48]

SDMA and chronic kidney disease

SDMA is an inactive stereoisomer that is produced concomitantly with ADMA.[51] The synthesis of ADMA is affected by the reaction between superoxide anions and nitric oxide, which produces peroxynitrate, which results in tissue damage.[52] SDMA is related to endothelial dysfunction and has a similar role to creatinine in the calculation of GFR. SDMA is excreted in the urine. SDMA, compared to ADMA, is more commonly found in patients with ESRD and is a more sensitive biomarker of alteration of renal function; therefore, SDMA can be treated as a specific biomarker.[43] A study by Patel *et al*. (2019) also showed that SDMA is a stronger predictor for mortality risk in patients with CKD than ADMA.[53] SDMA can stimulate ROS production, which induces proinflammatory effects in patients with CKD.[54] In another study, it was found that in acute inflammation, ADMA but not SDMA is decreased. This became the initial question of whether SDMA and ADMA have different metabolic pathways and pathophysiological roles.[51]

In this study, the results showed that SDMA had a significant negative correlation with eGFR (p=0.00, r=-0.648; strong correlation) and a significant positive correlation with ACR (p=0.03, r=0.349; weak correlation). This can be interpreted as follows: the lower the eGFR is and the higher the ACR is, the more SDMA is detected. Another study also showed that there was an inverse correlation between SDMA and eGFR in patients with renal dysfunction; however, it was better at detecting CKD in early stages.[55] SDMA also increases with creatinine in patients with CKD. Apparently, creatinine is less sensitive, and its detection is delayed[56]; therefore, SDMA has become a novel option to detect a decrease in GFR more accurately at earlier stages.[57] Another study showed that there was an increase in SDMA at 6 hours after a 60% decrease in GFR, which reached the peak at 24 hours after nephrectomy and lasted for 7 days.[57] In this study, we found a significant increase of SDMA level in late CKD stages and in dialysis patients (p=0.000 for both), showing that SDMA could predict CKD progression and be reduced by hemodialysis. However, how dialysis affects SDMA levels is not well known. Although initially SDMA was thought of no use, recent research shows that it has been a remarkable marker of renal function, with ESRD patients on dialysis showing the highest SDMA levels.[58] We also found increased SDMA level in patients with DM (p=0.003). Elevated SDMA is associated with many diseases related with endothelial dysfunction, including DM. A possible explanation is the increased activity of arginine methyltransferase along with hyperglycemia, leading to increased SDMA synthesis.[59,60]

Limitations of the study

The limitation of this study was the lack of a healthy control group; therefore, the differences between the levels of the three oxidative stress markers in healthy people and patients with CKD are unknown. Another limitation was that we only collected samples from a single center, limiting the generalization of our results. In addition, some samples were CKD stage 5 with hemodialysis, in which the hemodialysis procedure itself could influence the data of these oxidative stress markers.

Conclusions

In patients with CKD in Indonesia, the oxidative stress markers 8-OHdG, SDMA, and ADMA correlated with the levels of eGFR and ACR, representing the level of severity of CKD. There were also significantly difference in 8-OHdG, SDMA, and ADMA levels among CKD stages, between dialysis and non-dialysis, DM and non-DM patients. In conclusion, 8-OHdG, ADMA, and SDMA levels can be used as prognostic markers and are potential candidates for future therapies in patients with CKD.

Data availability

Underlying data

Harvard Dataverse: The role of oxidative stress markers in Indonesian Chronic Kidney Disease (CKD) patients https://doi.org/10.7910/DVN/ATSYBZ.[61]

The project contains the following underlying data:

- Riset Cardiorenal 56.tab (raw per subject data)

Consent

Written informed consent for publication of the participants' details was obtained from the participants.

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