

# The importance of oxidative stress markers in Indonesian patients with chronic renal disease

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## INTRODUCTION

Chronic kidney disease (CKD) is one of the no communicable illnesses with the highest incidence and fatality rates. In 2017, 697.5 million people had all-stage CKD, and 1-2 million people died from it. According to a Korean study, patients with CKD had a mortality rate of 134 per 1000 patients per year, which is greater than patients with Diabetes Mellitus (DM) or hypertension who do not have CKD, who have a mortality rate of 34 per 1000 patients per year. This finding revealed that CKD is a public health problem that costs the health-care system a lot of money in both rich and developing countries, including Indonesia. According to the findings of the 2018 Basic Health Research, 0.38% of Indonesian residents, or 739,208 people, have CKD. This number is higher than the findings of Basic Health Research from 2017, which found that the prevalence of CKD was 0.2% at the time. Oxidative stress plays a significant role in the progression and death of CKD patients. 8-Hydroxy 2-deoxyguanosine (8-OHdG) was linked to an elevated risk of death in individuals with CKD who had varying levels of estimated glomerular filtration rate in a prior study (eGFR) [1]. In individuals with CKD stage 3-4 (eGFR between 25 mL/min/1.73 m<sup>2</sup> and 40 mL/min/1.73 m<sup>2</sup>), asymmetric dimethyl arginine (ADMA), which suppresses nitric oxide both in vivo and in vitro, is a powerful predictor of progression. In patients with CKD, an elevated level of Symmetric Dimethyl Arginine (SDMA), which functions similarly to ADMA, is linked to an increased risk of death. Several researchers have found a link between oxidative stress indicators and CKD in general; however, studies of this association in the Indonesian community are still scarce. As a result, we chose to investigate the relationship between 8-OHdG, SDMA, and ADMA and CKD severity as determined by the Albumin-Creatinine Ratio (ACR) and eGFR.

According to the findings, the number of male patients (31/56, 55%) was slightly higher than the number of female patients (25/56, 45%); however, there was no statistically significant difference between gender and the prevalence of CKD. We also discovered that the patients' average age was 57, which is consistent with the rising frequency of CKD with age. The structure, physiology, and cytology of the kidneys will change as we get older. The changes that occur, such as a decreased number of nephrons due to chronic glomerulonephrosis, disrupt kidney physiological processes, resulting in a decrease in GFR as one becomes older [2]. Patients from all stages of CKD were included in this study. According to the findings, the majority of patients were in stage 5 (42.8%), followed by stage 3 and 4 (23.2%) for both, stage 2 (7.1%), and stage 1 (0.1%) (3.6%) The number of patients who had previously had hemodialysis increased (39%). Hemodialysis is a synthetic kidney replacement that removes wastes and excess water from the blood, primarily in individuals with poor renal function. The role of hemodialysis in CKD patients with GFRs greater than 15 mL/min/1.73 m<sup>2</sup> is unknown, according to most guidelines. With an average systolic blood pressure of 138.9 mmHg and diastolic blood pressure of 78.3 mmHg, the majority of the patients (89.3%) had a history of hypertension. These findings show that hypertension affects the vast majority of CKD patients, which are both a cause and an effect of the disease. Furthermore, we discovered that a substantial percentage of patients (75%) had diabetes mellitus, with an average HbA1c level of 6.851.67%.

According to data from the Indonesian Family Life Survey (IFLS-5), hypertension and diabetes mellitus are the key risk factors for CKD [3].

The most common cause of end-stage renal disease is Diabetic Kidney Disease (DKD) (ESRD). Despite aggressive treatments such as hyperglycemia management, blood pressure control, and renin-angiotensin system blockades, the prevalence of DKD remains high. Increased proximal tubular glucose reabsorption via the sodium-glucose transporter lowers the distal supply of solutes to the macula densa in DKD. Increased local angiotensin II production promotes vasoconstriction at the efferent arteriole, whereas decreased tubule-glomerular feedback may expand the afferent arteriole, boosting glomerular perfusion. High intra-glomerular pressure and glomerular hyper-filtration will result. An anthropometric assessment revealed that the majority of patients (57%) were obese. Dyslipidemia is a common lipid profile abnormality in people with kidney disease, with high triglycerides and total cholesterol, elevated LDL followed by low, normal, or increasing HDL.

Oxidative stress is one of the risk factors for kidney injury. 8-OHdG, a result of nucleic acid oxidation, is one of the markers of oxidative stress shown to be elevated in individuals with CKD. 8-OHdG, also known as 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG), is free radicals that are regularly discovered as a result of oxidative injury and are frequently used as markers of oxidative stress and carcinogenesis. This biomarker also aids in the detection of micro vascular and macro vascular problems. Because 8-OHdG is excreted in both plasma and urine, it is easily quantified. The amount of oxidative stress indicators, such as 8-OHdG, is higher in patients with CKD. In this study, 8-OHdG and eGFR had a substantial positive association ( $p=0.00$ ,  $r=0.51$ ; moderate correlation); whereas, 8-OHdG and ACR had a significant negative correlation ( $p=0.025$ ,  $r=-0.030$ ; extremely weak correlation). This is in line with recent research, which found that higher levels of 8-OHdG were directly proportionate to higher eGFR and inversely linked with ACR [4]. This is in contrast to prior research that linked an elevated level of oxidative stress biomarkers, such as 8-OHdG, to CKD development. Unlike SDMA and ADMA, which were detected in the blood, 8-OHdG was measured in the urine. Renal function has a direct effect on the ability to filter and remove solutes such oxidant stress indicators, which could be one explanation. As a result, those with poor kidney function may have had the most difficulty filtering biomarkers at the glomerular level and/or producing oxidative stress analyses in the urine. These anomalies would result in low urine concentrations. Because kidney function may modify the exposure measurements of interest, this is referred to as reverse causation in epidemiologic literature.

Dialysis patients had a considerably lower 8-OHdG level than non-dialysis patients ( $p=0.000$ ). This is in line with a study by Navarro et al (2019), who found that when dialysis is first started, the membrane and dialysate promote inflammation and a large increase in ROS formation. After dialysis, the levels of oxidized LDL were observed to be greater. However, xanthine oxidase activity and 8-OHdG levels are much lower after dialysis, showing that oxidative stress indicators are efficiently filtered throughout the dialysis process and that dialysis could diminish

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oxidative stress markers. We also discovered that DM patients had considerably higher levels of 8-OHdG than non-DM patients ( $p=0.000$ ). ADMA is a strong inhibitor of endogenous Nitric Oxide Synthase (NOS). This chemical can build up in the body and induce endothelial dysfunction, high blood pressure, and proteinuria, all of which contribute to the advancement of cardiovascular disease and renal failure. Increased blood pressure, extracellular matrix production, and per tubular capillary decimation are all caused by ADMA synthesis, which can lead to chronic kidney failure [5]. In patients with CKD and reduced endothelial function, previous investigations demonstrated an increase in ADMA levels due to reduction of Nitric Oxide (NO) discharge. Endothelial dysfunction is caused by ADMA competing with L-arginine to inhibit NOS. The regulation of vascular tone and blood pressure are two of the many roles of NO in the body; consequently, if NOS is inhibited, both of these systems will be impaired. A prior study found a strong positive connection between increasing ADMA levels and carotid intima-media thickness in patients with CKD, indicating that this biomarker can detect atherosclerosis in individuals with CKD.

There was a negative association between ADMA and eGFR in this study ( $p=0.00$ ,  $r=-0.476$ ; moderate correlation). Other studies have also demonstrated a strong negative connection between increasing plasma ADMA content and a decrease in eGFR; however, the specific mechanism is still unknown. In this study, we discovered that late CKD stage and dialysis patients had considerably higher ADMA levels than non-dialysis patients ( $p=0.000$  for both). Increased levels of ADMA have been linked to the progression of CKD in earlier investigations, particularly in patients who get routine hemodialysis. Hemodialysis patients with ESRD showed greater ADMA levels than controls. Other independent characteristics, such as age, sex, and smoking history, should be taken into account. Genetic variables are another important thing to consider. Increased ADMA levels have been linked to genetic polymorphisms, particularly the G-449 variant in the DDAH2 gene, in previous investigations. We also discovered that DM patients had significantly higher ADMA levels than non-DM patients ( $p=0.004$ ). SDMA is an inactive stereoisomer created at the same time as ADMA. The interaction between superoxide anions and nitric oxide, which forms peroxynitrate and causes tissue damage, affects the synthesis of ADMA. SDMA is linked to endothelial dysfunction and plays a similar role in GFR calculation as creatinine. SDMA is passed through the urine.

SDMA is more commonly observed in individuals with ESRD and is a more sensitive biomarker of renal function change than ADMA; hence it can be regarded as a specific biomarker. SDMA can cause pro-inflammatory effects in CKD patients by increasing ROS generation. Another study discovered that ADMA, but not SDMA, is reduced in acute inflammation. The question then became whether SDMA and ADMA have distinct metabolic pathways and pathogenic effects.

ADMA is a powerful determinant of insulin resistance in type 2 diabetes and may play a key role in worsening vascular damage. Because there was no healthy control group in this investigation, the variations in levels of the three oxidative stress indicators between healthy people and patients with CKD remain unknown. Another restriction was that we only took samples from one location, which limited the generalizability of our findings. Furthermore, several samples had CKD stage 5 and were on hemodialysis, which could have influenced the results of these oxidative stress indicators. The oxidative stress indicators 8-OHdG, SDMA, and ADMA linked with the levels of eGFR and ACR, which represent the severity of CKD in Indonesian patients with CKD. There were also significant differences in 8-OHdG, SDMA, and ADMA levels between CKD stages, dialysis and non-dialysis patients, and diabetic and non-diabetic individuals. Finally, the levels of 8-OHdG, ADMA, and SDMA can be employed as prognostic markers and may be candidates for future therapeutics in CKD patients.

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