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Symmetric Dimethylarginine as a Biomarker for Chronic Kidney Disease

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ABSTRACT

Symmetric dimethylarginine (SDMA), is a post-translationally stable catabolic product of arginine-methylated proteins that plays an important role in basic cellular metabolism. SDMA is an endogenous biomarker of kidney function that has been widely used in veterinary medicine. Symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) are 2 constant products of L-arginine proteolysis that undergo methylation. SDMA is almost completely excreted by the kidneys after filtration making SDMA an ideal GFR biomarker candidate. Apart from that, SDMA has several advantages as a biomarker of kidney function, namely that it is not affected by non-renal factors that influence creatinine and cystatin C. Apart from that, SDMA also increases earlier than other biomarkers.

1. Introduction

Chronic kidney disease (CKD) is a global public health problem with increasing prevalence and incidence, poor prognosis, and high costs. Data from World Kidney Foundation In 2015, 11-13% of the population worldwide was affected by CKD. Based on data from the Global Burden of Disease In 2010, the prevalence of CKD increased by 29.3%. CKD was the 27th leading cause of death in 1990, increased to 18th in 2010, and further increased to 12th in 2017. Based on data from Global Burden of Disease 2010 in 2017, as many as 1-2 million people in the world died from CKD, and this figure is predicted to increase in 2040 to 2.2 to 4.0 million cases. Globally, in 2017, CKD caused more deaths than tuberculosis or human immunodeficiency virus (HIV), and the number of CKD

deaths is almost the same as the number of deaths due to accidents. Treatment costs for CKD in the United States reach 48 billion dollars per year and consume 6.7% of the total health budget. In Indonesia in 2012, the total cost of hemodialysis covered by Health Insurance was 227 billion rupiahs, and it is a medical procedure that absorbs the largest portion of health costs. In 2015, financing for health services by the Social Security Administration Agency (BPJS) for health increased from 2.2 trillion rupiahs to 2.68 trillion rupiahs compared to the previous year. CKD treatment is the second largest funding source from BPJS Health after heart disease.¹⁻³

Early identification of patients with CKD is important to be able to carry out early intervention and slow the progression to kidney failure. Currently,

kidney function measurements are generally used biomarker serum creatinine and urinalysis. However, this biomarker is sub-optimal for detecting kidney disease at an early stage. Monitoring renal function in CKD requires biomarkers that provide rapid, non-invasive, and specific measurements that correlate well with renal tissue pathology. In addition, serum creatinine, which is currently widely used as a biomarker of kidney function, is known to have the weakness of being influenced by several non-renal factors such as food intake, certain therapies, and muscle mass. Apart from that, serum creatinine also only increased 2 times the normal value after 50% nephron damage occurred.⁴ Research on kidney function biomarkers leads to symmetric dimethylarginine (SDMA), a post-translationally stable catabolic product of arginine-methylated proteins that play an important role in basic cellular metabolism. SDMA is an endogenous biomarker of kidney function that has been widely used in veterinary medicine. Symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) are 2 constant products of L-arginine proteolysis that undergo methylation. SDMA is almost completely excreted by the kidneys after filtration, making SDMA an ideal GFR biomarker candidate. Apart from that, SDMA has several advantages as a biomarker of kidney function, namely that it is not affected by non-renal factors that influence creatinine and cystatin C. Apart from that, SDMA also increases earlier than other biomarkers. This study aimed to discuss several actual findings and the role of SDMA in the pathogenesis of CKD and its potential as a CKD biomarker.

SDMA as biomarker predictors of CKD

Biomarkers are defined as parameters of structural, biochemical, physiological, or genetic changes that indicate the emergence and severity or progression of the disease. Currently, kidney function measurements generally use the biomarkers serum creatinine, blood urea nitrogen (BUN) levels, and urinalysis. However, this biomarker is suboptimal for detecting kidney disease at an early stage. The ideal

renal biomarker criteria are noninvasive, highly sensitive and specific, increase rapidly, correlate with the amount of kidney injury, can provide risk stratification and prognostic information, are applicable across a wide range of populations, are able to identify possible mechanisms of injury (prerenal, intrarenal, postrenal), are highly stable over time and across a wide range of temperatures and PH, and does not interfere with the drug.⁴ ADMA and SDMA have been known to biochemists for the past four decades. ADMA is considered a marker of endothelial dysfunction, while SDMA, as its structural isomer, is little studied and without clinical utility. In early 2000, SDMA was known to be an independent risk factor for cardiovascular disease along with ADMA. Until now, SDMA has been used as a biomarker of endogenous renal function in veterinary medicine. This SDMA is inert, consistently produced by histone hydrolysis with post-translational methylation of arginine residues, and almost exclusively eliminated by the kidney after filtration, making it an ideal candidate for a GFR marker.^{5,6}

SDMA has a strong correlation with GFR

GFR is the best index that describes overall kidney function and has an important role in the diagnosis, classification, management, and evaluation of CKD. GFR can only be determined by measuring the clearance of a substance from the blood into the urine. However, for the clearance of this substance to truly reflect GFR accurately, the substance must meet several characteristics, namely being freely filtered in the glomerulus, produced in constant amounts, not secreted or reabsorbed by the renal tubules, not eliminated extra-renal and physiologically inert. To date, there hasn't been one biomarker known to produce endogenous products produced by the human body that meet all of these characteristics. As a result, laboratories use exogenous markers such as iothalamate and iohexol as reference methods for determining GFR.^{7,8}

SDMA is excreted exclusively in the kidneys. SDMA is eliminated via the kidneys by >90%. The small size

of the SDMA molecule, namely 202 g/mol, and its positive charge allow it to be filtered freely without reabsorption or secretion in the tubules. Meanwhile, a small portion of elimination occurs through enzymatic cleavage and degradation that is not related to the kidneys. SDMA does not bind to proteins in contrast to ADMA, which binds to plasma proteins. Because of this, serum SDMA concentrations are increased in humans with chronic kidney disease, and serum SDMA concentrations are strongly inversely correlated with GFR. The clinical implication is that the correlation between ADMA and GFR is much weaker than the correlation between SDMA and GFR because the protein-bound fraction of ADMA inhibits glomerular filtration. So, SDMA is more representative for use as a marker of kidney function.^{9,10}

SDMA inhibits the production of nitric oxide (NO), as previously explained, and has a multi-functional role in many diseases. After protein turnover, SDMA and its structural isomer ADMA are released as free-SDMA. ADMA is extensively metabolized and is involved in the regulation of nitric oxide production, whereas SDMA is inert. In addition, SDMA is produced constantly and eliminated mainly through the kidneys, making SDMA considered a superior biomarker for kidney damage.^{11,12}

SDMA is highly correlated with cystatin C, mGFR, and serum creatinine in adults with normal kidneys and kidneys with reduced function. El-Khoury et al., in their study, compared SDMA levels with cystatin C, creatinine, and the eGFR equation with direct measurement of GFR with an exogenous marker, namely the radioactive iothalamate method in 22 men and 18 women aged between 21 years and 76 years. This population is people with normal renal function and renal insufficiency at various levels based on GFR measured using the exogenous marker iothalamate. SDMA plasma concentrations were significantly lower in adults with GFR > 90 mL/min/1.73 m² compared to adults with GFR < 60 mL/min/1.73 m² with a mean of 0.45 µM versus 1.09 µM, with marks cut off. The point plasma concentration of SDMA in CKD patients is 0.65 µM. From this study, it was found that SDMA

correlates more strongly inversely with mGFR than creatinine but is equivalent to cystatin C and the eGFR equation, which uses the formula modification of diet in renal disease (MDRD) and chronic kidney disease epidemiology collaboration (CKD-EPI), so it can be concluded that SDMA is a marker of good kidney function.¹³

Other studies have also reported a strong correlation between SDMA and kidney function in humans. This research includes research that also compares the performance of SDMA with GFR measured using biomarker gold standards or well-characterized exogens such as inulin and iothalamate. This study reports that the correlation between SDMA and GFR is quite strong, ranging from 0.78 to 0.84, and includes healthy populations as well as CKD and type 1 diabetes. Worsening kidney function will result in the accumulation of several compounds that should be excreted by the kidneys in the body. Several types of solutes that experience retention have been shown to have the potential to induce blood vessel damage. A group of solutes that are progressively retained in CKD are guanidine compounds, including SDMA. SDMA is closely related to chronic inflammation in CKD patients. SDMA in vitro stimulates the production of reactive oxygen species (ROS) monocytes by increasing ROS production after fMLP stimulation. SDMA causes vascular damage by inhibiting NO synthesis in endothelial cells by becoming a transport competitor for L-arginine, an NOS substrate, which results in an increase in ROS. This effect is associated with enhanced Ca²⁺ entry into monocytes. SDMA can indirectly affect NO synthesis activity by interfering with the absorption of arginine through the cationic amino acid transporter CAT and changing eNOS to uncoupled, which produces superoxide anion. SDMA is not an inert metabolite that is only excreted by the kidneys but is a compound that can cause oxidative stress in the renal blood vessels. High SDMA concentrations are correlated with mortality rates in the general population.¹⁷⁻²⁰

In another study to investigate the pro-inflammatory properties of SDMA directly, it was

proven that SDMA increased the expression of TNF- α and IL-6 of monocytes intracellularly. Apart from that, SDMA also increases NF- κ B activation in monocyte cells, which can encourage a potential mechanism to increase cytokine expression. These results suggest that SDMA has a proinflammatory effect on monocytes, which ADMA, as its structural analog, cannot demonstrate. So, apart from SDMA not only being a marker of kidney function but also an important molecule for measuring and evaluating renal excretory function in CKD patients, increased SDMA levels are also associated with inflammation and progression of CKD.²¹

SDMA increases earlier on CKD

Associated with the progression of CKD, SDMA levels increase gradually with a significant value compared to the levels of its structural analog ADMA. Another study comparing the increase in SDMA and ADMA levels in CKD patients showed that SDMA levels increased gradually and significantly starting from CKD patients in stages G2, G3, and G4 compared to controls and compared to ADMA. ADMA levels experienced a relatively more moderate increase and reached significance compared to controls, which was only seen after CKD stages G4, G5, and stage G5 had undergone dialysis.¹⁰ Other research states that the increase in SDMA levels is earlier than urea and creatinine and is comparable to the development of kidney disease in dogs. This research was carried out on eight male dogs with hereditary nephropathy and four healthy male dogs. The samples were measured periodically for SDMA, serum creatinine, and GFR levels using exogenous markers. From this study, it was found that the increase in SDMA levels occurred 17 months earlier before the increase in creatinine. SDMA identifies a decline in renal function earlier than creatinine and GFR. The average increase in creatinine detects <50% damage to kidney function, while SDMA consistently detects kidney function damage when <30% damage occurs, whether using general reference limits or serial monitoring. This study also demonstrated reliable measurement of SDMA in

serum and plasma.²² Another study showed that 24 patients who were kidney transplant donors also stated that there was an increase in SDMA levels 6 hours after unilateral nephrectomy. Patients who become donors have their SDMA levels checked before becoming donors, and their SDMA levels are checked serially after unilateral nephrectomy, which means there has been a 50% reduction in kidney function. In this study, it was found that there was a significant increase in SDMA levels, namely from 0.571 ± 0.120 to 0.659 ± 0.135 mol/L.²³

SDMA has high specificity

SDMA is more specific to be used as a marker of kidney damage than creatinine and cystatin C, the CKD marker that is currently most widely used to estimate GFR (eGFR). This is because SDMA is not affected by non-renal factors that have been proven to influence creatinine and cystatin C, such as lean body mass, food intake, inflammation, diabetes, and estrogen therapy, thereby reducing its sensitivity and specificity for estimating GFR. SDMA also has consistent levels in several species, such as dogs and cats, and has been used as a marker to assess kidney function in veterinary medicine.^{24,25}

SDMA is more specific in describing kidney function than ADMA. As previously explained, ADMA is a structural isomer of SDMA, which is also excreted in the kidneys, but it is not as promising as SDMA as a candidate marker for kidney function because it is not specific for the kidneys. ADMA is metabolized enzymatically, and only 20% is excreted through the kidneys. The circulating ADMA can be transported to organs such as the kidneys, brain, and liver for enzymatic degradation. There are three enzymes that metabolize ADMA, namely dimethylarginine dimethylaminohydrolyase-1 (DDAH-1), -2 (DDAH-2) into citrulline and dimethylamine as well alanine-glyoxylate aminotransferase 2 (AGXT2) transaminases ADMA into keto- (NG, NG-dimethylguanidino) valeric acid (DMGV). Apart from that, plasma ADMA levels also depend heavily on factors that influence the expression and activity of DDAH and AGXT2, such as

hyperglycemia and angiotensin II levels.²⁶

Chronic administration of SDMA infusion has been proven not to affect kidney function or kidney histology, so it can be concluded that SDMA is not a direct cause of kidney injury. In another study, eight-week-old male mice were given an SDMA infusion of 250 mol/kg/day for 28 days. SDMA infusion is administered using a mini osmotic pump. The following parameters were monitored for glomerular filtration rate using exogenous markers fluoresceinyl thiocarbamoyl-inulin, heart function through echocardiography, and blood pressure. The samples were examined for SDMA levels in the second and fourth weeks, and a histological examination of kidney tissue was carried out in the fourth week. The results showed a significant increase in SDMA levels from 0.26 ± 0.10 to 3.49 ± 1.66 mol/L in 4 weeks, but GFR did not change (1224 ± 351 compared to 1017 ± 345 mL/min/g body weight, n.s.) at 4 weeks when compared with the start of the study. From the results of the renal histological examination, the histological changes did not reveal the effect of fibrosis or eNOS expression. In addition, there was no effect of SDMA on systolic blood pressure (106 ± 12 compared to 111 ± 18 mmHg) or on ejection fraction (54.2 ± 1.7 compared to $58.4 \pm 1.9\%$).²⁷

Based on investigations to compare the diagnostic performance of serum SDMA, cystatin C, and creatinine to detect decreased GFR in dogs with and without CKD, it was found that SDMA has high specificity as a biomarker of CKD. This research was conducted on 97 dogs consisting of 67 dogs with a diagnosis and suspicion of CKD and 30 healthy dogs. Scintigraphy examination was performed on all of these dogs to assess the estimated glomerular filtration rate (mGFR). Then, in this study, the sensitivity and specificity results for SDMA were 87%, almost the same as creatinine and much better than cystatin C, with figures of 90% and 72%, respectively.²⁸

2. Conclusion

Symmetric dimethylarginine (SDMA) has optimal potential with GFR as a reflection of kidney function, is specific for kidney function, and increases earlier than other biomarkers.

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