The Association Between Uric Acid and Symmetric Dimethylarginine Levels in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis

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ABSTRACT

***Background**: Uric acid (UA) levels are associated with increased risk of cardiovascular events and mortality in hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients. In a study with a population of healthy young adults and HD there was a correlation between high blood uric acid levels and blood symmetric dimethylarginine (SDMA) level. However, in CAPD population, there are still conflicting data on the mechanism of increased risks related to uric acid levels. This study aimed to assess the association between uric acid levels and SDMA in the subjects undergoing CAPD.* **Methods:** *This was a cross – sectional study conducted in all the adults who underwent CAPD for at least three months in tertiary hospital in Jakarta, Indonesia. Subjects already on uric lowering therapy, pregnant or lactating women, and those with a history of malignancy were excluded. Uric acid and SDMA level were measured at the same time patients controlled to outpatient clinic. Bivariate analysis was performed using the Mann – Whitney test and multivariate analysis performed using logistic regression test.* **Results:** *A total of 55 subjects were included. The median level of UA was 7.30 $\pm$ 1.59 mg/dl and 33 subjects (60%) had UA levels of 7 mg/dl or higher. The median SDMA level was 633.73 $\pm$ 231.54 ng/mL. Subjects with UA levels > 7 mg/dl had significantly higher SDMA levels compared to subjects with UA levels $\leq$ 7 mg/dl (721.58 $\pm$ 220.57 vs 501.95 $\pm$ 182; P < 0.001). The cut – off value of SDMA 536 ng/mL was obtained from the receiver operating characteristic (ROC) curve with sensitivity 81.8%, specificity 63.6%, PPV 77.78% and NPV 73.68%. After fully adjusted with the confounders, the determinant factors in this study were diabetes mellitus (OR: 7.844; CI95%: 1.899 – 32.395: P value: 0.004) and dyslipidemia (OR: 6.440; CI95%: 1.483 – 27.970; P value: 0.013) as risk factors.* **Conclusion**: *In CAPD patients, UA levels above 7 mg/dl were associated with increased SDMA levels. This study demonstrates the determinant factors regarding association between UA level and SDMA in CAPD patients were diabetes mellitus and dyslipidemia. The cut – off value of SDMA above 536 ng/mL were significant to increased risk of cardiovascular events.*

***Keywords**: uric acid, SDMA, CAPD.*

INTRODUCTION

Peritoneal dialysis (PD) is not very popular as a treatment choice for end stage renal disease (ESRD) patients in Indonesia. The prevalence was only 2% in 2018 and continuous ambulatory peritoneal dialysis (CAPD) is the only type of PD system available in Indonesia.[1] The prevalence of cardiovascular disease (CVD) in ESRD patients on dialysis was 50% and it was 20 times higher than in the general population.[2] The cause of death from cardiovascular disease in dialysis patients is multifactorial.[2,3]

Hyperuricemia is known to be associated with increased oxidative stress, inflammation, and endothelial dysfunction by inhibiting nitric oxide function. A study reported that hyperuricemia increased the risk of all – cause and cardiovascular disease related mortality in CKD especially in hemodialysis (HD) patients.[4] However, despite hyperuricemia being suggested as a risk factor in HD population, there are still controversies in PD population. Uric acid (UA) levels in HD population presents in J – shape trends whereas PD population present in U – shape trends of mortality.[5,6]

In addition to uric acid (UA), some uremic toxins, including symmetric dimethylarginine (SDMA), were shown to be associated with cardiovascular disease.[7] As a valuable and sensitive marker of renal function, SDMA is also an independent risk factor for cardiovascular disease and mortality.[5,7] Symmetric dimethylarginine (SDMA) showed a vital role in the inflammatory process and ROS generation. An in vitro study assessing ten guanidino compounds suggested SDMA as a compound with the most significant role in vascular damage and the secretion of proinflammatory mediators.[8] SDMA along with uric acid is the most potent endogenous inhibitor of nitric oxide synthase with higher levels in patients with end stage renal disease (ESRD). SDMA has been an outstanding marker of renal function both in human an in animal models, with ESRD patients on dialysis showing the highest SDMA levels.[7] Yassir et al had been demonstrated that there was a significant association between UA and SDMA levels in chronic twice – weekly HD.[9]

However, there is still a lack of understanding about the association between uric acid and SDMA levels in PD patients especially CAPD patients. This study aimed to assess the association between the levels of UA and SDMA in the subjects undergoing CAPD. Therefore, this study can be applied in future management of PD patients in order to prevent cardiovascular manifestations.

METHODS

This cross-sectional study was conducted in the CAPD outpatient unit of Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia, from June to August 2021. We consecutively included all patients aged 18 years and older undergoing CAPD for at least three months in our hospital. The subjects who were already on uric acid lowering therapy, pregnant or lactating women, and patients with a history of malignancy were excluded.

History taking, physical examination, and blood tests were obtained. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m^2). Based on the WHO Asia Pacific classification, BMI cut-offs were regarded as the following: normal (18.5 - 22.9 kg/m^2), underweight (< 18.5 kg/m^2), overweight (23 - 24.9 kg/m^2), obese I (25 - 29.9 kg/m^2), and obese II (> 30 kg/m^2). The patient's smoking history, the duration of CAPD, and the presence of diabetes and hypertension were recorded from medical records. Blood pressure was measured using Omron HEM-7203 meter and categorized as < 140 mmHg, 140 - 160 mmHg, and > 160 mmHg.

Venous blood samples were collected from each subject and stored in EDTA-containing tubes. The biochemical workup included uric acid, SDMA (liquid chromatography (LC)-Tandem mass spectrometry (MS/MS). Based on the mean UA levels obtained from previous study by Chang W et all in 2018, UA level was categorized into > 7 mg/dl and ≤ 7 mg/dl.[5]

The collected data is then analyzed by using SPSS for Windows programs. The data was analyzed using an un – paired t – test. In addition, bivariate analysis was performed using the Mann – Whitney test and multivariate analysis performed using logistic regression test. P – Values of < 0.05 were considered statistically significant.

The Ethics Committee of the Faculty of Medicine, Universitas Indonesia, approved the study with the approval number of KET-467 / UN2.F1 / ETIK / PPM.00.02 / 2021. All the participants included in this study gave informed consent freely and voluntarily. The participants were given an opportunity to ask their questions, to all of which we provided adequate responses. None of the participants were coerced to give consent.

RESULTS

Characteristics of Subjects present in **Table 1**. The study was conducted on patients who undergo CAPD in outpatient clinic of RSCM Jakarta, involving 55 people as the subject of the study. The participants mean age was 40.71 ± 14.39 years old (min: 18, max: 71) and males constituted 63.6% of the subjects. The median duration of CAPD was 27 months (min: 13, max: 42). The major cause of ESRD was glomerulonephritis (47.3%), diabetes mellitus (25.5%), and hypertension (25.5%). We found that the mean UA level was 7.30 ± 1.59 mg/dl and 33 subjects (60%) had UA level 7 mg/dl or higher. Meanwhile, the mean SDMA level in all 55 subjects was 633.73 ± 231.54 ng/mL.

Subjects with UA levels > 7 mg/dl had significantly higher SDMA levels compared to subjects with UA levels ≤ 7 mg/dl (721.58 ± 220.57 vs 501.95 ± 182; P < 0.001). (**Table 2**)

The cut – off value of SDMA 536 ng/mL was obtained from the receiver operating characteristic (ROC) curve with sensitivity 81.8%, specificity 63.6%, PPV 77.78% and NPV 73.68%. After fully adjusted with the confounders, the determinant factors in this study were diabetes mellitus (OR: 7.844; CI95%: 1.899 – 32.395: P value: 0.004) and dyslipidemia (OR:

Table 1. Demographic characteristics of study subjects.

Variables	N=55
Gender, n (%)	
□ Man	35 (63.6)
□ Women	20 (36.4)
Age (years), mean (SD)	40.71 (± 14.39)
Categorical of Age, n (%)	
□ ≤ 45 years	20 (36.4)
□ > 45 years	35 (63.6)
BMI (Kg/m^2), mean (SD)	23.17 (± 4.30)
Categorical of BMI, n (%)	
□ Normal	29 (52.7)
□ Underweight	10 (18.2)
□ Overweight	13 (23.6)
□ Obesity 1	3 (5.5)
□ Obesity 2	0 (0.0)
Hypertension, n (%)	
□ Yes	50 (90.9)
□ No	5 (9.1)
Diabetes mellitus, n (%)	
□ Yes	14 (25.5)
□ No	41 (74.5)
Dyslipidemia, n (%)	
□ Yes	29 (52.7)
□ No	26 (47.3)
Duration of CAPD, n (%)	
□ > 3 years	17 (30.9)
□ ≤ 3 years	38 (69.1)
Duration of CAPD (months), Median	27 (13-42)
Ureum (mg/dl), Median	97.6 (79.7-117.0)
Creatinin (mg/dl), mean (SD)	11.61 (± 4.71)
Hemoglobin (g/dl), mean (SD)	9.46 (± 1.58)
Anemia (Hb < 11 g/dl), n (%)	
□ Yes	45 (81.8)
□ No	10 (18.2)
Hypoalbuminemia (Albumin < 3.5 g/dl), n (%)	
□ Yes	24 (43.6)
□ No	31 (56.4)
The use of dialysate concentration glucose base 2.5% > 2x a day, n (%)	
□ Yes	21 (38.2)
□ No	34 (61.8)
History of Peritonitis, n (%)	
□ Yes	17 (30.9)
□ No	38 (69.1)
Membrane Type, n (%)	
□ High transporter	29 (52.7)
□ Low transporter	26 (47.3)
Cause of ESRD, n (%)	
□ Glomerulonephritis	26 (47.3)
□ Diabetes mellitus	14 (25.5)
□ Hypertension	14 (25.5)
□ Kidney Stone	0 (0.0)
□ ADPKD	1 (1.8)
SDMA, mean (SD)	633.73 ± 231.54
Uric Acid, mean (SD)	7.30 ± 1.59
Categorical of Uric Acid, n (%)	
□ > 7 mg/dl	33 (60.0)
□ ≤ 7 mg/dl	22 (40.0)

DM, diabetes melitus; BMI, body mass index; SD, standard deviation; *SDMA, Symmetric Dimethylarginine; ADPKD, Autosomal Dominan polycystic kidney disease.*

6.440; CI95%: 1.483 – 27.970; P value: 0.013) as risk factors. (**Table 3 – 5**)

Table 2. Uric Acid to SDMA level.

Variables	Uric Acid Category		P
	> 7 mg/dl	≤ 7 mg/dl	
SDMA	721.58 ± 220.57	501.95 ± 182	<0.001

DISCUSSION

This study shows a significant association between UA and SDMA levels in 55 subjects under CAPD. We found that elevated UA levels (> 7 mg/dl) were associated with higher SDMA levels compared to subjects with UA levels ≤ 7 mg/dl (721.58 ± 220.57 vs 501.95 ± 182; P < 0.001). Our study was the first to evaluate serum

Table 3. Cut – off SDMA based on ROC curve.

Variables	SDMA Level		PR (CI 95%)	p
	> 536 ng/mL	≤ 536 ng/mL		
Category Uric Acid				
> 7 mg/dl	28 (84.8)	5 (15.2)	2.333 (1.318-4.131)	<0.001
≤ 7 mg/dl	8 (36.4)	14 (63.6)		

Table 4. Confounding factors related to SDMA level.

Confounders	SDMA Level		P
	> 536 ng/mL	≤ 536 ng/mL	
Age, n (%)			
≤ 45 years	8 (40.0)	12 (60.0)	0.007
> 45 years	28 (80.0)	7 (20.0)	
Obesity, n (%)			
Yes	1 (33.3)	2 (66.7)	0.272
No	35 (67.3)	17 (32.7)	
Diabetes mellitus, n (%)			
Yes	6 (42.9)	8 (57.1)	0.054
No	30 (73.2)	11 (26.8)	
Hypertension, n (%)			
Yes	34 (68.0)	16 (32.0)	0.327
No	2 (40.0)	3 (60.0)	
Dyslipidemia, n (%)			
Yes	16 (55.2)	13 (44.8)	0.159
No	20 (76.9)	6 (23.1)	
Duration of CAPD, n (%)			
> 3 years	8 (47.1)	9 (52.9)	0.107
≤ 3 years	28 (73.7)	10 (26.3)	
Anemia, n (%)			
Yes	30 (66.7)	15 (33.3)	0.723
No	6 (60.0)	4 (40.0)	
Hypoalbuminemia, n (%)			
Yes	16 (66.7)	8 (33.3)	1.000
No	20 (64.5)	11 (35.5)	
The use of dialysate concentration glucose base 2.5% > 2x a day, n (%)			
Yes	12 (57.1)	9 (42.9)	0.467
No	24 (70.6)	10 (29.4)	
History of Peritonitis, n (%)			
Yes	9 (52.9)	8 (47.1)	0.318
No	27 (71.1)	11 (28.9)	
Membrane Type, n (%)			
High Transporter	19 (65.5)	10 (34.5)	1.000
Low Transporter	17 (65.4)	9 (34.6)	

Table 5. Multivariate analysis.

Variables	OR (CI 95%)	Delta OR	p
Crude OR: Uric Acid to SDMA	9.800 (2.702-35.546)		0.001
Adjusted OR:			
+ Age	7.788 (2.014-30.115)	**25.83%**	0.003
+ DM	7.844 (1.899-32.395)	7.13%	0.004
+ Duration of CAPD	6.747 (1.574-28.915)	**16.25%**	0.010
+ Dyslipidemia	6.440 (1.483-27.970)	4.76%	0.013

SDMA level and its association with serum UA level in subject under CAPD.

Yassir et al had demonstrated that there was a significant association between UA and SDMA levels in chronic twice – weekly HD.[9] Uric acid is a product of purine metabolism which mainly excreted by the kidneys.[9,10] Consequently, hyperuricemia is highly prevalent in CKD patients.[3,5,6,11] So, UA serum concentration depends on the rate of purine metabolism and the efficiency of its renal clearance, which is easily affected by dialysis.[5,6,10]

The clinical implications of hyperuricemia in CAPD patients are still controversial. Studies showed that elevated UA levels in CAPD revealed as U – Shaped rather than J – Shaped uric acid mortality.[5,11] Based on Chang et al and Dong et al Studies, hyperuricemia is a risk factor for all cause and cardiovascular mortality.[5,11] Uric acid may act as a potent pro – inflammatory cytokines which can lead to the generation of other uremic toxins such as SDMA.[7]

As an uremic toxin, SDMA is a naturally generated amino acid that is removed from the body by the kidneys (> 90%).[7] As a low molecular weight water soluble uremic toxin, SDMA is rapidly cleared during dialysis.[7] In our study, the mean SDMA level in all 55 subjects was 633.73 $\pm$ 231.54 ng/ml and cut – off value of SDMA 536 ng/mL was obtained from the receiver operating characteristic (ROC) curve with sensitivity 81.8%, specificity 63.6%, PPV 77.78% and NPV 73.68%. This findings were slightly lower than HD population based on reported by Yassir et al.[9]

SDMA plays an important role in CKD development and progression. An elevation in SDMA level activates pro – inflammatory cytokines and also activates reactive – oxygen species (ROS) which in turn promotes the creation of modified high – density lipoprotein (HDL), causing HDL dysfunction.[7,9] After fully adjusted with the confounders, the determinant factors in this study were diabetes mellitus (OR: 7.844; CI95%: 1.899 – 32.395: P value: 0.004) and dyslipidemia (OR: 6.440; CI95%: 1.483 – 27.970; P value: 0.013) as risk factors.

The limitation of this study is that due to the nature of the study design, we could not assess the temporal relationship. Not all confounders were evaluated in this study which might have attenuated the association between UA and SDMA levels. In this study, we also did nor evaluate cardiovascular outcomes. This study was a single center study with small sample size which makes still difficult to ascertain if there is a clear linkage between UA and SDMA in CAPD patients. Nutritional assessment is also not included in this study which plays a role in increasing human resources and uric acid levels.

This study can be applied in future management of PD patients in order to prevent cardiovascular manifestations. However, another study should be held with cohort prospective and RCT regarding SDMA levels associated with risk factors and SDMA levels associated with PD adequacy, respectively.

CONCLUSION

In CAPD patients, UA levels above 7 mg/dl were associated with increased SDMA levels. This study demonstrates the determinant factors regarding association between UA level and SDMA in CAPD patients were diabetes mellitus and dyslipidemia. The cut – off value of SDMA above 536 ng/mL were significantly associated with increased risk of cardiovascular events.

However, it remains a challenge to determine the role of UA in the metabolic pathway of SDMA. Referring to the study's limitations, the

therapeutic consequences of our findings remain unclear, and other cohort studies are needed to confirm such findings and assess the adverse outcomes of this phenomenon in CKD patients who undergoing dialysis.

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