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Co-Activity of Uric Corrosive and Consistent Dimethyl Arginine as a Marker of Cardiovascular Infection in Hemodialysis Patients Two Times/Week

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Abstract

Background: In a study abroad, the relationship between high blood uric acid levels and cardiovascular disease in HD patients three times a week showed different results. Symmetric dimethyl arginine (SDMA) is a known marker of cardiovascular disease in a number of epidemiological studies, including in the HD patient population. In a study with a population of healthy young adults there was a relationship between high blood uric acid levels and blood SDMA level. This study need to know the relationship between blood uric acid levels and blood SDMA level in HD patients twice a week.

Methods: This study was an analytical study with a cross-sectional design in 78 HD patients twice a week. This study analyzed the relationship between blood uric acid levels and confounding factors with increasing blood SDMA levels.

Results: Data analysis using the Mann Whitney test found a significant difference in mean SDMA levels (P=0.027) between blood uric acid levels ≤ 8 mg/dL and >8 mg/dL. Age>65 years old (P=0.029), hypertension (P=0.005) and type of dialyzer (P=0.046) are factors that can increase SDMA levels from the results of the stratification analysis other than blood uric acid levels >8 mg/dL.

Conclusion: In twice-weekly hemodialysis patients, a high blood uric acid level >8 mg/dL was associated with increased blood SDMA levels as a marker of cardiovascular disease. Age >65 years and hypertension were also associated with increased mean SDMA levels. Hemodialysis using a high flux dialyzer was associated with lower SDMA levels.

Keywords: Uric acid; SDMA; Hemodialysis

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Introduction

The number of patients undergoing hemodialysis (HD) is increasing in Indonesia where in 2017 as many as 77892 patients increased to 132142 patients in 2018 [1]. The mortality rate from cardiovascular disease in HD patients was 20 times higher than in the general population [2]. The cause of death from cardiovascular disease in HD patients was multifactor [3].

Uric acid has been shown to be associated with cardiovascular disease. In the human body uric acid can be an antioxidant in normal and pro-oxidant levels in high levels [4-10]. The limitation of high blood uric acid levels which have a pro-oxidant effect exceeds the antioxidant effects that play a role in causing cardiovascular disease to date is still debated [10]. The relationship and limits of high blood uric acid levels that play a role in causing cardiovascular disease in HD patients are also still in debate because various studies show different results [11, 12] Preliminary studies on 13 HD patients twice a week at RSCM found average pre-HD uric acid levels ranged from 8.17 mg/dL in the HD range of 3 days and 9.35 mg/dL in the 4-day HD range past sunday higher compared to HD patients three times a week in previous studies and studies in PGK populations who have not undergone HD [9,12] HD patients twice a week in RSCM with high pre-HD blood uric acid levels may still have pro-oxidant effects on cardiovascular disease.

Some uremic toxins have been shown to be associated with cardiovascular disease such as phospat, p-cresol, indoxyl sulfate, homocysteine, AGEs, Asymmetric dimethylarginine (ADMA) and Symmetric dimethylarginine (SDMA) [13].

Studies in healthy young adult populations showed a link between increased SDMA levels and high blood uric acid levels instead of ADMA [14]. SDMA uremic toxins in some studies were used as cardiovascular disease markers in the general population, PGK patients who had not undergone HD and HD populations [15-21]. So far there have been no studies showing the relationship

of high uric acid levels with increased blood SDMA levels in HD populations.

Study Method

Study cut latitude conducted in PGTA patients who undergo HD period of June 2020. This research was conducted from January to November 2020 at Dr. Cipto Mangunkusumo Hospital RSCM. The study subjects were selected by consecutive sampling method. The inclusion criteria of the study subjects were PGTA patients who underwent HD twice a week for a minimum of three months, willing to be the subject of research. Meanwhile, the criteria for exclusion of the subject are: 1) Taking drugs lowering uric acid and antioxidant. 2) Pregnant or nursing. 3) Cancer.

On the subject, interviews, physical examinations and blood tests were conducted. Furthermore, laboratory analysts conducted on blood samples of subjects for examination of SDMA levels and uric acid. Examination using human blood or plasma EDTA with volume: 300 uL. Blood stability: 1 day at 2-80°C, 7 days at -20°C, 193 days at -70°C. Sampling with SST tubes and not hemolysis. The inspection method is Liquid Chromatography (LC)-Tandem Mass Spectrometry (MS/MS).

The collected data is then analyzed by using SPSS for Windows programs. The data was analyzed using an unpaired T test. In addition, the Whitney Mann test was used to assess the relationship between quality of life and continuous variables. Analysis stratafikasi to see perancu variables related to SDMA.

Results

The study was conducted on patients who undergo HD twice a week 4.5 to 5 hours in the HD Unit of RSCM Jakarta, involving 78 people as the subject of the study. The demographic characteristics of the subject can be seen in **Table 1**. Analysis of the relationship between uric acid and SDMA. Analysis of the efficacy of perancu variables in **Table 2**. Analysis between SDMA and HD quality **(Table 3)**. Analysis of dialyzer type with SDMA **(Table 4)**.

Variable	N=78
Symmetric dimethyl arginine, mean (Standard Intersection)	633, 82 (± 253.67)
Uric acid, mean (Standard Intersection)	8, 82 (± 1.99)
Categorical of uric acid, n (%)	
>8 mg/dL	50 (64)
≤ 8 mg/dL	28 (36)
Gender, n (%)	
Man	34 (43, 6)
Women	44 (56, 4)
Age (years), mean (SB)	50, 94 (±13, 58)
Categorical of age, n (%)	
18-40 years	15 (19, 2)
41-65 years	49 (62, 8)
>65 years	14 (18, 0)
BMI (kg/m2), mean (SB)	23, 27 (±4, 35)
Categorical of BMI, n (%)	
Normal	32 (41, 0)
Underweight	8 (10, 3)
Overweight	17 (21, 8)
Obesity 1	16 (20, 5)
Obesity 2	5 (6, 4)
Hypertension, n (%)	
Yes	60 (76, 9)
No	18 (23, 1)
Diabetes Mellitus, n (%)	
Yes	29 (37,2)
No	49 (62, 8)
Dyslipidaemia, n (%)	
Yes	62 (79, 5)
No	16 (20, 5)
Long HD (Month), Average(SB)	78, 47 (±71, 58)
Old category HD (Month), n (%)	
<36 Month	23 (29, 5)
36-60 Month	21 (26, 9)
>60 Month,	34 (43, 6)
Adequacy HD (KT/V), Average (SB)	1, 84 (±0, 36)
Category adequacy HD, n (%)	
YES (≥ 1, 8)	47 (60, 3)
NO (<1, 8)	31 (39, 7)
Ultrafiltration, Average (SB)	4046, 67 (± 1038, 89)
Diuresis ≥ 250 cc/day, n (%)	
YES	11 (14, 1)
NO	67(85, 9)
Cause PGK, n (%)	
1. Glomerulonefritis	31 (39, 7)
2. Diabetes Mellitus	29 (37, 2)
3. Hypertension	16 (20, 5)
4. Kidney stones	1 (1, 3)
5. Autosomal Dominant polycystic kidney disease	1 (1, 3)

Table 1: Demographic characteristics of research subjects undergoing hd.

Types of Conducers	SDMA levels in the uric acid group		P
Age			
18-40 years	738 (557, 2-851, 30)	555, 25 (513, 65-856, 5)	0, 489
41-65 years	550, 10 (430, 75-889, 80)	528, 55 (432, 45-605, 45)	0, 572
>65 years	776, 85 (542, 75-1100, 67)	457, 30 (309, 05 -635, 95)	1 0, 029
Diabetes Melitus			
YES	550, 10 (383, 35-904, 10)	456, 40 (340-543, 05)	0, 144
NO	684, 5 (484, 5-891, 95)	569, 2 (498, 10-672, 5)	0, 350
Dyslipidaemia			
YES	613, 30 (477, 90-921, 95)	523, 35 (464, 76-607, 05)	0, 078
NO	691, 8 (432, 4-768, 9)	412, 2 (313, 78-627, 40)	0, 202
Hypertension			
YES	727, 9 (518-920, 7)	498, 10 (354, 0-569, 2)	0, 005
NO	475, 2 (382, 4-720, 05)	589, 4 (498, 95-714, 35)	0, 258
Obesity			
YES	927, 85 (443, 63-1040)	415, 10 (340, 15-712, 90)	0, 222
NO	600, 85 (479, 25-810, 43)	526, 30 (484, 5-610, 80)	0, 098
Long Haemodialysis			
<36 Month	711, 25 (265, 40-919, 20)	382, 10 (278, 32-515, 88)	0, 240
36-60 Month	557, 20 (488, 40-952, 50)	526, 30 (471, 35 -640, 10)	0, 426

>60 Month	691, 80 (477, 90-863, 85)	536, 70 (441, 35-708, 40)	0, 280
Adequacy Haemodialysis			
YES	727, 9 (488, 4-905)	531, 5 (487, 97-605, 45)	0, 046
NO	Obesity 1	Obesity 1	Obesity 1
NO	550, 10 (349, 10-903, 2)	457, 3 (408, 90-829, 4)	0, 306

Table 2: Differences in the mean SDMA levels in the two uric acid groups with various types of confounders.

Variable	Adequacy HD (KT/V online)		P
	YES	NO	
SDMA	668, 39 (± 227, 82)	581, 40(± 284, 37)	0, 034
Uric acid	8, 80 (± 1, 70)	8, 48 (± 1, 60)	0, 372

Table 3: The difference in mean SDMA and blood uric acid levels on HD adequacy.

Variable	High Flux (Fresenius)	Low Flow (B Brown)	P
SDMA	557, 597 (± 194, 619)	678, 929 (± 274, 845)	0, 026

Table 4: The difference in the mean SDMA blood level against the type of dialyzer.

Discussion

Characteristics of the study subject

The most CKD causes in the study population were glomerulonephritis as much as 31%, followed by DM as much as 29% and hypertension as much as 16%. This data is different from the one reported by IRR in 2018 where the most PGK causes were hypertension as much as 36%, followed by DM as much as 28% and glomerulonephritis as much as 10% [1]. Although there are differences in PGK causes, patients who undergo HD in RSCM already have some traditional risk factors that can cause high PKV abnormalities.

Traditional risk factors such as old age, male sex, hypertension, DM, dyslipidemia, and obesity were consistently shown by various studies increasing mortality due to cardiovascular disease in the general population and CKD patients who had not undergone HD [3]. At the time of the study was conducted in HD patients, only traditional risk factors of old age and DM were still consistently showing an increase in mortality due to PKV. Traditional risk factors such as male sex, hypertension, dyslipidemia, obesity show inconsistencies [3,22-28].

The low frequency of DM and the average age compared to overseas research does not necessarily cause both risk factors to play fewer roles in causing PKV abnormalities in HD patients in RSCM. Age risk factors and DM remain the causative factors of PKV consistently shown in recent studies that increase mortality rates in the HD patient population [3,23-25].

The latest study by gender found both men and women had almost the same frequency of deaths from cardiovascular disease or women losing protective effects to cardiovascular disease in the HD population [24].

Hypertension is a traditional risk factor associated with an increase in mortality due to cardiovascular disease in the general population and CKD that has not undergone HD [3]. In the HD population many studies show different results. Several studies showed that in populations with low pre-HD blood pressure, high mortality rates due to cardiovascular disease compared to those with high pre-HD blood pressure may be associated with intradialytic hypotension. Several studies showed that using Ambulatory Blood Pressure Monitoring (ABPM) and interdialytic blood pressure examined by Home Blood Pressure Monitoring (HBPM) method, high blood pressure showed an increase in death rate due to cardiovascular disease in HD patients [3,26].

Dyslipidemia and obesity have been shown to increase mortality due to cardiovascular disease in the general population and CKD who have not undergone HD [3]. The opposite results were obtained in studies conducted in HD populations where HD populations suffering from dyslipidemia and obesity were found to have lower mortality rates due to cardiovascular disease compared to HD populations that did not have dyslipidemia or obesity. Dyslipidemia and obesity are good markers of nutrition in the HD population. In HD populations that do not suffer from obesity or dyslipidemia tend to experience malnutrition associated with malnutrition, inflammation and atherosclerosis syndrome (MIA syndrome) which causes a high mortality rate due to cardiovascular disease [3,27,28].

Studies in this population found the average pre-HD uric acid level was 8.82 (1.99 mg/dL). When using limits on uric acid levels in the general population and PGK that have not undergone HD, most of the HD population in RSCM may already have cardiovascular disease abnormalities due to the pro-oxidant effects of uric acid through oxidative stress processes and chronic inflammation [4-9].

The study by Latif [29], Park [30], and Kim [31] as well as colleagues found in the HD population three times a week the average pre-HD uric acid level was <7 mg/dL. This level is lower than that obtained in this study where at that level uric acid is an antioxidant so it has a protection effect on cardiovascular disease. HD twice a week in RSCM seems ineffective for lowering high levels of uric acid to pre-HD blood acid levels that are antioxidants. Pre-HD uric acid in HD twice a week in RSCM may still be pro-oxidant which can increase the incidence of cardiovascular disease.

This study obtained an average blood SDMA level as a marker of PKV of 633.82 (253.67 ng/mL), almost 6 times the upper limit of the normal value of blood SDMA levels [32]. To date the limit of blood SDMA levels that cause PKV cannot be determined in HD population. The study by Vanholder [33] and colleagues reported average blood SDMA levels in HD patients as a uremic toxin was 640.3 ± 212.1 ng/mL. Studies by Meinitzer [15] and colleagues in the general population showed the fourth quartile population with blood SDMA levels (127.26 ng/mL) compared to the lower quartile found a high mortality rate due to PKV with hazard ratio of 2.82 (IK 95% 2.14-3.42). Studies on PGK patients who have not undergone HD by Emrich [17] and colleagues showed the highest quartile population with blood SDMA levels (260.58 ng/mL) obtained higher mortality rate due to PKV compared to the quartile below. When using the limit of blood SDMA levels above, HD patients in RSCM may have enough cardiovascular disease.

Several studies on methane analysis by Schlesinger [34] and colleagues showed that each increase in blood SDMA levels by 202 ng/mL from the basic value obtained an increased incidence of cardiovascular disease. When using the upper limit of normal blood SDMA levels (135 ng/mL) or limits of blood SDMA levels that cause an increase in the mortality rate due to cardiovascular disease in the general population and CKD who have not undergone HD as the basic value as mentioned above causes the population of HD in RSCM is likely to suffer from high enough PKV [15,17].

Difference in average SDMA levels to uric acid

This study shows that there are statistically meaningful differences in average SDMA levels between populations with blood uric acid levels of ≤ 8 mg/dL with populations with blood uric acid levels >8 mg/dL. The results of this study are similar to those reported by the Tenderenda-Banasiuk [14] study and colleagues although using different limits of uric acid and population where uric acid affects increased blood SDMA levels. The study also showed that SDMA's multivariate analysis was related to cardiovascular disease risk factors such as hs-CRP and systolic blood pressure. Various studies have also shown HRA uremic toxin as a marker of PKV [15-21].

Average blood SDMA levels in the uric acid group >8 mg/dl is 649 ng/mL is almost the same when compared to studies by Vanholder [33] and colleagues that is 640.3 ± 212.1 ng/dl where at this level SDMA acts as a uretic toxin against cardiovascular disease. The study by Boelaert [35] and colleagues at the time of the initial dialysis of SDMA levels of HD patients was 416.12 (165.64 ng/mL). Several studies in meta-analysis by Schlesinger [34] and colleagues showed each increase in SDMA levels by 202 ng/mL from the basic value of the increasing incidence of cardiovascular disease. When using blood SDMA levels studied by Boelaert [35] and colleagues as a basic value, the population of this study with pre-HD blood acid levels of >8 mg/dL may already have high SDMA levels as a marker of cardiovascular disease. These results showed the population of HD in RSCM with pre-HD blood acid levels of >8 mg/dL was associated with increased blood SDMA levels as a marker of cardiovascular disease.

The average value of pre-HD uric acid levels in this study was higher compared to previous studies. HD therapy twice a week in RSCM seems ineffective for lowering pre-HD blood uric acid levels to levels that are antioxidant. Pre-HD uric acid levels in HD patients twice a week still remain high causing pro-oxidant effects on cardiovascular. Oxidative stress will increase blood SDMA levels as a marker of cardiovascular disease [36,37]. Another strategy is needed to reduce pre-HD blood uric acid levels to ≤ 8 mg/dL levels in to lower blood SDMA levels as a marker of cardiovascular disease. Increasingly frequent HD frequency, regulating protein intake and giving drugs lowering blood uric acid levels proved very effective in lowering blood uric acid levels [29,30,38-40].

Differences in average SDMA levels in two groups of uric acid with different types of counfounding factors

The results showed several other factors also increased average blood SDMA levels in addition to high blood uric acid levels, namely >65 years old, hypertension, and HD adequateness. The analysis above indicates that the increase in SDMA levels is caused by multifactors in HD patients.

Studies by Jeon [41] and colleagues showed high blood uric acid levels in HD patients should join the DM risk factors to increase mortality from cardiovascular disease especially if HD patients already have cardiovascular disease before. The study by Zawada [42] and colleagues also showed high levels of uric acid will cause an increase in mortality due to cardiovascular disease when it comes to body mass composition (lean body mass and fat body mass). These studies show the cause of cardiovascular disease abnormalities in HD patients is caused by multifactors. Uric acid should join other risk factors to cause cardiovascular disease.

Age risk factors (>65 years old) led to an increase in mortality rates in HD patients. Older HD patients generally have lower levels of uric acid compared to younger ones where it may be related to catabolism or lower protein intake [23]. In this population the mortality rate from cardiovascular disease and any higher cause associated with MIA syndrome [3,40]. This study shows >65 years of age with high uric acid levels obtained further increases blood SDMA levels as a marker of cardiovascular disease. Studies by Coric [23] and colleagues show old age is associated with chronic inflammation (high levels of C-reactive protein). Chronic inflammation is associated with oxidative stress [43]. Oxidative stress can increase blood SDMA levels through the activation of PRIMTs type 2 [2,37] enzyme Studies by Patel [44] and colleagues showing increased SDMA concentration in older populations and increasing the risk of death from cardiovascular disease.

Hypertension can increase blood uric acid levels through tissue ischemia so that there is protein damage that further increases purine metabolism [45]. Hypertension can also increase blood SDMA levels although the exact mechanism is not yet clear the possibility through oxidative stress that stimulates the enzyme PRMTs type 2 in the metabolism of SDMA [20,37].

This study showed hypertension in populations with blood uric acid levels of >8 mg/dL was obtained to further increase blood SDMA levels as a marker of cardiovascular disease. The study by Tenderenda-Banasiuk [14] and colleagues as well as Gamil [46] and colleagues showed a link between hypertension and increased blood SDMA levels.

The study in HD population causes cardiovascular disease to be multifactoral which may be associated or exacerbated by increased blood SDMA levels.

When looking at the average blood SDMA levels among the population with blood uric acid levels ≤ 8 mg/dL in the population aged >65 years, hypertension and HD adequacy obtained in a row is ± 450 ng/mL, ± 500 ng/mL, ± 500 ng/mL with the difference in average levels of human resources in a row ± 330 ng/mL, ± 227 ng/mL, ± 227 ng/mL compared to blood uric acid levels >8 mg/dL. Average blood SDMA levels based on blood uric acid levels ≤ 8 mg/dL to perancu age >65 years, hypertension and acidulation is almost the same ± 500 ng/mL. This level may be the limit of SDMA levels in HD patients twice a week in RSCM who

do not have cardiovascular disease abnormalities. Differences in human resources levels based on uric acid group showed age is very influential on increasing SDMA levels in addition to high uric acid levels although hypertension and HD adequateness can also affect it. HD patients with high uric acid levels and old age are most likely to have high enough SDMA levels to cause cardiovascular disease abnormalities. Intensive therapy needs to be done to inhibit the increase in SDMA levels especially if the patient also suffers from hypertension.

Comparison of average levels of uric acid and blood SDMA with HD quality

The results of the above analysis obtained reverse results between HD adequacy that achieved adequacy and did not achieve adequacy with blood SDMA levels between the groups of uric acid levels >8mg/dL with uric acid levels (8 mg/dL). Re-analysis was carried out between blood SDMA levels and uric acid with HD adequacy. The results of the analysis found no meaningful difference in average blood uric acid levels to the achievement of HD quality targets. The same results were reported by Nemati [47] and colleagues as well as Eloot [48] and colleagues in his study who showed in HD patients decreased blood uric acid levels not related to HD adequateness but related to nutrition. In previous explanations have also been shown by increasing the frequency of HD can lower blood uric acid levels more compared to HD frequently that is not frequent. Nutritional therapy and blood uric acid level lowering drugs should also be considered to lower uric acid levels ≤ 8 mg/dL which is proven to improve the external in HD patients not by increasing HD [38-40].

Bivariate analysis shows that there are significant differences in average blood SDMA levels towards the achievement of HD quality targets. The results of this study were not the same compared to studies by Eloot [49] and colleagues as well as Cupisti [50] and colleagues who showed the decrease in SDMA levels was not related to HD adequateness but related to nutrition. The study by Meyer [51] and colleagues also showed no decrease in SDMA levels by improving HD appecularization. Although statistically different means that those who do not achieve HD adequacy have a lower average blood SDMA level compared to those that achieve HD adequacy. It seems that HD adulation using urea kinetics cannot be used to assess SDMA molecules although both uremic toxins with small molecular weight because the distribution volume and molecular weight of SDMA is greater than urea [51,52]. The analysis was carried out using the online implementation formula KT/V where the value is very dependent on the value of K which is the clients urea, T is the time and V is the volume of urea distribution (60% dry BB). This analysis was conducted to find out which values are related to the cleaning of SDMA molecules. In this study, some patients used Low flux dialyzer (B Brown machine) and others used High Flux dialyzer (Fresenius machine) with different K values. Analysis results found that patients using High Flux Dialyzer secreted more SDMA molecules than those using low flux dialyzers and were statistically meaningful. Studies by Grooteman [53] and colleagues showed different results, low flux and High Flux dialyzers have a clean value to SDMA molecules that are statistically no different because SDMA includes molecules with small molecular weight. SDMA molecular cleansing in this study depends largely on individual factors. The study unfortunately used only a very small sample of subjects (15 people) and did not distinguish SDMA molecular cleansing based on HD frequents. On twice-weekly hemodialysis High flux dialyzers may be indispensable for lowering SDMA levels as a marker of cardiovascular disease.

Dialysis time determines the achievement of HD quality. The study's population of only three people underwent 4.5 hours of dialysis and the remaining 5 hours underwent dialysis so it could not be analyzed. The study by Eloot [48], Cupisti [50] Meyer [51] and colleagues showed that the increase in HD adequacy by prolonging HD time was not found to have a meaningful relationship with decreased SDMA levels. Studies by Shafi [18] and colleagues also show that prolonging dialysis cannot lower SDMA levels more. It seems that the timing of dialysis in this study did not affect the decrease in SDMA levels more. HD adulation is also determined by the volume of urea distribution (a frequently used method is 60% of dry BB). The larger the distribution volume, the smaller the HD deviation. Analysis of bivariate with motede spearman correlation between dry BB and SDMA levels obtained correlation that is statistically meaningless. Urea distribution volume with SDMA is very different because SDMA requires a large distribution volume compared to urea to diffuse effectively in HD process. This is why HD adulation calculation based on urea distribution volume (urea kinetics) cannot be used for SDMA molecules [51,52].

A good therapy to release more SDMA molecules in the population of this study is to use High Flux dialyzer as shown above. The Cheung [54] study and colleagues in the multicenter HEMO study showed High flux compared to low flux dialyzers showed lower mortality rates due to any cause. The Kim [55] study and colleagues also showed HD patients with low residual renal function using a High flux dialyzer showed better survival rates compared to using a Low flux dialyzer. Whether high flux dialyzers are associated with better SDMA molecular spawning need further study with more methods.

Limitations of Study

The limitation of this study is that this study of latitude with populations that have uric acid levels of >8 mg/dL is not the same as the population that has uric acid levels of ≤ 8 mg/dL because very few patients have low uric acid levels. Comparison of SDMA and uric acid levels in HD population twice a week with three times a week is not directly for the population in Indonesia. Nutritional assessment is also not included in this study which plays a role in increasing human resources and uric acid levels.

Conclusion

In twice-weekly hemodialysis patients, a high blood uric acid level >8 mg/dL was associated with increased blood SDMA levels as a marker of cardiovascular disease. Age >65 years and hypertension were also associated with increased mean SDMA levels. Hemodialysis using a high flux dialyzer was associated with lower SDMA levels.

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