

ORIGINAL ARTICLE

THE ROLE OF SYMMETRICAL AND ASYMMETRIC DIMETHYL-L-ARGININE AS BIOMARKERS IN DIALYSIS-DEPENDENT AKI PATIENTS

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Received 6th September 2021.

Accepted 11th October 2021.

Published 3rd December 2021.

Summary

Introduction: Symmetrical and Asymmetric dimethyl-L-arginine were previously discovered in urine, the present study explored the link between acute kidney injury (AKI) and modulation in the level of these biomarkers.

Methods: Ninety volunteers were recruited in the current study, sixty of them were dialysis-dependent AKI patients, their ages ranged between 29-70 years, 13 were diabetic and 47 were non-diabetics patients. Thirty healthy subjects were recruited as a control group. Blood urea, serum creatinine, uric acid, glucose, lipid profile, albumin, hemoglobin, levels were measured using an automated analyzer (SK3002b). Asymmetric dimethyl-L-arginine (ADMA) and symmetric dimethyl-L-arginine (SDMA) serum concentrations were measured using ELISA.

Results: The findings of the current study demonstrated a significant decrease in hemoglobin and serum albumin levels alongside an increase in the serum creatinine, uric acid, and serum triglyceride (TG) in the patients when compared to the apparently healthy controls. Serum concentrations of ADMA and SDMA were significantly lower in healthy controls compared to the patients. **Conclusion:** These data confirm the assumption which assumes that both, ADMA and SDMA serum levels are sensitive markers of reduced renal function and serum SDMA is more sensitive than ADMA in dialysis-dependent AKI patients.

Key words: symmetric dimethyl-L-arginine; biomarker; dialysis; acute kidney injury; asymmetric dimethyl-L-arginine; dimethyl-L-arginine

Introduction

Acute kidney injury (AKI) is described as a rapid reduction in kidney function that occurs within a week or less which may cause a loss in kidney functions, cardiovascular disease, or even death (1). The incidence of AKI is estimated to be 20–200 per million worldwide community, 7–18% in the hospital's patients, and 50% of the intensive care patients (2). A worldwide statistic estimated that 2 million people die every year as a result of AKI, on the other hand, the survivors of AKI are developing a threat of chronic kidney disease (CKD) and end-stage renal disease (ESRD) (3).

Several clinical tools were used to measure AKI such as plasma creatinine, blood urea nitrogen, the fractional excretion of sodium (FeNa), and the presence/absence of urinary casts. However, the use of these markers for the detected at an early stage of AKI is so difficult (4). Numerous biomarkers in urine and plasma have recently been explored for the early diagnosis and development of AKI (5). These biomarkers have the aptitude to play a substantial role in the prediction of many AKI consequences (diagnosis and/or prognosis), whether they are short-term or long-term (6,7,8,9,10).

Methyl arginine amino acid derivatives are expelled as a protein breakdown product in the urine and their levels have thus increased in various clinical situations, such as neurological diseases and tumor disorders. The kidney is the main way by which SDMA is excreted, as a result, many renal function parameters do show a close association with SDMA. SDMA has been recommended as a good biomarker of renal function assessment in specific demographic groups (11). In the patients with chronic renal disease it is claimed to be associated with tumour necrosis factor- α (TNF- α) and interleukin (IL-6) levels, thus it is more substantial than ADMA (12).

Because the common transport pathway for both free ADMA and SDMA is comparable to that of L-arginine, they can be carried within or outside the cell through the cationic amino acid transporter (CAT) family (13). As a result, they can be delivered into key organs including the brain, liver, and kidney for the enzymatic breakdown process (14).

Endothelial dysfunction can be induced by ADMA due to its ability to inhibit NO synthase directly which in turn affects the endothelia and, therefore, contributes to atherosclerosis development (15). While SDMA does not precisely block NO synthase, this could limit NO generation secondarily by inducing intracellular arginine shortage as a result of competition for the cationic amino acid transporter in the endothelial cellular membranes (16). Hence, it will increase the renovascular resistance and will cause a decrease in renal perfusion as a result of the reduced NO availability (17).

Several studies have found a clear link between higher SDMA and ADMA levels, decreased endothelial-dependent vasodilation, and cardiovascular morbidity and mortality in various groups, including individuals with renal illness (18). It was reported that there was an increment in serum levels of ADMA and SDMA in patients with mild to moderate CKD in comparison with healthy individuals (19). These differenced cases to the end-stage renal disease (ESRD) (20). The current study aimed to assess the role of ADMA and SDMA as biomarkers in dialysis-dependent AKI patients.

Materials and methods

Subjects: The total sample size enrolled in the present study was 90 individuals (60 patients and 30 healthy control subjects) as enlisted in (Table 1). The patient group involves; 13 diabetics and 47 were non-diabetics patients. The dialysis was performed three times a week 4 hours per session. The mean period of dialysis was 34 \pm 3 months. During the dialysis process, routinely heparin was used as an anticoagulant. The participant's medical history of cardiovascular events was recorded and defined based on the clinical and laboratory investigations.

Specimens and methods

Venous blood samples: about 5 ml of blood were collected between 9.00 a.m. and 10.00 a.m. from each individual of the studied groups and divided into 2 portions, one portion of 4.5 ml of each sample was added into plain tubes and kept in a water bath at 37°C for 15 minutes for blood coagulation to ensue. Serum specimen were collected by centrifugation of blood at 3000 rpm for 5 minutes. The serum was then frozen at -20°C until completing the collection of all samples. The other blood portion (0.5 ml) was used directly for the measurement of hemoglobin levels.

Laboratory analyses

Blood urea, serum creatinine, uric acid, glucose, lipid profile, albumin, hemoglobin, levels were measured using an automated analyzer (SK3002b). Asymmetric dimethyl-L-arginine and symmetric dimethyl-L-arginineserum concentrations were measured using ELISA kits (Elabscience, USA). All the tests were done within 5 days of sampling.

Statistical analysis

The results of this study were presented as mean± SD. Normal distribution test and similarity of variances were performed for parameters values in all groups. Then, unpaired t-test was applied for the comparison of study groups. The associations between measured parameters were tested using Pearson's correlation coefficient. P values <0.05, 0.01, 0.001 respectively were used to test the variation between the studied groups.

Results

The baseline data of the studied participants are given in Table 1. The demographic characteristics were represented in Table 1. Diabetes patients were present only in 13 (21.6%) of the studied patients.

Table 1. The baseline data of the studied subjects.

Variables	Diabetic Patients (n = 13)	Non-diabetic patients (n=47)	Controls (n = 30)
Males	8	35	18
Females	5	12	12
Mean Age (years)	46±7.5	42±6.1	41±6.8
Mean Weight (kg)	58.2 ± 4.6	64.3 ± 5.2	72 ± 3.0
Mean BMI (kg/m ²)	23.1 ± 0.9	24.7 ± 0.5	23.9 ± 0.4

The results of the measured parameters were shown in table 2 and 3. Table 2 showing the biochemical data results of the study participants. Hemoglobin level was significantly lower in the patient groups (diabetic and non-diabetic) in comparison with the control group. Blood urea, serum creatinine and uric acid in the patient's groups was significantly higher compared to the healthy controls. Serum triglyceride level in the patients were significantly increased in comparison to the control group. while there was a significant decrease in the serum albumin level in the patients compared to the healthy control group. No significant changes were observed between healthy control group and patients' group in the glucose, total protein and cholesterol levels respectively.

Table 2. Showing the biochemical data results of the study participants.

Parameters	Diabetic Patients (n = 13)	Non-diabetic patients (n=47)	Controls (n = 30)
Glucose (mg/dl)	138.6 ± 19.8*	104.2 ± 16.8 [#]	88 ± 9.6
Hemoglobin (g/dl)	11.6 ± 0.3*	10.1 ± 0.4 [#]	14.3 ± 0.4
Blood urea (mg/dl)	70.5 ± 11.2*	61.1 ± 16.8 [#]	31.8 ± 9.6
Creatinine (mg/dl)	6.7 ± 0.6*	9.2 ± 0.1 [#]	0.76 ± 0.1
Uric acid (mg/dl)	5.74 ± 0.6*	3.81 ± 0.6 [#]	3.4 ± 0.3
Total protein (g/dl)	7.2± 0.7*	4.87± 0.4 [#]	7.3 ± 0.5
Albumin (g/dl)	5.3 ± 0.46*	3.76 ± 0.07 [#]	4.3 ± 0.16
Triglycerides (mg/dl)	188 ± 17.5*	148 ± 23.1 [#]	89.2 ± 5.8
Total cholesterol (mg/dl)	153 ± 8.4*	165 ± 3.4 [#]	162 ± 9.4

Mean values ± SD. P<0.01, * there is a significant difference between diabetic patient and control, ^ there is a significant difference between non-diabetic patient and control, #there is a significant difference between diabetic and non-diabetic patient.

Concentrations of ADMA and SDMA were significantly lower in the healthy control group compared to the patient's group as ADMA concentrations were increased more than two folds in the patient's groups compared to those of the control group. SDMA concentrations, on the other hand, was about sevenfold higher in the patient's groups more than the control group.

Table 3. Levels of ADMA and SDMA in the study volunteers.

Parameters	Diabetic Patients (n = 13)	Non-diabetic patients (n=47)	Controls (n = 30)
ADMA (μM)	$0.86 \pm 0.09^*$	$0.72 \pm 0.13^{* \#}$	0.35 ± 0.06
SDMA (μM)	$2.65 \pm 0.3^*$	$2.01 \pm 0.3^{* \#}$	0.33 ± 0.04

Mean values \pm SD. $P < 0.01$, * there is a significant difference between diabetic patient and control, ^ there is a significant difference between non-diabetic patient and control, # there is a significant difference between diabetic and non-diabetic patient.

ADMA levels were positively correlated with albumin ($r = 0.31$; $P < 0.05$), blood urea ($r = 0.49$, $P < 0.05$), and creatinine ($r = 0.41$, $P < 0.05$), on the other hand ADMA were negatively correlated with hemoglobin ($r = -0.23$, $P < 0.05$), total protein ($r = -0.25$, $P < 0.05$), albumin ($r = -0.43$, $P < 0.05$), triglycerides ($r = -0.37$, $P < 0.05$), and total cholesterol ($r = -0.27$, $P < 0.05$).

SDMA levels were positively correlated with blood urea ($r = 0.51$, $P < 0.05$), and creatinine ($r = 0.61$, $P < 0.05$), on the other hand, age ($r = -0.34$, $P < 0.05$), BMI ($r = -0.29$, $P < 0.05$), Triglycerides ($r = -0.21$, $p < 0.05$) and total cholesterol ($r = -0.26$, $P < 0.05$) were inversely correlated with SDMA. Both ADMA and SDMA concentrations shows no significant association with the other remnant parameters.

Discussion

There was an increased interest in the last decade to discover and develop a new biomarkers linked to kidney injury. One of the main particular interests is the ability to utilize the methylarginines (ADMA and SDMA) pathophysiological role due to their involvement in renal diseases. High serum levels of ADMA (21) and SDMA (22) are proposed to identify the development of CKD in patients. According to previous researches, ADMA was linked to endothelial dysfunction as it has been discovered as a nitric oxide synthase inhibitor (23), and increase monocyte adhesion, platelet aggregation, superoxide radical production, smooth muscle cell proliferation, and migration and LDL oxidation (15). SDMA on the other hand competes with L- arginine on the transporting process into the cells and therefore inhibits the production of NO (16). The other mechanism is to modifying high-density lipoprotein (HDL) particles and, as a result, toll-like receptor 2 will be activated. The modified HDL particles become mediators of oxidative stress and subsequently lose their protective properties (24).

During the development process of CKD both ADMA and SDMA accumulate in the serum and urine (19). Some studies suggested that there is a strong association between SDMA and GFR, as a result, it was suggested that SDMA can be added to, or even substitute, the measurement of the creatinine as a renal function endogenous marker (16).

The literature demonstrated that plasma concentration of DMAs and reported it to be low in healthy subjects, however, control values differ distinctly (25). Many authors reported that Dimethyl arginine's concentrations are increased in kidney patients (26).

Another trial on preclinical models discovered a link between SDMA levels and creatinine clearance. Kielstein et al. reported that SDMA levels increased by more than 400% when relative to our data (27). On the other hand, Leone et al, reported a similar (up to four-fold) increase in the construction of both ADMA and SDMA, however, their study was limited to following up only 15 volunteers (6 controls and 9 hemodialysis patients) (23). A study conducted by Kielstein et al., 2003, in chronic renal failure, concluded that the enhanced concentration of SDMA is inversely correlated to creatinine clearance (26).

Correlation tests didn't show an association between creatinine and ADMA concentrations. This result agreed with Schmidt and Baylis study, 2000, (28), and Nijveldt et al., 2002, (29). It was thought that ADMA elimination from the bloodstream is much more reliant on di-methylarginine di-methylamino-hydrolase (DDAH) metabolism than on GFR (30). Therefore, two studies stated that the catabolism, in this case, could be defined as the ADMA

inhibitory compensation effects on nitric oxide synthase (31). Another study reported that ADMA concentration decrease during hemodialysis session, however, hemodialysis is not suitable for long-term removal of dimethyl-arginines.

Litterature detected a high significantly increase in the dimethylarginines in all chronic kidney patients (33). The SDMA increase was more pronounced than other dimethyl-argenins, indicates the association of the SDMA with renal function. Additionally, there was a significant positive relationship among levels of creatinine and SDMA which indicated that SDMA may have a remarkable value as a biomarker for kidney function (26).

Dimethylarginine catabolism research has recommended that the kidneys are practically entirely liable for dimethylarginine elimination (34), on the other hand only 10% of ADMA is cleared out by the kidneys. Dimethylarginine dimethylaminohydrolase might further metabolize the non-excreted part to L-citrulline (35). The ADMA levels in the current study were under the levels of the other studies (36).

The ADMA concentration was statistically higher in the hemodialysis patients compared to the control group, and due to its significant role as an indicator of inflammation, this result suggests that the patients of hemodialysis are more sensitive to oxidative stress and/or inflammation. A study that supported this hypothesis, claimed that hemodialysis patients have decreased capacity of antioxidants and an increased state of inflammation (37).

The high levels of ADMA without any correlation with creatinine levels were not indicated as a result of deficiency of the removal of this substance from the kidney. This disruption could be a result of activity dysregulation of the DDAH enzyme due to many pathophysiological disorders such as inflammation and oxidative stress (26). The DDAH enzyme was perhaps downregulated as a consequence of uremia, which is defined as a substantial increase in creatinine and BUN concentrations in CKD patients. This mechanism may be aided by the inflammation related to chronic uremia. As a result, the rise in ADMA levels seems to be more likely due to the aforementioned component inhibiting the DDAH enzyme.

It was indicated that there was a strong correlation between ADMA levels, the cardiovascular event rate, and to all-cause of mortality in hemodialysis patients (38). Research on a small sample of healthy smokers, (young males) published in the same issue found that ADMA predicted the events of acute coronary diseases (39), and chronic heart failure (40). As a result of these findings, another study demonstrated that the levels of ADMA can predict the carotid intimal thickening progression in hemodialysis patients,(41) It also demonstrates a link between ADMA levels and left ventricular hypertrophy in the same studied group. Clinical trial data have shown comparable findings supports the idea of ADMA ability to anticipate cerebrovascular events, all-cause mortality, severe cardiac diseases, and renal disease progression, and it has been reported that every 0.1 mol/ L rise in ADMA rates increased the chances of progression to hemodialysis and death by up to 20%.

Conclusion

There was a significant increase in ADMA concentrations, as it increased by two folds only, whereas the SDMA increment was over seven-fold inpatient compared to the control. These findings confirm the hypothesis who assumes that both, ADMA and SDMA is a sensitive renal function marker and SDMA is more sensitive than ADMA in dialysis-dependent AKI patients.

Acknowledgment

The authors of this review article are very grateful the College of Pharmacy / University of Mosul.

Adherence to Ethical Standards

Not applicable

Conflict of Interest

The authors have no conflicts of interest regarding the publication of this article.

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