RELATIONSHIP BETWEEN ASYMMETRIC DIMETHYLARGININE (ADMA) AND ATHEROSCLEROSIS IN CHRONIC RENAL FAILURE PATIENTS

By

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ABSTRACT

Background: Serum ADMA level was high in hemodialysis patients as compared to healthy control population. Increase in ADMA levels may play a role in atherosclerosis dependent morbidity and mortality. **Objective:** Assessment of the relationship between serum ADMA and atherosclerosis. **Patients and Methods:** Serum ADMA was measured using ADMA ELISA Kit; atherosclerosis was assessed by non-invasive methods including FMD and CIMT in 3 groups (50 ESRD patients undergoing hemodialysis, 25 CKD patients and 25 healthy control subjects). **Results:** CKD and ESRD patients on regular hemodialysis have significantly greater ADMA, CIMT and lesser FMD than do control subjects with normal renal function. Both groups of patients have higher cholesterol and triglycerides levels than do control subjects which could be related to serum ADMA. Serum albumin was reduced in hemodialysis and CKD patients. It has an inverse correlation with serum ADMA. **Conclusion:** Patients of CKD and hemodialysis have earlier endothelial dysfunction than do control group and this explained why they have higher incidence of cardiovascular morbidity and mortality. Integration of ADMA into currently applied risk scores still needs to be validated.

Key words: Dimethylarginine, hemodialysis, brachial artery, endothelium.

INTRODUCTION

Asymmetric dimethylarginine (ADMA) is an analog of L-arginine that inhibits in vivo nitric oxide (NO) synthesis by competing with L-arginine at the active site of NO synthase (NOS). NO is a potent vasodilator that plays a critical role in maintaining vascular homeostasis through its anti-atherogenic and anti-proliferative effects on the vascular wall **(Franceschelli et al., 2013)**. ADMA is associated with endothelial dysfunction **(Serg et al., 2011)**.

Serum ADMA level was high in hemodialysis patients as compared to healthy control population which may play a role in atherosclerosis dependent morbidity and mortality **(Vatansev et al., 2014)**. In chronic kidney disease , ADMA is an independent marker of progression of renal disease, vascular complications and mortality **(B?ger and Schwedhelm, 2011)**.

Plasma ADMA is an important biochemical marker of micro vascular disease progression in the kidney and might play an important role in the

development of end organ damage in essential hypertension (**Fujii et al., 2008**).

Serum ADMA was related reversely to flow mediated dilation (FMD) of brachial artery. In multiple regression analysis, ADMA was the only independent determinant of FMD (**Xia et al., 2010**).

There is a strong relationship between ADMA and FMD in hyper-cholesterolemia. ADMA is the basic modulator of % FMD among all tested atherogenic risk biomarkers in severe hypercholesterolemia (**Kitova et al., 2008**).

Traditional risk factors such as plasma cholesterol and triglycerides levels were significantly associated with asympto-matic carotid atherosclerosis. High serum concentrations of ADMA were associated with carotid atherosclerotic lesions as measured by carotid intimal media thickness (CIMT) and may represent a new non-traditional marker of asympto-matic carotid atherosclerosis (**Riccioni et al., 2014**).

Cardiovascular disease due to atherosclerosis is the leading cause of death in patients with chronic kidney failure. Patients with chronic kidney disease exhibit evidences of early and exaggerated vascular and cardiac remodeling, i.e. arteriosclerosis and left ventricular hypertrophy (**Sibal et al., 2010**). Cardiac non-traditional risk factors specific to chronic kidney failure as volume overload, hyper- parathyroidism, uremia, anemia and endothelial dysfunction may also play a role in the process of atherosclerosis (**Cibulka and Racek, 2007**).

The aim of this study was to assess serum ADMA levels and their relationship to endothelial dysfunction, carotid intima-media thickness (CIMT) and brachial artery flow mediated dilation (FMD) in chronic renal failure (CRF) patients on conservative treatment as well as hemodialysis (HD) patients.

PATIENTS AND METHODS

This study included 100 subjects. They were divided into three groups:

Group1: This group included 50 CRF patients who underwent regular hemo-dialysis (HD) three times weekly, each dialysis session were performed in 3 hours. Blood access was through arteriovenous fistula (AVF). The duration of hemo-dialysis ranged between 29 and 100 months with a mean of 58.38 ± 19.83 months. Their age ranged between 19 and 81 years with a mean of 45.8 ± 13.7 years. Thirty one of them were males and 19 were females.

Group 2: This group included 25 CKD patients on conservative treatment (stage 4). Their creatinine clearance ranged from 15.12 to 28 ml. /min. with a mean of 20.34 ± 3.8 ml./min. Creatinine clearance was calculated by the Cockcroft–Gault formula. For men, the formula was (140-age) $\times$ (weight in Kg) / 72 $\times$ serum creatinine. For women, this result was multiplied by the factor 0.85 (**Cockcroft, and Gault, 1976**). They were 13 males and 12 females. The age of this group ranged between 29 and 75 years, with a mean of 48.6 ± 12.9 years.

Group3: This group included 25 normal healthy subjects used as controls. Thirteen of them were males and 12 were females.

Their ages ranged between 25 and 75 years, with a mean of 47.4 ±14.06 years.

Exclusion criteria:

● CKD stage 1.2.3.

● Irregular hemodialysis patients.

● Symptomatic carotid artery disease (CAD) that necessitated revascularization therapy or recent endovascular interventions.

Collected data from all groups included:

1. Full medical history (familial diseases, concomitant diseases, pharmacotherapy used, and smoking).

2. Physical examination including blood pressure measurement, heart, chest and abdomen examination and body weight.

3. Lab. Investigations: CBC, blood urea nitrogen (BUN), serum creatinine, serum albumin, estimated glomerular filtration rate (GFR) in stage 4 CKD group, serum cholesterol and serum triglycrides.

● The **serum ADMA** concentration was assessed by the ADMA ELISA kit **(Bio Assay Technology Laboratory, 2016 - Bouras et al., 2013).** Serum samples were collected from patients prior to dialysis, then samples were allowed to clot for 10-20 minutes at room temperature. Samples were centrifuged and stored at -20 ℃ temperature. The test was based on binding of ADMA from samples to coated antibody on the microwells, bound ADMA was detected by horseradish peroxidase (HRP) labled detection antibodies. Assay range of the test was 2ng/ml. to 600 ng/ml. Sensitivity of the test was 1.21 ng/ml.

● Assessment of **flow-mediated vasodilation (FMD)** of brachial artery according to the American College of Cardiology guidelines **(Corretti et al., 2002).**The brachial artery was scanned 5 – 15 cm above the antecubital fossa. Resting diameter was measured, and then a blood pressure cuff was inflated around the arm to at least 50 mmHg above SBP for 4.5 minutes. A measurement of maximum diameter was taken 45 – 60 seconds after cuff release. Distance was measured from the anterior to the posterior M lines (media–adventitia interface). USG machine with high resolution (B) scan 7.5Hz linear accelerator was used to assess brachial artery diameter and its changes.

FMD = [(post-deflation diameter– resting diameter) / resting diameter] $\times$ 100

● Assessment of **intima-media thickness (IMT)** of carotid arteries. Common carotid artery (CCA) was measured by high-resolution B-mode ultrasonography with a 7.5-MHz transducer . Measurements of CCA diameter and CCA-IMT were always performed opposite to the side of atrioventricular shunts 2 cm beneath the bifurcation. Measurements of CCA-IMT were done on the far wall at the same level as the diameter measurements.

Statistical methods

The data were entered, coded and processed on computer using Statistical Packaged for Social Science *(IBMSPSS version 22, 2013).* The level $P \leq 0.05$ was considered the cut-off value for significance. Tests used in the study were [**Chi-Square test χ^2, Fisher exact test, one way ANOVA, Post Hoc Tests (mean**

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difference and P value), **Pearson correlation** for quantitative variables, and **ROC curve** was used to test Sensitivity & specificity of quantitative variable].

95% and margin of error of 5% in population 93.

RESULTS

Cross sectional study was applied on 50 hemodialysis patients, 25 CKD stage 4 patients and 25 healthy control subjects. Sample size was calculated using sample size calculator with confidence level of

There was a statistical significant difference between the three groups regarding the mean of weight with higher body weight of control group than patient groups. However there was no statistical significant difference between the three groups regarding the age and sex with a higher percentage of male than female in all studied groups **(Table 1)**.

Table (1): Descriptive data of studied groups.

Group\Parameter	Group 1 CRF	Group 2 CKD	Group 3 Control	Pvalue
	Mean ± SD			
Age (yr.)	45.8±13.7	48.6±12.9	47.4±14.06	>.050
Weight (Kg.)	74.8±8.07	72.4±7.8	78.5±10.7	<0.050*
	n(%)			P value
Sex Male	31(62)	13(52)	13(52)	>0.050
Female	19(38)	12(48)	12(48)	

ANOVA = analysis of variance χ^2 = Chi-Square   SD=   standard deviation
CRF = chronic renal failure   CKD= chronic kidney disease

There was a statistical significant difference between the three groups regarding the mean of ADMA, IMT and FMD, with a higher mean of ADMA and

IMT in patients groups than control group. However there was a higher mean of FMD in control group than patients groups **(Table 2).**

Table (2): Comparison of ADMA , IMT and FMD in studied groups.

Group\Parameter	Group 1 CRF	Group 2 CKD	Group 3 Control	ANOVA	P-value
	Mean ± SD				
ADMA (ng./ml.)	39.64±9.2	35.03±8.39	20.93±2.17	47.482	<0.001**
IMT(mm.)	0.86±0.13	0.87±0.13	0.48±0.08	86.448	<0.001**
FMD%	6.02±1.73	5.98±1.85	17.62±3.69	220.012	<0.001**

ADMA =Asymmetric dimethylarginine
 IMT =intima-media thickness   FMD=   flow mediated dilatation

There was a statistical significant difference between the three groups regarding the mean of creatinine, hemoglobin, albumin, cholesterol and triglyceride. There was a higher mean of creatinine, cholesterol and triglycerides in hemodialysis and CKD 4 groups than in control group. However, there was a lower mean of hemoglobin, albumin in hemodialysis and CKD 4 groups than in control group **(Table 3).**

Table (3): Laboratory investigation among studied groups.

Parameter \ Group	Group 1 CRF	Group 2 CKD	Group 3 Control	P-value
	Mean ± SD			
Creatinine (mg./dl.)	8.96±4.05	4.16±0.45	0.69±0.19	<0.001**
Hgb (gm./dl.)	10.62±1.99	9.21±0.87	14.10±1.24	<0.001**
Albumin (gm./dl.)	3.90±0.60	3.14±0.43	4.44±0.60	<0.001**
Cholesterol (mg./dl.)	164.1±43.1	228.7±66.6	124.2±31.4	<0.001**
TG (mg./dl.)	196.5±143.1	153.1±90.6	93.8±21.9	0.001**

There was a statistical significant positive correlation between ADMA and creatinine, IMT, cholesterol, triglycride. However there was a statistical significant negative correlation between ADMA and FMD, hemoglobin, albumin **(Table 4).**

Table (4) :Correlation between ADMA and different variables .

Variables	r	P-value
Creatinine (mg./dl.)	0.547	<0.001**
IMT(mm.)	0.552	<0.001**
FMD%	-0.625	<0.001**
Age (yrs.)	-0.133	>0.05
Hemoglobin (gm./dl.)	-0.510	<0.001**
Albumin (gm./dl.)	-0.209	<0.05
Cholesterol (mg./dl.)	0.214	<0.05
Triglycride (mg./dl.)	0.322	0.001**
Body weight(Kg.)	-0.123	>0.05
GFR	-0.296	>0.05

r= Pearson Correlation

Best cutoff value of ADMA was 24.73 with sensitivity 98%, specificity 58% . So ADMA value was significant in diagnosis of CRF as area under curve (AUC) was 0.820, and p-value <0.001 **(Table 5).**

Table (5): Validity of ADMA in diagnosis of CRF.

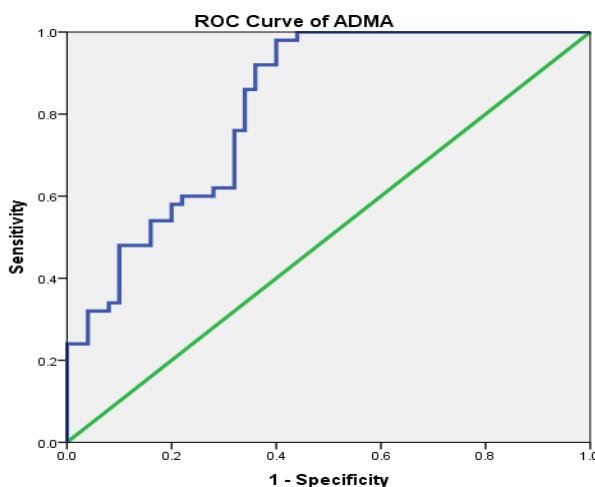| Cut off value	24.73
Sensitivity	98 %
Specificity	58%
Area under the curve (AUC)	0.820
Standard error	0.042
95% Confidence interval	0.739 - 0.902
Significance level (P-value)	<0.001[**]

Figure (1): Receiver operating curve analysis of ADMA, (AUC) = 0.820. Best cutoff value of ADMA was 24.73 with sensitivity 98%, specificity 58%.

Figure (2): Measurement of IMT using Doppler US in a hemodialysis patient. IMT thickness = 1.2 mm. The increased IMT was directly linked to high levels of serum ADMA which was responsible for increased morbidity and mortality in these patients.

DISCUSSION

In the current study, serum ADMA levels were significantly higher in hemodialysis patients and in CKD stage 4 patients than in control group **.** This could be due to higher levels of protein methylation, increased rate of protein turnover, decreased excretion and decreased activity of DDAH enzymes that is effective in catabolism of ADMA **(Vatansev et al., 2014).**

Our results went in agreement with the results reported by **B?ger &Schwedhelm (2011) and Vatansev et al. (2014)** who found that plasma ADMA levels were significantly increased in patients undergoing HD , suggesting that there was pathophysiological role of ADMA in these patients with cardiovascular diseases.

In our study, serum albumin level of dialysis patients and CKD stage 4 patients was significantly lower as compared to healthy control group which could be explained by the interrelationship between hypoalbuminemia, inflammation, malnutrition and atherosclerosis due to appetite suppression and increased catabolism by inflammatory cytokines. Also, hypoalbuminemia lead to decreased antioxidant capacity **(Kalantar-Zadeh et al., 2001)**. **Kalantar-Zadeh et al. (2005)** showed an association between serum albumin level and CVD in hemodialysis patients and stated that hypoalbuminemia could be a strong predictor of mortality in dialysis patients.

Similar results were obtained by **Joki et al. (2006)** who demonstrated that patients in predialysis chronic renal failure with carotid plaque had lower serum albumin level and that hypoalbuminemia was an excellent reflection of cardiovascular diseases.

Our study revealed that FMD values in brachial artery were significantly lower in hemodialysis patients and CKD stage 4 patients in comparison to that in controls . Our results could be explained by the fact that endothelial dysfunction is considered to be a systemic issue. Albuminuria leads to a reduction in the endothelium-dependent vascular relaxation response in glomerular endothelial cells **(Satoh, 2012)**. Potential mediators between kidney function and endothelial function included ADMA and TNF- α **(Chong et al., 2014)**. Similar results were found by **Recio-Mayoral et al. (2011) and Shukla et al. (2015)** who observed that hemodialysis and CKD stage 4patients had reduced FMD values as compared to controls. **Chong et al. (2014)** found an inverse relationship between renal function and FMD in symptomatic peripheral arterial disease.

In the current study, there was an inverse relationship between serum ADMA and endothelial function as measured by FMD. Probably, the chronic inflammation documented in these patients may be considered the mechanistic link between ADMA and vascular damage. Similar results were obtained by **Yilmaz et al. (2008)** who stated an inverse relationship between serum ADMA and FMD.

The current study revealed that levels of serum cholesterol as well as triglycrides levels were significantly higher in hemodialysis patients and CKD stage 4 patients as compared to that in controls. Serum triglycerides elevated in CRF because of dysfunction of TG degradation resulted from insufficient mitochondrial beta-oxidation of fatty acids. Hyper-insulinemia was the main factor increasing synthesis of TG and decreasing the activity of lipoprotein lipase **(Cibulka et al., 2005).** Our results went in agreement with the results obtained by **Chong et al. (2014) and Shukla et al. (2015)** who stated that chronic renal failure patients suffered from dyslipidemia that was associated with endothelial dysfunction.

Our study revealed that there was a statistical significant positive correlation between ADMA, creatinine, CIMT, cholesterol and triglycerides. However, there was a statistical significant negative correlation between ADMA and FMD, hemoglobin and albumin. Also, the significant positive correlation between ADMA, cholesterol and triglycerides could be explained by the fact that elevated levels of oxidized LDLs lead to a reduction in DDAH activity thus increased ADMA levels **(Feng et al., 2008)**. **Riccioni et al. (2014)** stated that total cholesterol, triglycerides plasma concentrations and high serum ADMA levels were significantly associated with asymptomatic carotid atherosclerosis as measured by CIMT .

In the present study, there was a positive correlation between ADMA and carotid intima-media thickness (CIMT) which could be attributed to endothelial dysfunction resulted from increased ADMA levels and other traditional risk factors of atherosclerosis. These results went in agreement with the results obtained by **Riccioni et al. (2014)** who stated that high serum concentrations of ADMA were associated with carotid atherosclerotic lesions as measured by CIMT and may represent a new marker of asymptomatic carotid atherosclerosis.

Hafner et al. (2014) found that there was elevated levels of ADMA, decreased flow mediated dilatation, enlarged intima-media thickness in symptomatic peripheral arterial disease that was linked to increased cardio-vascular risk. Also, **Janda et al. (2015)** confirmed that in chronic renal failure and in CKD stage 4 patients, Radial artery calcifications and

intimal atherosclerotic changes frequently coexist and this was significant predictor of mortality, independent of dialysis status.

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العلاقة بين ثنائى ميثيل الارجنين غير المتماثل وتصلب الشرايين في مرضى الفشل الكلوى المزمن

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خلفية البحث : يرتفع مستوي مادة ثنائى ميثيل الأرجنين غير المتماثل في مصل مرضي الفشل الكلوي المزمن بالمقارنة بالأشخاص الأصحاء وربما يؤدي ارتفاع نسبة ثنائى ميثيل الأرجنين غير المتماثل في أولئك المرضي إلي حدوث الأمراض والوفيات الناتجة عن تصلب الشرايين .

الهدف من البحث: تقييم العلاقة السببية بين إرتفاع مستوي مادة ثنائى ميثيل الأرجنين غير المتماثل في مصل مرضي الفشل الكلوي وحدوث تصلب الشرايين.

المرضي وطرق البحث: تم قياس نسبة ثنائى ميثيل الأرجنين غير المتماثل في مصل المرضي بإستخدام القياس المناعي المرتبط بالإنزيمات (الايليزا) وتم الإستدلال علي وجود تصلب الشرايين في المرضي بإستخدام وسائل غير تداخلية وهي تشمل سمك جدار الشريان السباتي وقياس النسبة المئوية لاتساع الشريان العضدي الناتجه عن التدفق الدموي في ثلاث مجموعات (٥٠ مريض فشل كلوي مزمن و٢٥ مريض قصور كلوي مزمن من الدرجة الرابعة و٢٥ شخص سليم كمجموعة مقارنة) .

النتائج : مرضي الفشل الكلوي المزمن ومرضي قصور الكلي المزمن من الدرجة الرابعة يمتلكون مستويات أعلي من مادة ثنائى ميثيل الأرجنين غير المتماثل في أمصالهم بالإضافة إلي زيادة في سمك جدار الشريان السباتي ونقص في النسبة المئوية لإتساع الشريان العضدي الناتج عن التدفق الدموي بالمقارنة بالأشخاص الذين يمتلكون وظائف كلي طبيعية وأفادت النتائج أيضا أن كلا المجموعتين لديهما مستويات أعلي من الكولستيرول والدهون الثلاثية في أمصالهم مقارنة بالأشخاص الطبيعيين وهو ما قد يكون مرتبطا بإرتفاع مستوي مادة ثنائى ميثيل الأرجنين غير المتماثل وأوضح البحث أن كلا المجموعتين تمتلكان مستويات منخفضة من الألبومين في الدم مقارنة بالأشخاص الطبيعيين وهو ما يتناسب عكسيا مع إرتفاع مستوي مادة ثنائى ميثيل الأرجنين غير المتماثل في مرضي الفشل الكلوي المزمن ومرضي القصور الكلوي المزمن من الدرجة الرابعة.

الإستنتاج : مرضي الفشل الكلوي المزمن ومرضي القصور الكلوي المزمن من الدرجة الرابعة يعانون من إعتلال مبكر للخلايا الطلائية عما يحدث في الأشخاص الطبيعيين وهذا يفسر حدوث نسبة أعلي من الإصابة بالأمراض والوفيات الناجمة عن إعتلال القلب والأوعية الدموية في أولئك المرضي وأن إدخال مادة ثنائى ميثيل الأرجنين غير المتماثل في مقياس المخاطر المستخدم حاليا يحتاج للتقييم في المستقبل.