RESEARCH

Open Access

Asymmetric dimethylarginine serum concentration in normal weight and obese CKD patients treated with hemodialysis

Elham Alipoor[1,2], Shiva Salehi[2], Sahar Dehghani[2], Mehdi Yaseri[3] and Mohammad Javad Hosseinzadeh-Attar[1,2*]

Abstract

Introduction Asymmetric dimethylarginine (ADMA), a cardiovascular risk factor, increases in renal failure. The aim of this study was to investigate ADMA levels in normal weight and obese patients on hemodialysis.

Methods In this cross-sectional study, 43 normal weight and 43 obese patients on regular hemodialysis were examined. Malnutrition-inflammation score (MIS), anthropometry, circulating ADMA, lipid profiles including triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and lipid ratios, glucose homeostasis parameters, blood pressure, and high-sensitivity C-reactive protein (hs-CRP) were assessed.

Results Serum levels of ADMA were significantly lower in the obese compared to the normal weight patients (10268.2 ± 10092.4 vs. 13765.2 ± 9951.3 ng/l, $P = 0.03$). At the same time MIS score (6.1 ± 2.4 vs. 10.7 ± 3.2, $P < 0.001$), systolic blood pressure (119 ± 26.8 vs. 134.2 ± 24.7 mmHg, $P = 0.018$) and mean arterial pressure (91.3 ± 18.6 vs. 100.9 ± 15.9 mmHg, $P = 0.028$) were significantly lower in the obese than the normal weight group. Fasting blood glucose ($P = 0.045$), TG/HDL ($P = 0.03$), TC/HDL ($P = 0.019$), and LDL/HDL ($P = 0.005$) ratios, and hs-CRP ($P = 0.015$) levels were significantly higher in the obese than in the normal weight group.

Conclusion Circulating ADMA was significantly lower in obese than in normal weight patients on hemodialysis, which was concomitant with lower MIS, indicating a better nutritional inflammatory status, and lower blood pressure.

Keywords Asymmetric dimethylarginine, Hemodialysis, Malnutrition inflammation score, Obesity

*Correspondence:
Mohammad Javad Hosseinzadeh-Attar
hosseinzadeh.md.phd@gmail.com; mhosseinzadeh@tums.ac.ir
[1]Cardiac Primary Prevention Research Center, Cardiovascular Diseases Research Institute, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, No#44, Hojjatdoost St., Naderi St., Keshavarz Blvd, Tehran, Iran
[3]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Chronic kidney disease (CKD) is associated with an increased risk of atherosclerosis and cardiovascular mortality. In end-stage renal disease (ESRD), cardiac events account for more than half of all deaths [1]. Endothelial dysfunction as a result of reduced nitric oxide (NO) bioavailability is a key factor in the progression of atherosclerosis. Asymmetric dimethylarginine (ADMA), a competitive inhibitor of endothelial NO synthase (eNOS), is associated with endothelial dysfunction, inflammation, and oxidative stress in cardiovascular diseases and renal failure [2, 3]. ADMA has also been

implicated in lipid metabolism and hypercholesterolemia, hypertension, insulin resistance and diabetes.

ADMA accumulation has been described in patients with different degrees of renal failure [4, 5]. Some reasons for the accumulation of ADMA in CKD patients include increased protein methylation and turnover, decreased ADMA metabolism by dimethylarginine dimethylaminohydrolase (DDAH), and impaired renal function [6]. ADMA levels increase in the early stages of CKD, even before GFR declines. ADMA has a relatively low molecular weight. In ESRD, contrary to expectations, some studies have failed to show significant elimination of ADMA after dialysis, even with high-flux membranes or hemodiafiltration. Changes in DDAH activity, inflammatory cytokines and PH may be involved in these controversies [7].

ADMA is also known as an adipokine, because the genes encoding its biosynthesis and metabolism are also located in adipose tissue as well [8]. Adipokines may be associated with inflammation, cardiovascular risk factors, and protein energy wasting (PEW) in ESRD [9, 10]; however, few studies have investigated these peptides considering the role of body mass status. ADMA levels are elevated with increasing body mass index (BMI) and insulin resistance in individuals with normal renal function [11]. However, studies investigating changes in ADMA levels in relation to body weight status in CKD patients have yielded conflicting results. While, one study found a positive correlation between ADMA and BMI in kidney transplant recipients, which was attributed to hypercholesterolemia and oxidative stress-induced disruption of DDAH activity [12], some others showed no significant relationship between ADMA concentration and BMI and overweight in CKD [13, 14]. On the other hand, one study showed an association of high ADMA levels with low BMI and albumin levels in hemodialysis patients, indicating poor nutritional status and abnormal protein metabolism [15].

Given the recognition of ADMA as a cardiovascular risk factor, its elevation in renal failure, and the controversies about its changes with BMI status in hemodialysis, the aim of this study was to investigate ADMA concentrations in normal weight and obese patients on hemodialysis in relation to nutritional status and cardiometabolic risk factors.

Materials and methods
Design and patients
In this comparative cross-sectional study, 43 normal weight ($18.5 \leq$ BMI < 25 kg/m^2) and 43 obese (BMI ≥ 30 kg/m^2) patients with ESRD (glomerular filtration rate < 15 mL/min) who had been on regular hemodialysis for more than six months were evaluated. Patients with a history of any endocrinopathies other than diabetes, inflammatory and immune disorders, organ failure, malignancy, or recent acute illness (such as trauma, infection, myocardial infarction, or cerebrovascular accident) were not eligible for this study. Additionally, patients treated with glucocorticoids, taking high doses of dietary supplements, with recent intentional weight changes, smokers and drug addicts were not included in this study. Patients were recruited from hemodialysis units affiliated with medical universities. All participants have completed and signed a written informed consent form.

Assessments
A 10-hour fasting venous blood sample was collected prior to dialysis, and serum was stored at -80 °C after centrifugation. Anthropometric indices were assessed using standard techniques immediately after completion of hemodialysis to minimize the effect of fluid overload.

The malnutrition inflammation score (MIS) consists of 10 questions, 7 of which are subjective global assessment (SGA) items, in addition to BMI level, and blood levels of albumin and total iron binding capacity (TIBC). Each item is scored from 0 (normal) to 3 (severe), and the total score ranges from 0 to 30, with higher scores indicating more severe PEW [16]. Mean dietary intakes of energy and protein were extracted from dietary recalls of two dialysis and two non-dialysis days, using Nutritionist IV software (N Squared Computing, San Bruno, CA, USA).

Serum ADMA levels were determined using an enzyme-linked immunosorbent assay (ELISA) kit (Crystal Day Biotech Co., China). Serum levels of fasting blood glucose (FBG), albumin, transferrin, lipid profiles including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and high-sensitivity C-reactive protein (hs-CRP), and creatinine were measured by standard biochemical methods using commercial kits (Pars-Azmoon, Tehran, Iran). TIBC was calculated as transferrin×1.25. Serum insulin levels were measured using a radioimmunoassay kit (DiaSource, Louvain-la-Neuve, Belgium), and homeostatic model assessment for insulin resistance (HOMA-IR) was calculated based on relevant formulas.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the sitting position after 10 min of rest. Mean arterial pressure (MAP) was calculated as (SBP+2 DBP)/3.

Fresenius 4008s dialysis machine, PS13 low-flux (Meditechsys Co, Tehran, Iran) dialyzer membrane, and 200–300 ml/min blood flow were used as the standard dialysis unit protocol in this study. The Kt/V was calculated as "-ln{[(post BUN/pre BUN)- (0.008×t)]+[4-(3.5×post BUN/pre BUN)] × 0.55×UF/V}" [17].

Statistical analysis

The mean, standard deviation (SD), frequencies, and percentages were used to present the results of this research. The Kolmogorov-Smirnov test was used to test the normality of the distribution of the variables. To compare differences in variables between the two study groups, the Chi-Squared test was used for nominal variables, and the Independent Sample t-test and Mann–Whitney test were used for continuous variables, as appropriate. Bivariate correlations were used to assess the relationship between ADMA and other variables. A general linear model was used to assess the effect of potential confounders, including age, sex, and diabetes. To find the most important factors associated with ADMA levels, a general linear model with LR backward model selection method was performed on variables that showed a p-value<0.2 in univariate analyses, including BMI, waist circumference, TC, LDL, MIS, diabetes, dietary intake of protein (%), and energy, in addition to age, sex, and diabetes. The final model was reported by adjusted regression coefficient (Aβ), corresponding 95% confidence interval (CI), and P values. All statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, IBM Corp., Version 22.0. Armonk, NY, USA). P values less than 0.05 were considered statistically significant.

Table 1 General characteristics, anthropometric indices, and nutritional status of the study population

		Normal weight (n=43)	Obese (n=43)	P
Sex	Male	25 (58.1)	16 (37.2)	0.084 *
	Female	18 (41.9)	27 (62.8)	
Age (yr)		57.7±14.5	57.1±10.7	0.314 **
Duration of dialysis (month)		47.9±36.6	46.8±38.5	0.769 **
Kt/V		1.3±0.6	1.3±0.5	0.766 **
Diabetes		13 (31.0)	23 (53.5)	0.048 *
Weight (kg)		55.3±7.2	83.1±10.5	<0.001 **
BMI (kg/m^2)		21.8±2	33.4±2.9	<0.001 **
Waist circumference (cm)		83.5±8.5	111.4±8.5	<0.001 **
MIS		10.7±3.2	6.1±2.4	<0.001 **
Albumin (mg/dl)		4.1±0.4	4.1±0.3	0.869 **
TIBC (mg/dl)		188.5±50.8	209.2±60.6	0.09 ***
Energy (kcal/kg)		33.2±12.7	32.2±13.9	0.681 **
Protein (g/kg)		1.4±0.5	1.3±0.6	0.167 ***

Values are presented as mean±SD or frequency (%)

* Based on Chi-Square test

** Based on Mann–Whitney test

*** Based on t-test

Results

General characteristics and nutritional status

There were no significant differences in sex (*P*=0.084), age (*P*=0.314), hemodialysis duration (*P*=0.769), or dialysis adequacy (*P*=0.766) between the obese and normal weight groups. Approximately 54% of the obese group and 31% of the normal weight group had diabetes (*P*=0.048). Statistically significant differences in dry weight, BMI, and waist circumference were observed between the two groups (*P*<0.001) (Table 1).

The MIS score was significantly lower in the obese patients than in the normal weight patients (*P*<0.001). No other differences in nutritional status parameters such as albumin and TIBC or dietary intakes of energy and protein were observed between the two study groups.

ADMA

The present study showed significantly lower circulating levels of ADMA in the obese patients compared to the normal weight patients (10268.2±10092.4 vs. 13765.2±9951.3 ng/l, *P*=0.028). This significant difference remained unchanged after adjustment for the effects of age, sex, and diabetes (*P*=0.03) (Table 2). Additionally, when patients were divided into two groups based on median values of waist circumference, ADMA levels were slightly lower in patients with higher abdominal obesity (10369.3±10588.7 vs. 13494±9908.1 ng/l, *P*=0.05). There were no significant differences in ADMA levels when patients were categorized based on hs-CRP or HOMA-IR levels (data not shown).

There were significant inverse associations between ADMA and dry body weight (*r*=-0.236, *P*=0.03) and BMI (*r*=-0.266, *P*=0.014) in this study. No other significant relationship was observed between ADMA concentration and other cardiometabolic risk factors (*P*>0.05, data not shown).

The final logistic regression model from the backward selection model showed that age and BMI were the most important determinants of ADMA concentration. Each unit increase in age (Aβ=-0.237, 95% CI: -0.014 to 0, *P*=0.046) and BMI (Aβ=-0.253, 95% CI: -0.031 to -0.001, *P*=0.033) was associated with approximately about 0.24 and 0.25 unit decrease in ADMA levels, respectively.

Cardiovascular risk factors

The results showed significantly higher FBG (*P*=0.045), TG/HDL ratio (*P*=0.030), TC/HDL ratio (*P*=0.019), LDL/HDL ratio (*P*=0.005), and hs-CRP levels (*P*=0.015) in the obese group than in the normal weight group after adjustment for age, sex, and diabetes (Table 2). In the current study, significantly lower SBP (*P*=0.018) and MAP (*P*=0.028) and a marginally lower DBP (*P*=0.054) values were observed in the obese group compared with

Table 2 Circulating ADMA, biochemical parameters and blood pressure of the study population

	Normal weight (n = 43)	Obese (n = 43)	P_1	P_2	P_3
ADMA (ng/l)*	13765.2 ± 9951.3	10268.2 ± 10092.4	0.028 **	0.027	0.03
TG (mg/dl)	146.3 ± 138.4	196.4 ± 144.1	0.002 ***	0.136	0.269
TC (mg/dl)	139.8 ± 40.9	153.8 ± 48.9	0.154 **	0.188	0.143
HDL (mg/dl)	43.2 ± 10.5	38.4 ± 15	0.092 **	0.041	0.058
LDL (mg/dl)	72.4 ± 26.4	81.3 ± 28.8	0.142 **	0.161	0.07
TG/HDL	3.5 ± 3.6	5.7 ± 5.4	0.001 ***	0.024	0.03
TC/HDL	3.5 ± 1.9	4.5 ± 2.4	0.007 ***	0.023	0.019
LDL/HDL	1.8 ± 0.9	2.4 ± 1.2	0.007 ***	0.01	0.005
FBG (mg/dl)	104.6 ± 32	140 ± 67.4	0.013 ***	0.003	0.045
Fasting insulin (μIU/mL)	39.4 ± 45.2	38.3 ± 33.3	0.796 ***	0.898	0.51
HOMA-IR	10.1 ± 13.4	13.1 ± 13	0.26 ***	0.317	0.984
Creatinine (mg/dl)	8.9 ± 2.3	9.6 ± 2.7	0.268 **	0.061	0.023
hs-CRP (mg/dl)	6.9 ± 6.9	9.4 ± 8	0.317 ***	0.047	0.015
SBP (mmHg)	134.2 ± 24.7	119 ± 26.8	0.002 ***	0.026	0.018
DBP (mmHg)	84.2 ± 12.3	77.4 ± 15	0.011 ***	0.055	0.054
MAP (mmHg)	100.9 ± 15.9	91.3 ± 18.6	0.004 ***	0.034	0.028

* Mean ± SD values were reported based on the main ADMA values. P value was obtained based on t-test using log 10 transformed values

** Based on t-test

*** Based on Mann–Whitney test

P_1: P in the crude model

P_2: P adjusted for age and sex based on General Linear Model

P_3: P adjusted for age, sex and diabetes based on General Linear Model

the normal weight group after adjustment for potential covariates. No differences in other lipid profiles, creatinine and insulin resistance were observed between the two study groups.

Discussion

The results of this study showed a significantly lower ADMA concentration in the obese compared to the normal weight patients on hemodialysis. This finding was associated with lower MIS, presenting better nutritional and inflammatory status, and lower blood pressure in the obese group. Age and BMI were the most important determinants of ADMA concentration in this study.

In contrast to the current findings, a study found a positive relationship between ADMA concentration and BMI, dry body weight, and fat mass in CKD patients [12]. It has been suggested that obesity-associated hypercholesterolemia and oxidative stress disrupt DDAH activity, leading to an increase in ADMA levels [12]. However, similar to our findings, another study showed an inverse relationship between BMI and serum albumin with ADMA levels in hemodialysis patients. It has been suggested that poor nutritional status and abnormal protein metabolism correlate with higher ADMA concentration [15]. The current results also showed lower MIS levels in the obese group than in the normal weight group, which is a valid indicator of nutritional and inflammatory status in CKD. In addition, in patients on peritoneal dialysis, those with PEW based on subjective global assessment and other scores, have been shown to have higher ADMA levels than the group with good nutritional status. Patients with PEW and higher ADMA levels also had lower mean BMI, body fat percentage, and lean body mass, which were not significantly different from the non-PEW group [18]. Additionally, ADMA has been suggested as a potential biomarker for cancer cachexia, as skeletal muscle wasting may be a source of circulating ADMA and it may also contribute to impaired muscle protein synthesis as well [19].

Uremic malnutrition is associated with a variety of disorders, including hemodialysis-related catabolism, hormonal and metabolic changes, and chronic inflammation [20]. Inflammatory cytokines such as interleukin-6 and tumor necrosis factor alpha suppress appetite and promote muscle wasting and hypoalbuminemia [21]. Loss of muscle and adipose tissue and inflammation ultimately lead to an increased risk of cardiovascular disease and death [22]. Thus, the malnutrition-inflammation-cachexia syndrome appears to be involved in the obesity paradox observed in ESRD and other chronic diseases [23]. The obesity paradox refers to lower morality in overweight and obese patients with ESRD and some other diseases. Obesity may reduce the risk of malnutrition and PEW [24]. Greater body mass provides protection against significant protein loss in the inflammatory response. Other potential mechanisms include the priority of short-term survival benefits of obesity over its long-term deleterious effects, better short-term hemodynamic stability, altered cytokine profiles, and more effective sequestration of uremic toxins in obese patients [25]. Based on models of normal renal function, a direct relationship between ADMA concentration and increasing body fat mass was expected. Previous data suggest that although obesity may be protective in ESRD, this effect is limited to those with normal or high muscle mass. In fact, patients with high BMI due to high body fat showed no survival benefit [26]. Thus, the obese patients in this

study, who also had lower MIS and signs of wasting, may have a higher proportion of muscle mass, which partly justifies the lack of higher ADMA levels in this group. It seems that the lower ADMA concentration, a well-recognized cardiovascular risk factor, in the obese patients in this study is consistent with the better outcomes that have been extensively proposed in this BMI group in other studies [27].

There are some reports on the effects of aspirin, statins, antihypertensive and hypoglycemic medications on ADMA levels; however, the exact effects of each drug are not yet known [28]. In general, NOS substrates and medications that decline ADMA concentration are expected to reduce blood pressure. The normal weight group in this study had higher ADMA concentrations despite higher intake of antihypertensive medications. The increasing or decreasing effects of different classes of antihypertensive medications, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [29–31], and even drugs within a subclass, such as captopril vs. enalapril [29, 32], on ADMA levels are controversial. Additionally, the obese patients had lower blood pressure. It is not clear that whether ADMA levels are directly affected by antihypertensive medications or are influenced by changes in blood pressure [7]. Thus, overall, these medications do not seem to be a major determinant of ADMA levels in this study. Future studies should clarify the exact effect of different drugs on ADMA concentration.

Patients with obesity had lower SBP, MAP, and slightly lower DBP with concomitant lower ADMA concentration compared to the normal weight group. The relationship between ADMA and blood pressure is well known because ADMA reduces the bioavailability of NO [33], which could result in impaired vasodilation, vascular stiffness, and organ perfusion, as well as impaired anti-thrombotic and anti-inflammatory effects [34]. Some studies have also reported a direct correlation between ADMA and CRP/hs-CRP concentrations in advanced renal disease [13, 35]. However, the effect of BMI or nutritional status was not considered. In contrast to these results, in the current study, the mean hs-CRP level was higher in the obese group compared with the normal weight group, which was in the opposite direction with lower MIS and ADMA levels in the obese patients. Another study showed that peritoneal dialysis patients with PEW and high ADMA levels also had increased hs-CRP concentrations compared to the non-PEW group. However, no direct correlation between ADMA and hs-CRP was observed in these patients [18].

The association of ADMA with dyslipidemia and other metabolic risk factors is controversial. Some studies have failed to show an association between ADMA levels and cardiometabolic risk factors including LDL [36],

while others suggest a direct association with TC and LDL levels [37]. It has also been shown that high levels of ADMA are associated with elevated TG rather than LDL [38]. It has been suggested that native or oxidized forms of LDL may upregulate the expression and activity of protein arginine methyltransferases, which increase ADMA levels [39]. Despite studies reporting an association between ADMA and LDL levels, statin therapy had no effect on circulating ADMA [40]. A significant strong and direct relationship between IR and ADMA levels has been described in normal renal function [39]. It was also found that in obese patients, ADMA levels were higher in those with IR compared to non-IR group [11]. Some mechanisms relate to the lack of access to NO in conditions associated with IR [41]. Thus, part of the unexpected results in ADMA levels in the obese group may be due to the lack of significant differences in IR compared to the normal weight patients.

Changes in the activity of DDAH under various conditions can lead to changes in ADMA levels. ADMA is catabolized by DDAH to dimethylamine and citrulline, and the DDAH activity is controlled by complex regulatory mechanisms [42]. It has been shown that mice overexpressing DDAH gained more weight after a high fat diet compared to eNOS-deficient mice. However, the increased NO bioavailability associated with higher DDAH levels led to the downregulation of markers of differentiated adipocytes. Additionally, some genes involved in protection against oxidative stress were upregulated in white adipose tissue of mice with DDAH overexpression [43], which may reduce the nitrosative stress caused by elevated levels of the free radical NO [44]. High DDHA levels may be responsible, at least in part, for the lower ADMA levels in the obese group.

The liver removes significant amounts of ADMA from the systemic circulation [45]. Malnutrition could affect various aspects of liver metabolic function through peroxisomal and mitochondrial dysfunction [46]. Thus, liver function, which was not assessed in the current study, may also play a role in determining ADMA levels in the study groups. Additionally, it has been reported that the synthesis and concentration of uremic toxins, such as ADMA, may be lower in larger patients because the main visceral organ that produce them (intestine and liver) have a lower mass relative to body weight and the distribution volume is greater in high BMI. The higher ratio of fat and muscle mass to visceral mass would be associated with lower levels of uremic toxins and the better outcomes as they are taken up and metabolized by these tissues [47, 48].

This study has some limitations, including the relatively small sample size and the lack of data on DDAH and NO levels. In addition, due to the cross-sectional design of the study, the proposed mechanisms to justify the results

Alipoor *et al. BMC Nephrology*   (2024) 25:294

Page 6 of 7

should be considered as hypotheses. Having control groups of normal weight and obese individuals with normal renal function would help to better understand the distinctive changes of ADMA in health and ESRD with respect to body fat mass. Additionally, performing bioimpedance measurements could better reflect the precise relationship of body composition and dietary differences with ADMA levels and other cardiometabolic markers. This study included both diabetic and nondiabetic patients that may affect the results.

Conclusion

The results of the current study showed that serum concentrations of ADMA were significantly lower in obese compared to normal weight hemodialysis patients, which was associated with lower MIS, indicating a better nutritional-inflammatory status, and lower blood pressure. There were no significant relationships between serum ADMA levels and traditional cardiometabolic risk factors, except for an inverse relationship with dry body weight and BMI. Lower ADMA levels in the obese patients, as a known cardiovascular risk factor, are consistent with the previously proposed obesity paradox in obese patients on dialysis.

Abbreviations

ADMA	Asymmetric dimethylarginine
BMI	Body mass index
eNOS	Endothelial NO synthase
ESRD	End-stage renal disease
FBG	Fasting blood glucose
CKD	Chronic kidney disease
CI	Confidence interval
DBP	Diastolic blood pressure
DDAH	Dimethylarginine dimethylaminohydrolase
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment for insulin resistance
Hs-CRP	High sensitivity C-reactive protein
LDL	Low-density lipoprotein
MAP	Mean arterial pressure
MIS	Malnutrition inflammation score
NO	Nitric oxide
PEW	Protein energy wasting
SBP	Systolic blood pressure
SGA	Subjective global assessment
SD	Standard deviation
TG	Triglycerides
TC	Total cholesterol
TIBC	Total iron-binding capacity

Author contributions
Conceptualization & design: EA, MY, MJHA; Data gathering: EA, SS, SD; Data analysis: EA, SS, MY; Writing – drafting: EA, SS, SD; Writing – review & editing: MY, MJHA; Supervision: MJHA. All authors reviewed and approved the final manuscript.

Declarations

Ethics approval and consent to participate
The ethics committee of the Tehran University of Medical Sciences approved this study with ethics number IR.TUMS.VCR.REC.1396.4764. All participants have completed and signed an informed written consent. The study has been performed in accordance with the ethical standards of 1964 Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

References
1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32:S112–9.
2. Bouras G, Deftereos S, Tousoulis D, Giannopoulos G, Chatzis G, Tsounis D, et al. Asymmetric dimethylarginine (ADMA): a promising biomarker for cardiovascular disease? Curr Top Med Chem. 2013;13:180–200.
3. Yilmaz MI, Saglam M, Caglar K, Cakir E, Sonmez A, Ozgurtas T, et al. The determinants of endothelial dysfunction in CKD: oxidative stress and asymmetric dimethylarginine. Am J Kidney Dis. 2006;47:42–50.
4. Leone A, Moncada S, Vallance P, Calver A, Collier J. Accumulation of an endogenous inhibitor of nitric oxide synthesis in chronic renal failure. Lancet. 1992;339:572–5.
5. Zoccali C, Bode-Böger SM, Mallamaci F, Benedetto FA, Tripepi G, Malatino LS, et al. Plasma concentration of asymmetrical dimethylarginine and mortality in patients with end-stage renal disease: a prospective study. Lancet. 2001;358:2113–7.
6. Zoccali C, Kielstein JT. Asymmetric dimethylarginine: a new player in the pathogenesis of renal disease? Curr Opin Nephrol Hypertens. 2006;15:314–20.
7. Kielstein JT, Fliser D. The past, presence and future of ADMA in nephrology. Néphrologie thérapeutique. 2007;3:47–54.
8. Spoto B, Parlongo RM, Parlongo G, Sgro E, Zoccali C. The enzymatic machinery for ADMA synthesis and degradation is fully expressed in human adipocytes. J Nephrol. 2007;20:554–9.
9. Alipoor E, Esmaillzadeh A, Mahdavi-Mazdeh M, Yaseri M, Zahed NS, Hosseinzadeh-Attar MJ. The relationship of serum adipokines with malnutrition inflammation score in haemodialysis. Eur J Clin Invest. 2017;47:545–54.
10. Hosseinzadeh-Attar MJ, Mahdavi-Mazdeh M, Yaseri M, Zahed NS, Alipoor E. Comparative assessment of serum adipokines zinc-α2-glycoprotein and adipose triglyceride lipase, and cardiovascular risk factors between normal weight and obese patients with hemodialysis. Arch Med Res. 2017;48:459–66.
11. McLaughlin T, Stuhlinger M, Lamendola C, Abbasi F, Bialek J, Reaven GM, et al. Plasma asymmetric dimethylarginine concentrations are elevated in obese insulin-resistant women and fall with weight loss. J Clin Endocrinol Metab. 2006;91:1896–900. https://doi.org/10.1210/jc.2005-1441.
12. Teplan V, Schück O, Racek J, Lecian D, Haluzik M, Kudla M, et al. Asymmetric dimethylarginine in obesity after renal transplantation. J Ren Nutr. 2008;18:513–20.
13. Cifci A, Inal S, KAYA C. Asymmetric dimethyl arginine levels in chronic hemodialysis patients. Turk J Med Sci. 2014;44:606–10.
14. Małgorzewicz S, Lichodziejewska-Niemierko M, Aleksandrowicz-Wrona E, Świetlik D, Rutkowski B, Łysiak-Szydłowska W. Adipokines, endothelial dysfunction and nutritional status in peritoneal dialysis patients. Scand J Urol Nephrol. 2010;44:445–51.

Alipoor *et al. BMC Nephrology*   (2024) 25:294

Page 7 of 7

15. Cupisti A, Saba A, D'Alessandro C, Meola M, Panicucci E, Panichi V, et al. Dimethylarginine levels and nutritional status in hemodialysis patients. J Nephrol. 2009;22:623–9.

16. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001;38:1251–63.

17. Daugirdas JT. Simplified equations for monitoring Kt/V, PCRn, eKt/V, and ePCRn. Adv Renal Replace Ther. 1995;2:295–304.

18. Małgorzewicz S, Heleniak Z, Lichodziejewska-Niemierko M, Rutkowski B, Aleksandrowicz-Wrona E, Dębska-Ślizień A. Protein-energy wasting and asymmetric dimethylarginine in peritoneal dialysis patients. Acta Biochim Pol. 2018;65:581–4.

19. Kunz HE, Dorschner JM, Berent TE, Meyer T, Wang X, Jatoi A, et al. Methylarginine metabolites are associated with attenuated muscle protein synthesis in cancer-associated muscle wasting. J Biol Chem. 2020;295:17441–59. https://doi.org/10.1074/jbc.RA120.014884.

20. Ikizler TA. Poor nutritional status and inflammation: protein and energy: recommended intake and nutrient supplementation in chronic dialysis patients. Seminars in dialysis: Wiley Online Library; 2004. pp. 471–8.

21. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JDJTA. (2004) Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. 80:299–307.

22. Qureshi AR, Alvestrand A, Divino-Filho JC, Gutierrez A, Heimbürger O, Lindholm B et al. (2002) Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. 13:S28–36.

23. Kovesdy CP, Anderson JE, Kalantar-Zadeh, KJJotASoN. (2007) Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition-inflammation-cachexia syndrome. 18:304–11.

24. Alipoor E, Hosseinzadeh-Attar MJ, Mahdavi-Mazdeh M, Yaseri M, Zahed NS. Comparison of malnutrition inflammation score, anthropometry and biochemical parameters in assessing the difference in protein-energy wasting between normal weight and obese patients undergoing haemodialysis. Nutrition & Dietetics; 2017.

25. Park J, Ahmadi S-F, Streja E, Molnar MZ, Flegal KM, Gillen D, et al. Obesity paradox in end-stage kidney disease patients. Prog Cardiovasc Dis. 2014;56:415–25.

26. Beddhu S, Pappas LM, Ramkumar N, Samore M. Effects of body size and body composition on survival in hemodialysis patients. J Am Soc Nephrol. 2003;14:2366–72.

27. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, Kilpatrick RD, Horwich TB. Survival advantages of obesity in dialysis patients. Am J Clin Nutr. 2005;81:543–54. 81/3/543 [pii].

28. Sibal L, Agarwal C, D Home S, Boger PH R. The role of asymmetric dimethylarginine (ADMA) in endothelial dysfunction and cardiovascular disease. Curr Cardiol Rev. 2010;6:82–90.

29. Jiang J-L, Zhu H-Q, Chen Z, Xu H-Y, Li Y-J. Angiotensin-converting enzyme inhibitors prevent LDL-induced endothelial dysfunction by reduction of asymmetric dimethylarginine level. Int J Cardiol. 2005;101:153–5.

30. Gamboa JL, Pretorius M, Sprinkel KC, Brown NJ, Ikizler TA. Angiotensin converting enzyme inhibition increases ADMA concentration in patients on maintenance hemodialysis–a randomized cross-over study. BMC Nephrol. 2015;16:1–9.

31. Delles C, Schneider MP, John S, Gekle M, Schmieder RE. Angiotensin converting enzyme inhibition and angiotensin II AT1-Receptor blockade reduce the levels of Asymmetrical NG, N G-Dimethylarginine in Human essential hypertension. Am J Hypertens. 2002;15:590–3.

32. Yazıcı D, Gogas Yavuz D, Ünsalan S, Toprak A, Yüksel M, Deyneli O, et al. Temporal effects of low-dose ACE inhibition on endothelial function in type 1 diabetic patients. J Endocrinol Investig. 2007;30:726–33.

33. Leiper J, Nandi M. The therapeutic potential of targeting endogenous inhibitors of nitric oxide synthesis. Nat Rev Drug Discovery. 2011;10:277–91.

34. Brinkmann SJ, de Boer MC, Buijs N, van Leeuwen PA. Asymmetric dimethylarginine and critical illness. Curr Opin Clin Nutr Metabolic Care. 2014;17:90–7.

35. Ashokachakkaravarthy K, Rajappa M, Parameswaran S, Satheesh S, Priyadarshini G, PS MR, et al. Asymmetric dimethylarginine and angiopoietin-like protein-2 are independent predictors of cardiovascular risk in pre-dialysis non-diabetic chronic kidney disease patients. International urology and nephrology; 2020.

36. Fard A, Tuck CH, Donis JA, Sciacca R, Di Tullio MR, Wu HD et al. (2000) Acute elevations of plasma asymmetric dimethylarginine and impaired endothelial function in response to a high-fat meal in patients with type 2 diabetes. 20:2039–44.

37. Eid HM, Eritsland J, Larsen J, Arnesen H, Seljeflot IJA. Increased levels of asymmetric dimethylarginine in populations at risk for atherosclerotic disease. Eff Pravastatin. 2003;166:279–84.

38. Chan N, Chan J. Asymmetric dimethylarginine (ADMA): a potential link between endothelial dysfunction and cardiovascular diseases in insulin resistance syndrome? Diabetologia. 2002;45:1609–16.

39. Stuhlinger MC, Abbasi F, Chu JW, Lamendola C, McLaughlin TL, Cooke JP, et al. Relationship between insulin resistance and an endogenous nitric oxide synthase inhibitor. JAMA. 2002;287:1420–6.

40. Päivä H, Laakso J, Lehtimäki T, Isomustajärvi M, Ruokonen I, Laaksonen R. Effect of high-dose statin treatment on plasma concentrations of endogenous nitric oxide synthase inhibitors. J Cardiovasc Pharmacol. 2003;41:219–22.

41. Pope AJ, Karuppiah K, Cardounel AJJP. (2009) Role of the PRMT–DDAH–ADMA axis in the regulation of endothelial nitric oxide production. 60:461–5.

42. Ogawa T, Kimoto M, Sasaoka KJB, communications br. (1987) Occurrence of a new enzyme catalyzing the direct conversion of NG, NG-dimethyl-L-arginine to L-citrulline in rats. 148:671–7.

43. Razny U, Kiec-Wilk B, Wator L, Polus A, Dyduch G, Solnica B, et al. Increased nitric oxide availability attenuates high fat diet metabolic alterations and gene expression associated with insulin resistance. Cardiovasc Diabetol. 2011;10:1–14.

44. Beltrán B, Orsi A, Clementi E, Moncada S. Oxidative stress and S-nitrosylation of proteins in cells. Br J Pharmacol. 2000;129:953–60.

45. Nijveldt R, Teerlink T, Siroen M, Van Lambalgen A, Rauwerda J, Van Leeuwen PJCN. (2003) The liver is an important organ in the metabolism of asymmetrical dimethylarginine (ADMA). 22:17–22.

46. van Zutphen T, Ciapaite J, Bloks VW, Ackereley C, Gerding A, Jurdzinski A, et al. Malnutrition-associated liver steatosis and ATP depletion is caused by peroxisomal and mitochondrial dysfunction. J Hepatol. 2016;65:1198–208.

47. Kotanko P, Thijssen S, Kitzler T, Wystrychowski G, Sarkar SR, Zhu F et al. (2007) Size matters: body composition and outcomes in maintenance hemodialysis patients. 25:27–30.

48. Kotanko P, Levin NJTI. (2007) The impact of visceral mass on survival in chronic hemodialysis patients. 30:993–9.

Publisher's note