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Asymmetric Dimethylarginine in Patients with Ascending Aortic Aneurysms

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Abstract

Background: **Ascending thoracic aortic aneurysm (aTAA) is a heterogeneous group of disorders that involve impaired endothelial function. The nitric oxide (NO) synthase inhibitor asymmetric dimethylarginine (ADMA) serves as an endothelial dysfunction marker. Thus, we investigated ADMA levels in patients with aTAA.**

Methods: **Eighty-six patients with aTAA and 18 healthy individuals were enrolled. All patients underwent echocardiography. Plasma ADMA levels were measured using high-performance liquid chromatography.**

Results: **ADMA levels were higher in aTAA patients than in control patients (p = 0.034). According to the multivariable regression model, higher ADMA levels were associated with ascending aortic diameter (p = 0.017), smoking (p = 0.016), and log-transformed estimated glomerular filtration rate (eGFR, p = 0.005).**

Conclusion: **This pilot study demonstrates an association of ADMA with ascending aortic dilatation; however, further studies are needed to investigate whether increased ADMA levels underlie aTAA development.**

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Key Words:

Asymmetric dimethylarginine • Thoracic aortic aneurysm • Endothelial dysfunction

Introduction

Ascending thoracic aortic aneurysm (aTAA) is a severe pathology associated with aortic dissection and rupture [1]. The prevalence of aTAA in Western Europe is 0.8% [2]. According to previous autopsy data, aTAA prevalence in Russia is 0.16-1.6% [3]. Interestingly, aTAA is often not apparent before the onset of complications such as dissection of the ascending aorta, which is associated with a remarkably high risk of mortality. The 2-week mortality rate of patients with acute Type A dissection is 25-50% [4]. Replacement of the ascending aorta is associated with variable outcomes, depending on the urgency and time of surgery [5]. The predicted mortality rate for elective cases (3%) is much lower than that for non-elective cases (15%) [6]. While aTAA diameter is a conventional criterion for surgery, additional markers and parameters are needed for the diagnosis and monitoring of aTAA to prevent complications. Many researchers in the field have sought to identify good diagnostic and predictive biomarkers of aTAA [7, 8]; however, suitable markers are lacking, as the mechanisms underlying aTAA development are not entirely clear.

Asymmetric dimethylarginine (ADMA) is a nitric oxide (NO) synthase inhibitor and a well-known biomarker of endothelial dysfunction that is associated

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with different cardiovascular disorders [9, 10]. Although information on the role of ADMA in the pathology of cardiovascular disorders is continuously expanding, data regarding ADMA metabolism in patients with aTAA is limited. Thus, the aim of this study was to evaluate the relationship between ADMA levels and aTAA.

Materials and Methods

Ethics

The study protocol was approved by the local ethics committee of Federal Almazov North-West Medical Research Centre (15.05.2012, No. 0094). This study was performed according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Study Subjects

From May 2012 to December 2014, 104 patients were recruited from the Federal Almazov North-West Medical Research Centre inpatient department, and those who provided informed consent were included in the current study. Patients with aTAA caused by thoracic trauma or previous aortic surgery and those with heritable connective tissue disorders (Marfan syndrome and others) and inflammatory diseases of the thoracic aorta were excluded. Other exclusion criteria were aortic dissection, abdominal aortic aneurysms, malignancy, hepatic or renal failure, and class IV heart failure. In total, we included 86 patients with ascending aortic aneurysms: 62 patients with tricuspid aortic valve (TAV)- and 24 patients with bicuspid aortic valve (BAV)-associated aneurysms. The control group consisted of 18 age-matched individuals with normal TAVs and similar risk factors for cardiovascular diseases (CVDs). The control group patients were selected from patients admitted to the outpatient unit with one or more CVD risk factors . The groups were comparable in terms of baseline characteristics but differed with regard to ascending aortic diameter, according to the inclusion criteria.

Imaging

All patients underwent two-dimensional and Doppler echocardiography using the Vivid 7.0 system (GE Healthcare, Chicago, IL USA) according to current ECHO guidelines. Diagnosis of BAV was based on the presence of only two commissures, delimiting only two aortic valve cusps, as observed on short-axis imaging of the aortic valve. For quantification of the ascending aortic diameter, contrast-enhanced multisliced computed tomography (CT; Somatom Definition 128, Siemens, Munich, Germany) was performed for all patients with aTAA. The inclusion criteria for the aTAA group were ascending aortic diameter (maximal dimension) of ≥4.5 cm for patients with TAV and ≥4.0 cm for patients with BAV.

Blood Samples

Blood samples were collected in tubes containing 3.8% sodium citrate as the anticoagulant and centrifuged at 3,000 rpm for 15 min at 4°C immediately after collection. Plasma samples were frozen and stored at -80°C until analysis. Plasma ADMA levels were measured using high-performance liquid chromatography after solid-phase extraction using the cation-exchange cartridges Oasis MCX 1 cc/30 mg (Waters Corp., Milford, MA, USA), followed by derivatization with orthophthalaldehyde [11]. The concentration of total serum homocysteine (tHcy) was determined using the chemiluminescent microparticle method (Abbott Clinical Chemistry, Abbott Park, IL, USA).

Statistics

All statistical analyses were performed using Statistica for Windows 10.0 (StatSoft Inc., Tulsa, OK, USA). Normally distributed data are presented as average ± standard deviation (SD), while non-normally distributed data are presented as median (Q25, Q75). All p values < 0.05 were considered statistically significant. Variables with skewed distribution (estimated glomerular filtration rate [eGFR] and tHcy) were analyzed after logarithmic (log) transformation. The differences between normally distributed continuous values were assessed using an unpaired two-tailed *t*-test or one-way analysis of variance (ANOVA) with post-hoc Bonferroni test. Description of the qualitative variables (number and percentage) was carried out using the χ^2 test. Box plots were used to display a statistical summary of the median, quartiles, and extreme values. Spearman's rank correlation was used to determine correlations with continuous variables. Univariate and multivariate linear regression were performed to investigate the association of ADMA with different variables.

Results

Eighty-six patients had aTAA, and 18 had CVD risk factors but did not present with ascending aortic dilatation. The clinical parameters of the groups are presented in Table 1. ADMA plasma levels were higher in the aneurysm group than in the control ($p = 0.034$, Figure 1). In addition, a positive correlation between ADMA plasma levels and ascending aortic diameter was found (corrected $R^2 = 0.047$, $\beta = 0.239$, $p = 0.018$; Figure 2). The ADMA plasma levels, however, did not differ between patients with TAV (0.49 ± 0.1 µmol/L) and those with BAV (0.5 ± 0.12 µmol/L, $p = 0.6$).

ADMA levels were also correlated with log-transformed tHcy level ($rs=0.23$, $p = 0.025$) and eGFR ($\beta=-0.29$, $p = 0.004$; Figure 3); however, the Hcy levels did not differ between patients with aTAA and controls ($p = 0.79$). Smoking was strongly associated with higher ADMA levels (0.52 ± 0.11 µmol/L in smokers with aTAA vs. 0.46 ± 0.11 µmol/L in nonsmokers with aTAA; $p = 0.002$). According to linear regression analysis adjusted for smoking, smokers exhibited a stronger cor-

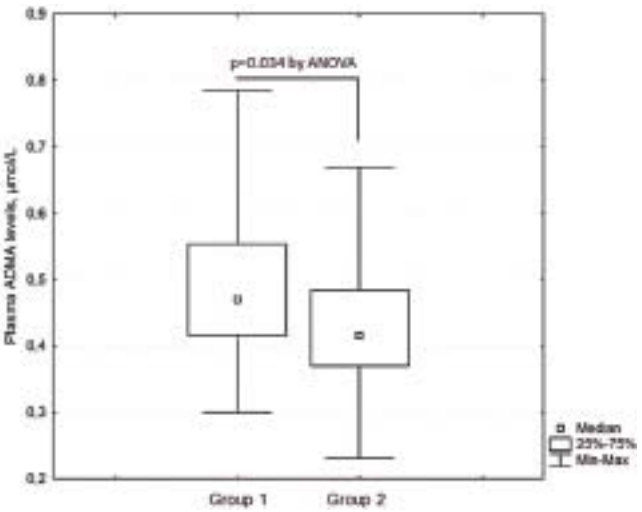

Figure 1. Comparison of median plasma asymmetric dimethylarginine levels between ascending thoracic aortic aneurysm patients (Group 1) and controls (Group 2) using analysis of variance (p = 0.034).

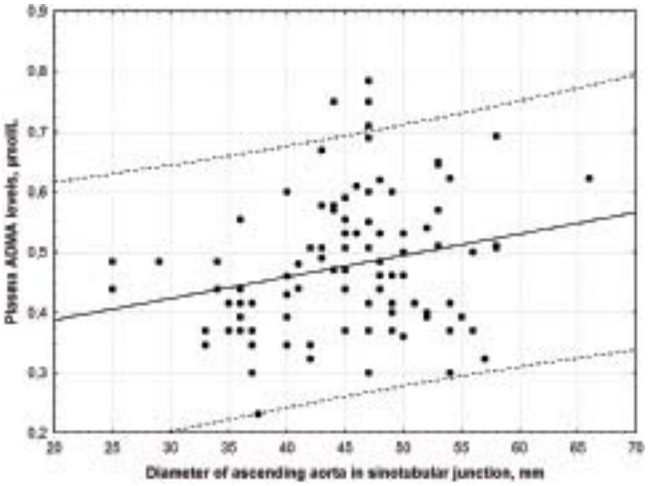

Figure 2. Linear regression of plasma asymmetric dimethylarginine levels (µmol/L) and the diameter of ascending aorta in sinotubular junction (corrected $R^2 = 0.047$; $\beta = 0.239$; $p = 0.018$). mm = millimeter.

Table 1. Characteristics of enrolled subjects.

	aTAA *n* = 86	Control *n* = 18	p
Demographic			
Age (y)	57.6 ± 8.6	55.1 ± 11.3	0.29
Obesity, n (%)	39 (45%)	10 (55%)	0.44
BMI (kg/m^2)	28.7 ± 4.7	30.6 ± 6.0	0.14
Smokers, n (%)	42 (48%)	8 (44%)	0.76
Smoking history (y)	25.8 ±11.9	18.6 ± 12.9	0.11
Cigarettes/day, n	19.17 ±10.91	15.5 ± 7.98	0.31
Hypertension, n (%)	73 (84%)	14 (78%)	0.54
Office systolic BP (mm Hg)	129 ± 14	134 ± 27	0.26
Office diastolic BP (mm Hg)	80 ± 11	85 ± 13	0.09
Coronary artery disease, n (%)	47 (55%)	9 (50%)	0.7
Lower extremity arterial occlusive disease, n (%)	4 (3%)	1 (6%)	0.35
Cerebrovascular disease, n (%)	11 (13%)	2 (11%)	0.41
Type 2 diabetes mellitus, n (%)	8 (9%)	2 (11%)	0.79
Echocardiography			
Aortic diameter in the sinuses of Valsalva (mm)	43.3 ± 5.6*	34.7 ± 3.9	<0.001
Diameter of ascending aorta in sinotubular junction (mm)	47.1 ± 6.2*	34.0 ± 3.5	<0.001
Maximal aortic diameter (mm)	49.1 ± 7.1*	35.3 ± 3.9	<0.001
Peak aortic gradient (mm Hg)	14 ± 17	8 ± 3	0.14

(*table continues*)

Table 1. (*Continued*)

	aTAA *n* = 86	Control *n* = 18	p
Contrast-enhanced multi-sliced computed tomography			
Aortic sinuses of Valsalva (mm)	44.9 ± 7.3		
Mid ascending aorta (mm)	49.5 ± 8.0		
Mid descending aorta (mm)	29.5 ± 6.7		
Abdominal aorta at the celiac axis origin (mm)	22.2 ± 7.3		
Laboratory data			
Total cholesterol (mg/dL)	90.0 ± 21.6	97.2 ± 28.8	0.23
LDL cholesterol (mg/dL)	54.8 ± 18.0	59.4 ± 25.2	0.36
eGFR (mL/min/1.73 m^2)	95.06 ± 27.9	102.1 ± 34.8	0.35
ADMA (µmol/L)	0.49 ± 0.11*	0.42 ± 0.1	0.034
C-reactive protein (mmol/L)	7.92 (0.78-9.57)*	2.64 (1.3-3.1)	0.22
tHcy (µmol/L)	13.8 ± 3.5	13.5 ± 7.1	0.79
Albumin (g/dL)	3.5 ± 0.4	3.6 ± 0.6	0.3
Medication			
Antihypertensive medications, n (%)	68 (79%)	14 (78%)	0.5
Angiotensin-converting enzyme inhibitors, n (%)	30 (35%)	5 (33%)	0.4
Angiotensin II receptor blockers, n (%)	11 (13%)	3 (17%)	0.3
Calcium channel blockers, n (%)	10 (12%)	4 (22%)	0.1
Beta-blockers, n (%)	46 (53%)	9 (50%)	0.4
Diuretics, n (%)	28 (32%)	6 (33%)	0.5
Statins, n (%)	24 (28%)	6 (33%)	0.7

ADMA = asymmetric dimethylarginine; aTAA= ascending thoracic aortic aneurysm; BMI= body mass index; BP= blood pressure; eGFR = estimated glomerular filtration rate (by CKD-EPI formula); LDL = low-density lipoprotein; tHcy = total homocysteine.
*Data presented as mean ± standard deviation and median (Q25:Q75).

relation between ADMA levels and aortic diameter (r = 0.31, p = 0.03) than nonsmokers (r = 0.23, p = 0.13; Figure 4). Furthermore, multiple regression analysis revealed that ascending aortic diameter, smoking, and eGFR were associated with ADMA levels (Table 2).

Discussion

It is known that aTAA is a multi-etiological disease. Strong evidence supports endothelial dysfunction in patients with aTAA, particularly in cases with BAV [12, 13]. NO plays a pivotal role in the regulation of vessel wall homeostasis by influencing endothelial cell function [14, 15], and the NO pathway may also be involved in BAV development [16]. Patients with BAV are believed to have low expression levels of endothelial NO synthase [17]. ADMA is a NO synthase inhibitor and a marker of endothelial dysfunction. Extensive clinical evidence suggests that CVD are associated with increased ADMA levels [17, 18]. Toker et al. [19] studied the development of atherosclerosis and dilatation of the abdominal aorta induced by acrylamide exposure in rats and found an association between these processes and increased ADMA levels. Based on this information, we speculated that high ADMA levels play a role in TAA formation. Yet, few studies on this topic have been performed in patients with aTAA [20, 21]. Most investigators compared ADMA levels in

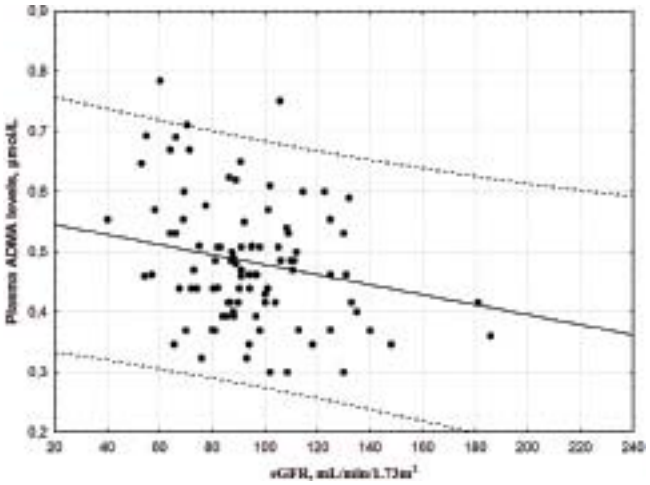

Figure 3. Correlation between log-transformed estimated glomerular filtration rate and plasma asymmetric dimethylarginine levels (corrected $R^2 = 0.073$; $\beta = -0.29$; $p = 0.004$).

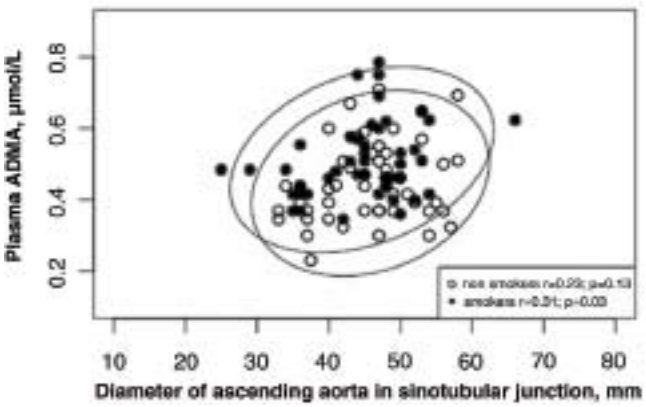

Figure 4. Adjusted linear regression of asymmetric dimethylarginine levels (µmol/L) and ascending aortic diameter according to smoking status ($r = 0.23$, $p = 0.13$ in nonsmokers; $r = 0.31$, $p = 0.03$ in smokers).

Table 2. Multivariate regression model of plasma ADMA level predictors.

Model	Unstandardized Coefficients		Standardized Coefficients	t	p
	B	SE			
Constant	0.685	0.282		2.425	0.018*
Age	0.0013	0.0016	0.096	0.833	0.407
Sex	-0.040047	0.024940	-0.169	-1.606	0.112
Smoking	0.055	0.022	0.258	2.473	0.016*
Body mass index	0.0008	0.0025	0.036	0.336	0.738
Diameter of ascending aorta	0.0044	0.0018	0.284	2.430	0.017*
Log eGFR	-0.120	0.042	-0.323	-2.865	0.005*
Log total homocysteine	-0.0004	0.0463	-0.001	-0.009	0.993
Aortic valve morphology	0.006	0.019	0.041	0.334	0.740

ADMA = asymmetric dimethylarginine; eGFR = estimated glomerular filtration rate (by CKD-EPI formula); Log = logarithm;. Regression summary: $r = 0.510$; adjusted $R^2 = 0.186$; $F(8,79) = 3.4791$, $p < 0.017$. *indicates significant $p < 0.05$.

patients with aTAA with healthy individuals without CVD risk factors. Thus, these studies did not assess the influence of commonly known risk factors on ADMA levels in patients with aTAA. Therefore, we compared ADMA plasma levels in patients with aTAA to those in individuals with common CVD risk factors.

Our data revealed significant differences in ADMA levels between patients with aTAA and control subjects with similar CVD risk factors. The results of this study are consistent with previous results. Drapisz et al. [21] noted that ADMA levels were associated with size of the aortic annulus, peak aortic velocity, aortic distensibility, aortic stiffness index, and aortic strain in patients with non-stenotic BAV; however, in contrast to our study, the study by Drapisz and colleagues included younger patients (range 24-33 years) and only patients with BAV. Intriguingly, in our study, we did not find any differences in ADMA levels between TAV and BAV patients, but our results disclosed a positive correlation between ADMA plasma levels and in-

creased ascending aortic diameter. Another previous study of only patients with BAV demonstrated that inflammation and endothelial dysfunction played a more important role in BAV with aortic stenosis than in aortopathy [20]. That study also reported an association between ascending aortic diameter and ADMA levels, albeit with borderline significance. Differences between the results of the previous studies and those of the present study may be partly explained by the younger age and the inclusion of very few smokers (2%) in the previous study as compared to the number of smokers (48%) included in the present study.

We also found a significant association between smoking and ADMA plasma levels, consistent with previous data [22, 23]. Regular cigarette smoking increases ADMA levels, as previously reported by Campesi et al. [22] and confirmed in our study. In the case of patients with common CVD risk factors, this correlation is stronger as a result of the initially higher ADMA levels caused by aTAA. In the present study, we found significant differences in the ADMA levels between nonsmoker aTAA patients and nonsmoker controls and comparable ADMA levels between smoker aTAA patients and smoker controls. No randomized prospective trials have investigated the effect of smoking cessation on TAA [24]; however, among patients with aTAA who smoke, the rate of aneurysm expansion is higher than that in nonsmokers [25].

Surprisingly, the multivariable model described a strong positive correlation between ADMA levels and ascending aortic diameter. Our study data correspond to those of a previous study by Ali et al. [20]. Nevertheless, our findings directly lead to the question of whether increased ADMA levels cause dilatation of the ascending aorta or merely reflect other pathologic processes in the vascular wall.

While our results are interesting, some limitations of this study should be acknowledged. This study did not include long-term prospective observation with repeated examinations and therefore, did not document a predictive value of ADMA levels as a biomarker of aTAA progression.

Conclusion

In the present study, a strong association between ascending aortic diameter and plasma ADMA levels was observed. Interestingly, the levels of ADMA did not differ between BAV and TAV patients, and the main risk factors that influenced the ADMA levels were smoking and eGFR.

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Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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