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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

# Increased plasma asymmetric dimethylarginine level is associated with ascending aorta dilatation: a case-control study

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## Abstract

**Background:** Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase.

**Aim:** We aimed to determine plasma ADMA levels in patients with ascending aorta dilatation in comparison to those without aorta dilatation, and to evaluate the diagnostic, predictive, and prognostic value of serum ADMA level for aorta dilatation.

**Methods:** This was a cross-sectional case-control study. A total of 104 consecutive patients (female/male, 35/69; mean age, 62.75 ± 13.11 years) diagnosed with ascending aorta dilatation (≥ 4.5 cm) on echocardiography (case group), and 52 age- and gender-matched patients (female/male, 17/35; mean age, 63.44 ± 7.56 years) with normal aorta dimensions (≤ 3.8 cm) (control group) were included. Routine biochemical and haematological analysis in addition to measurement of serum ADMA level were performed.

**Results:** The mean diameter of ascending aorta measured on echocardiography was 4.95 ± 0.57 cm and 3.34 ± 0.36 cm in patients with aorta dilatation and those without aorta dilatation, respectively ($p < 0.001$). Serum ADMA level was significantly higher in patients with aorta dilatation than in the control group (1.70 ± 1.12 μmol/L vs. 0.79 ± 0.76 μmol/L, respectively, $p < 0.001$). There was significant positive correlation between ADMA level and aortic diameter in Spearman correlation analysis ($r = 0.317$, $p < 0.001$). In linear regression analysis, ADMA was found to be a significant independent predictor of aorta diameter (Beta = 0.26, $p < 0.001$). Receiver-operator characteristic curve analysis also revealed that serum ADMA cut-off level over 0.29 μmol/L predicts aorta dilatation (≥ 4.5 cm) with 94% sensitivity and 92% specificity and with high accuracy (area under curve: 0.786; 95% confidence interval: 0.709–0.863, $p < 0.001$).

**Conclusions:** Serum ADMA level is diagnostic for ascending aorta dilatation with high sensitivity and specificity, and should be considered for use in clinical diagnosis of aorta dilatation.

**Key words:** aorta dilatation, asymmetric dimethylarginine, biomarker, diagnosis

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## INTRODUCTION

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide (NO) synthase. NO, which is released by the endothelium, is the most potent endogenous vasodilator. ADMA leads to impaired endothelial function by antagonising NO synthase and reducing NO generation [1–3]. It has been reported that increased serum and tissue ADMA level is related to cardiovascular diseases (CVD), including coronary artery disease, heart failure, and pulmonary hypertension [4, 5]. Serum ADMA level also increases in several other clinical conditions such as hyperhomocysteinaemia, renal failure, insulin resistance syndrome, diabetes mellitus, liver diseases, and preeclampsia. On the basis of this evidence, studies have recently focused on its role in clinical diagnosis and outcome of various CVDs, predicting response to treatment, and even treatment of endothelial dysfunction-related diseases [4, 6–9].

However, the role of ADMA in aorta dilatation has not been investigated extensively so far. Patients with aorta dila-

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tation are at risk of spontaneous aorta rupture or dissection, both of which are associated with high mortality rates [10]. Endothelial dysfunction is one of the underlying mechanisms for ascending aortic dilatation [11]. Thus, the determination of endothelial dysfunction by a non-invasive diagnostic method, i.e. biochemical biomarker, in patients with high risk of aorta dilatation will help to take early aggressive preventive measures for this highly fatal condition [12]. Based on its role in endothelial dysfunction and its relationship with CVD, studies on the circulating ADMA level in aorta dilatation should be increased.

In this study, we aimed to determine plasma ADMA level in patients with ascending aorta dilatation in comparison to those without aorta dilatation and to evaluate the diagnostic, predictive, and prognostic value of serum ADMA level for aorta dilatation.

## METHODS

### *Study design and population*

This was a cross-sectional case-control study into which 104 consecutive patients (female/male, 35/69; mean age, 62.75 ± 13.11 years) that were admitted to cardiology clinics and diagnosed with ascending aorta dilatation on echocardiography (case group), and 52 age- and gender-matched patients (female/male, 17/35; mean age, 63.44 ± 7.56 years) with normal aorta dimensions on echocardiography (control group) were included between November 2011 and March 2012. Exclusion criteria were congestive heart failure, renal failure, and chronic liver disease.

The study was approved by the local ethics committee (date 06.10.2011, no. 58) and was conducted in accordance with the latest version of the Declaration of Helsinki. All patients gave written informed consent before any study-related procedure.

### *Study data and outcomes*

The following data were recorded for each study patient: demographics, medical history including comorbidities, current drug treatment, and smoking status. Routine biochemical and haemogram analysis in addition to measurement of ADMA level were performed on blood samples collected into EDTA tubes after 12 h of fasting. Laboratory analysis included haemoglobin, haematocrit, lymphocyte count, white blood cell count, C-reactive protein, creatinine, glomerular filtration rate, glucose, glycated haemoglobin (HbA1c), total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride. For the assay of ADMA, collected blood samples were centrifuged at 2000 g to separate plasma, and stored at –70°C until assay. The plasma ADMA concentration was measured by a commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kit (Human ADMA, EASTBIOPHARM, Hangzhou, China) and read on a microplate reader (BIOTEK ELX800, USA) in ng/mL.

The primary outcome of the study was the serum level of ADMA in patients with aorta dilatation in comparison to those without aorta dilatation. The secondary outcome was predictive value of serum ADMA level for diagnosis of aorta dilatation.

### *Echocardiography and computed tomography*

All patients underwent detailed transthoracic Doppler echocardiographic examination through parasternal long axis using an echocardiography machine (model EPIQ 7G, Philips, USA) with a 3-MHz linear probe [13]. The diameter of the proximal ascending aorta was measured according to the American Society for Echocardiography guidelines [14]. An ascending aorta diameter ≥ 4.5 cm on echocardiography was classified as aorta dilatation in order to minimise the confounding effect of the patient's height (case group), and ≤ 3.8 cm as normal aortic diameter (control group). For patients with aorta dilatation, computed tomography (CT) scanning was performed using a second-generation, dual-source CT system (Somatom Definition Flash, Siemens Medical Solutions, Erlangen, Germany) to confirm the diagnosis and measure the diameter of the ascending aorta precisely. Scanning was performed throughout the RR interval in the retrospectively gated spiral acquisition mode. Patients received oral and/or intravenous beta-blocker premedication. CT acquisition was performed within a single breath hold. Eighty millilitres of contrast material (Ultravist 370, Bayer Schering, Berlin, Germany) was injected at a flow rate of 5 mL/s followed by a 20-mL saline flush. Technical parameters were as follows: detector collimation 128 × 0.6 mm, pitch 0.2, voltage 120 kV, current 300 mAs, and rotation time 280 ms. Multiplanar reformats were reconstructed on a syngo.via post-processing workstation (Siemens Healthcare, Erlangen, Germany). All CT scans were analysed by an experienced radiologist blinded to the patients' data.

### *Statistical analysis*

Study data were summarised by descriptive statistics (e.g. mean, standard deviation, frequency, and percentage). Parameters of patients with aorta dilatation and control group were compared with Student's t test for continuous variables and $\chi^2$ test for categorical variables. The linear regression analysis was performed to measure the strength of the linear relationship between independent clinical variables and proximal aorta diameter. Receiver-operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of serum ADMA level to distinguish patients with aorta dilatation. The area under the curve (AUC) values were calculated as a measure of the accuracy of the test. The sensitivity and specificity were calculated for each cut-off level of serum ADMA. Spearman correlation analysis was performed to evaluate the correlation between ADMA level and aortic diameter.

Table 1. Demographic, clinical, and laboratory findings of study groups

| | Patients with aorta dilatation (case group); n = 104 | Patients without aorta dilatation (control group); n = 52 | p |
|---|---|---|---|
| Age [years] | 62.75 ± 13.11 | 63.44 ± 7.56 | 0.725 |
| Gender (female/male) | 35/69 (33.7/66.3) | 17/35 (32.7/67.3) | 0.904 |
| Smoking | 23 (22.1%) | 10 (19.2%) | 0.678 |
| Diameter of aorta by echocardiography [cm]: | | | |
| Ascending aorta | 4.95 ± 0.57 | 3.34 ± 0.36 | **< 0.001** |
| Bicuspid aorta | 0.13 ± 0.34 | 0.0 ± 0.0 | **0.005** |
| Diameter of aorta by computed tomography [cm]: | | | |
| Ascending aorta | 4.93 ± 0.59 | – | – |
| Laboratory findings: | | | |
| ADMA [ng/mL] | 1.70 ± 1.12 | 0.79 ± 0.76 | **< 0.001** |
| Haemoglobin [g/dL] | 13.24 ± 1.73 | 13.75 ± 1.87 | 0.097 |
| Haematocrit [%] | 41.70 ± 7.41 | 42.58 ± 5.20 | 0.443 |
| Lymphocyte count [cells/mm$^3$] | 2.23 ± 1.04 | 2.37 ± 0.68 | 0.392 |
| Neutrophil count [cells/mm$^3$] | 4.99 ± 1.98 | 4.28 ± 1.88 | 0.033 |
| White blood cell count [cells/mm$^3$] | 8.00 ± 2.06 | 8.70 ± 2.80 | 0.080 |
| C-reactive protein [mg/L] | 16.04 ± 44.86 | 14.61 ± 43.29 | 0.850 |
| Creatinine [mg/dL] | 1.05 ± 0.22* | 0.87 ± 0.25 | **0.002** |
| GFR [mL/min/1.73 m$^2$] | 84.99 ± 24.62 | 90.45 ± 22.75 | 0.183 |
| Glucose [mg/dL] | 119.26 ± 46.43 | 140.10 ± 127.82 | 0.140 |
| HbA1c [%] | 6.02 ± 1.20 | 6.32 ± 1.81 | 0.226 |
| Total cholesterol [mg/dL] | 188.18 ± 39.02 | 200.67 ± 42.53 | 0.069 |
| LDL [mg/dL] | 116.31 ± 32.77 | 128.33 ± 32.77 | **0.032** |
| HDL [mg/dL] | 44.39 ± 12.48 | 44.92 ± 14.50 | 0.812 |
| Triglyceride [mg/dL] | 160.70 ± 88.34 | 184.15 ± 141.70 | 0.208 |
| Comorbidity: | | | |
| Diabetes mellitus | 25 (24.0%) | 13 (25.0%) | 0.687 |
| Hypertension | 61 (58.7%) | 19 (36.5%) | **0.009** |
| Coronary artery disease | 30 (28.8%) | 13 (25.0%) | 0.612 |
| Current drug treatment: | | | |
| Aspirin | 42 (40.4%) | 13 (25.0%) | 0.058 |
| ACE/ARB | 45 (43.3%) | 16 (30.8%) | 0.131 |
| Calcium channel blocker | 12 (11.5%) | 5 (9.6%) | 0.716 |
| Beta-blocker | 39 (37.5%) | 13 (25.0%) | 0.118 |
| Statins | 21 (20.2%) | 9 (17.3%) | 0.687 |

Data are presented as mean ± standard deviation or number and percentage (in brackets); *n = 34; ADMA — asymmetric dimethylarginine; GFR — glomerular filtration rate; HbA1c — glycated haemoglobin; LDL — low-density lipoprotein; HDL — high-density lipoprotein; ACE/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Statistical analysis was performed with SPSS software (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois, USA). Statistical level of significance was set at $p < 0.05$.

## RESULTS

Demographic, clinical, and laboratory variables were similar between case and control groups, except serum creatinine level and hypertension prevalence, both of which were significantly higher in patients with aorta dilatation (1.05 ± 0.22 mg/dL vs. 0.87 ± 0.25 mg/dL, $p = 0.002$ and 58.7% vs. 36.5%, $p = 0.009$, respectively) (Table 1).

Serum ADMA level was significantly higher in patients with aorta dilatation than in the control group (1.70 ± 1.12 ng/mL vs. 0.79 ± 0.76 ng/mL, respectively, $p < 0.001$) (Fig. 1).

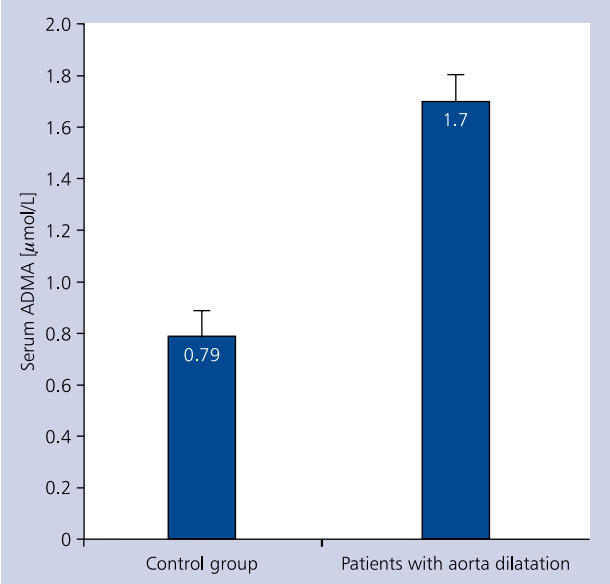


Figure 1. The mean serum asymmetric dimethylarginine (ADMA) level [ng/mL] in patients with aorta dilatation and the control group ($p < 0.001$). The vertical error bars represent standard error of the mean

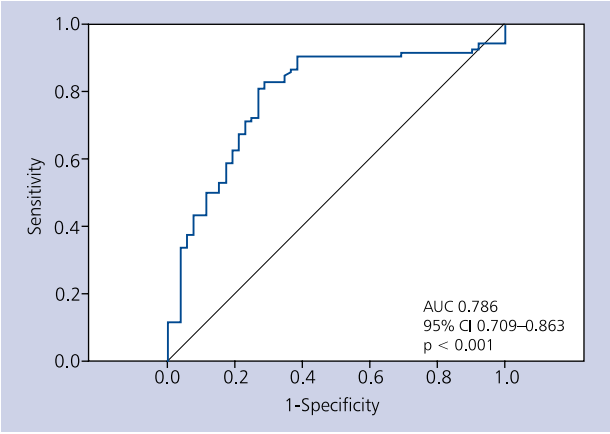


Figure 2. A receiver-operator characteristic curve and area under curve (AUC) of serum asymmetric dimethylarginine level in the prediction of aortic dilatation; CI — confidence interval

The mean diameter of ascending aorta measured on echocardiography was 4.95 ± 0.57 cm and 3.34 ± 0.36 cm in patients with aorta dilatation and those without aorta dilatation, respectively ($p < 0.001$). In patients with aorta dilatation on echocardiography, the diameter of aorta was measured as 4.93 ± 0.59 cm on CT. There was significant positive correlation between ADMA level and aortic diameter in Spearman correlation analysis ($r = 0.317$, $p < 0.001$). In linear regression analysis, ADMA was found to be a significant independent predictor of aorta diameter (Beta = 0.26, $p < 0.001$). ROC curve analysis also revealed that serum ADMA cut-off level over 0.29 μmol/L predicts aorta dilatation (≥ 4.5 cm) with 94% sensitivity and 92% specificity and with high accuracy (AUC: 0.786; 95% confidence interval [CI]: 0.709–0.863, $p < 0.001$) (Fig. 2).

## DISCUSSION

In the present case-control study, we primarily showed that serum ADMA level is increased in patients with ascending aorta dilatation, with a potential diagnostic value in clinical practice.

Patients with aortic dilatation or those with high risk of developing the condition are a special group of patients applying to cardiology clinics. These patients have high risk of developing spontaneous aortic rupture or dissection [10]. Early prediction and diagnosis are of crucial importance for these patients to take timely measures to prevent and treat aortic dilatation. Echocardiography is the most widely used diagnostic and screening tool for the measurement of aorta diameter and for diagnosis of aortic dilatation. However, there is need for more accessible, non-invasive, and inexpensive tests in clinical practice to confirm the diagnosis of aorta dilatation and to predict the outcome of patients [15]. The biomarkers of oxidative stress and endothelial dysfunction have been suggested to be used for this aim. Gamma-glutamyltransferase (GGT) and ADMA are potential biomarkers of aortic dilatation. However, studies are limited on the role of GGT or ADMA in clinical management of aortic dilatation. Demir et al. [16] reported high levels of GGT in patients with aortic dilatation compared to a control group. Drapisz et al. [17] reported high ADMA serum levels in proximal ascending aortic dilatation and impaired aortic elastic properties in non-stenotic bicuspid aortic valve patients. In contrast to this study, our patient population had no aortic valve disease, only ascending aortic dilatation. Still, we found that ADMA level was significantly increased in patients with aortic dilatation compared to those without the condition. As expected, serum creatinine level and hypertension prevalence were significantly higher in patients with aorta dilatation.

It has been known that endothelial NO synthesised by NO synthase has a protective effect on the vascular bed by providing a steady vasodilatation [18]. On the other hand, irregularity of NO synthase causes weaknesses in the vascular wall by changing the amount of elastin, an important component of extracellular matrix proteins [19, 20]. This weaknesses of the vascular wall, caused by the irregularity of NO, has been considered to be associated with the development of aneurysms [18]. There is increasing evidence that NO plays a significant role in aneurysmal diseases [21]. In an in vivo study by Paik et al. [22], nitrite levels, the major metabolite of NO, increased seven-fold in human aortic aneurysms as compared to normal aorta. Johanning et al. [21] showed that NO synthase inhibitors L-NAME and aminoguanidine limit

nitric oxide production and experimental aneurysm expansion in rats. This evidence suggests that NO plays an important role in aneurysm formation.

ADMA is a NO synthase inhibitor eliminated through degradation or renal excretion. Serum ADMA level may increase as a result of increased biosynthesis, impairment of metabolism, or reduced renal clearance [2]. Growing clinical evidence suggests that ADMA is an independent cardiovascular risk factor [23]. Although the association of high serum ADMA levels with CVD has been well established, evidence on the use of ADMA for diagnosis and outcome prediction of CVD is limited and conflicting [4, 7, 8, 24, 25]. Therefore, there is need for more evidence to implement the use of serum ADMA level in diagnostic and prognostic risk scoring of patients with CVD. In the present study, we found that ADMA is a significant independent predictor of aorta diameter; serum ADMA level over 0.29 μmol/L predicts aorta dilatation (≥ 4.5 cm) with 94% sensitivity and 92% specificity. However, it should be noted that although the correlation between ADMA level and aortic diameter is significant, it is weak (r = 0.317). Furthermore, in patients with aortic dilatation, the prevalence of hypertension and creatinine level, an indicator of renal insufficiency, were higher. Taking into account the structure of the ascending aorta wall, which had almost no muscle cells, but mostly collagen and elastic fibres, hypertension-related aortic distention could be the underlying aetiology for the increase in ADMA especially after the age of 60 years, as in our population. Therefore, the effects of hypertension and renal failure on ADMA level should be clarified in order to reach a more definitive conclusion on the diagnostic value of ADMA for aortic dilatation.

### Limitations of the study

The main limitation of the present study was its cross-sectional design, which does not allow evaluation of serum ADMA level over time in patients with aortic dilatation. For the same reason, we could not evaluate the serum ADMA level before development of aortic dilatation. Furthermore, because we could not follow patients over time and determine the exact mortality rate, we could not assess the prognostic value of ADMA. Thus, we could not comment on value of ADMA level as a predictive or prognostic factor for aortic dilatation. The limited sample size was also another limitation that precluded us from reaching a definitive conclusion on the predictive value of ADMA for aortic dilatation. Further studies are needed to add serum ADMA test to echocardiography for screening of patients at risk of aortic dilatation, e.g. those with family history. Nevertheless, this is among the first studies on serum ADMA level in patients with aortic dilatation, with promising results on the diagnostic value of ADMA for aortic dilatation.

## CONCLUSIONS

In conclusion, serum ADMA level is increased in aortic dilatation. A serum ADMA level over 0.29 μmol/L predicts aorta dilatation (≥ 4.5 cm) with 94% sensitivity and 92% specificity. Given that the measurement of serum ADMA level is a non-invasive and inexpensive procedure, it should be considered for use in clinical diagnosis of aorta dilatation. Before reaching a more definitive conclusion on the diagnostic value of ADMA for aortic dilatation, further studies should clarify whether ADMA level indicates dilatation of aorta or hypertension.

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***Conflict of interest:*** *none declared*

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# Zwiększone stężenie w osoczu asymetrycznej dimetyloargininy wiąże się z poszerzeniem aorty wstępującej: badanie kliniczno-kontrolne

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## Streszczenie

**Wstęp:** Asymetryczna dimetyloarginina (ADMA) jest endogennym inhibitorem syntazy tlenku azotu.

**Cel:** Badanie przeprowadzono w celu oznaczenia osoczowego stężenia ADMA u chorych z poszerzeniem aorty wstępującej w porównaniu z osobami bez poszerzenia aorty oraz oceny diagnostycznej, predykcyjnej i prognostycznej wartości stężenia ADMA w odniesieniu do poszerzenia aorty.

**Metody:** Do przekrojowego badania kliniczno-kontrolnego włączono 104 kolejnych pacjentów (kobiety/mężczyźni: 35/69; średnia wieku: 62,75 ± 13,11 roku) z rozpoznaniem poszerzenia aorty wstępującej (≥ 4,5 cm) ustalonym na podstawie badania echokardiograficznego (grupa przypadków) oraz 52 osoby dopasowane pod względem wieku i płci (kobiety/mężczyźni: 17/35; średnia wieku: 63,44 ± 7,56 roku) z prawidłowymi wymiarami aorty (≤ 3,8 cm) (grupa kontrolna). Oprócz oznaczenia stężenia ADMA w osoczu wykonano rutynowe badania biochemiczne i hematologiczne.

**Wyniki:** Średnie wymiary aorty wstępującej w badaniu echokardiograficznym wynosiły 4,95 ± 0,57 cm i 3,34 ± 0,36 cm, odpowiednio u chorych z poszerzeniem aorty i u osób bez poszerzenia aorty ($p < 0,001$). Stężenie ADMA w osoczu były istotnie wyższe u pacjentów z poszerzeniem aorty niż w grupie kontrolnej (odpowiednio 1,70 ± 1,12 μmol/l *vs*. 0,79 ± 0,76 μmol/l; $p < 0,001$). W analizie korelacji Spearmana wykazano istotną dodatnią zależność między stężeniem ADMA a poszerzeniem aorty ($r = 0,317$; $p < 0,001$). W analizie regresji liniowej stwierdzono, że stężenie ADMA jest istotnym niezależnym czynnikiem predykcyjnym wymiaru aorty (Beta = 0,26; $p < 0,001$). Ponadto, analiza krzywych ROC wykazała, że wartości powyżej punktu odcięcia stężenia ADMA w osoczu wynoszącego 0,29 μmol/l pozwalają na predykcję poszerzenia aorty (≥ 4,5 cm) z czułością wynoszącą 94% i swoistością równą 92%, przy wysokiej dokładności (pole pod krzywą: 0,786; 95% przedział ufności: 0,709–0,863; $p < 0,001$).

**Wnioski:** Stężenie ADMA w osoczu stanowi parametr diagnostyczny w odniesieniu do poszerzenia aorty wstępującej, który cechuje się wysoką wrażliwością i swoistością, dlatego należy rozważyć stosowanie go w celu ustalania klinicznego rozpoznania poszerzenia aorty.

**Słowa kluczowe:** poszerzenie aorty, asymetryczna dimetyloarginina, biomarker, diagnoza

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