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Serum asymmetric dimethylarginine levels in normotensive obese individuals

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Obesity is associated with an increased risk of developing insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, hypertension, premature atherosclerosis, and coronary artery disease. This study is designed to compare serum asymmetric dimethylarginine (ADMA) levels between obese individuals and controls.

Material/Methods: Fifty volunteers, 30 obese (13 men; mean age, 40±11 years) and 20 healthy controls (13 men; mean age, 44±10 years) were enrolled to this study. Measurement of ADMA was accomplished by high performance liquid chromatography.

Results: The mean body mass index of the obese group was significantly higher than that of the control group (35±4 vs 26±3 kg/m^2; *P*=.001). The mean waist circumference of the obese subjects was also significantly higher compared with controls (111±11 vs 93±10 cm; *P*=.001). No significant difference was found concerning age, sex, blood pressures, and biochemistry parameters. Serum ADMA levels were significantly higher in obese individuals compared with healthy controls (5.4±3.3 vs 3.1±1.8 µmol/L; *P*=.006). A weak but significant correlation was identified between serum ADMA concentration and the waist circumference (r=0.282, *P*=.047).

Conclusions: The results of the present study demonstrated that serum ADMA levels of normotensive obese individuals were significantly higher than healthy controls. Increased ADMA concentrations observed only in the obese group were deemed to be important regarding the development future of cardiovascular disease in the future.

key words: **asymmetric dimethylarginine • obesity**

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Background

Obesity is an increasing problem worldwide because of its social, economic, and medical consequences [1]. Obesity is associated with an increased risk of developing insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, hypertension, premature atherosclerosis, and coronary artery disease [2]. It has been reported that obesity is significantly correlated with left ventricular mass, systolic and diastolic dysfunction, and coronary artery disease risk factors [3,4]. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase [5]. In humans, elevated ADMA levels inhibit endothelium-dependent vasodilatation and lead to endothelial dysfunction [6–8]. Elevated ADMA levels have been shown to be associated with atherosclerosis, diabetes mellitus, renal dysfunction, dyslipidemia, and hypertension [9]. However, the concentration of ADMA in normotensive obese individuals with no other medical disorders is unknown.

The aim of this study was to compare serum ADMA levels of otherwise healthy, normotensive, obese individuals with healthy subjects in similar age groups and metabolic features.

Material and methods

Study population and design

This study was conducted on patients who were admitted to the Selcuk University Meram School of Medicine. The study was approved by the local ethics committee and written, informed consent was obtained from all volunteers. A total of 50 volunteers ≥18 years of age, including 20 nondiabetic normotensive healthy individuals and 30 obese patients, were included in the study. Individuals with chronic diseases and those using medications were excluded. Body mass index was calculated by dividing the weight (kg) by the height in meters squared (kg/m^2). Individuals with a body mass index of 30 kg/m^2 or more were considered obese. Among healthy volunteers, those with a body mass index of less than 30 kg/m^2 were included as controls. Waist circumference was measured with a soft tape in the standing position midway between the lowest rib and the iliac crest. Blood pressure was performed in the sitting position on both arms by a physician, after 15 minutes of rest, and the mean value was recorded. After 12 hours of fasting, a venous blood sample was collected from all participants, and the fasting blood glucose and lipid panel were measured. Glomerular filtration rate was measured by creatinine clearance according to the Cockroft-Gault formula [10].

Measurement of ADMA

Measurement of ADMA was accomplished by high performance liquid chromatography (HPLC), using the method described by Chen and associates [11]. In brief, 20 mg of 5-sulfosalisilic acid was added to 1 mL of serum, and the mixture was left in an ice bath for 10 minutes. The precipitated protein was removed by centrifugation at 2000 × *g* for 10 minutes. Ten µL of the supernatant, which was filtered through a 0.22-µm pore filter, was mixed with 100 µL of a derived reagent (prepared by dissolving 10 mg of *o*-phthaldialdehyde in 0.5 mL of methanol, with 2 mL of 0.4 m borate buffer [pH 10.0], and 30 µL of 2-mercaptoethanol added), and injected into the chromatographic system. Separation of ADMA was achieved with a 250×4.6 mm interior diameter Supelcosil C18 column with a particle size of 5 µm (Supelco, Bellefonte, PA, USA) using 50 mM sodium acetate (pH 6.8), methanol, and tetrahydrofurane as the mobile phase (A, 82: 17: 1; B, 22: 77: 1) at a flow rate of 1.0 mL/min. Serum levels of ADMA were measured by HPLC (HP Agilent 1100; Agilent Technologies, Palo Alto, CA, USA) with fluorescence detection. The areas of the peaks detected by the fluorescent detector (excitation, 338 nm; emission, 425 nm) were used for quantification.

Table 1. Baseline characteristics and ADMA levels.

Baseline characteristics	Control (N=20)	Obese (N=30)	P
Age, y	44±10	40±11	0.470
Male, n (%)	13 (65)	13 (43)	0.139
Body mass index, kg/m^2	26±3	35±4	**0.001**
Systolic blood pressure, mmHg	124±12	127±15	0.459
Diastolic blood pressure, mmHg	78±10	82±13	0.134
Waist circumference, cm	93±10	111±11	**0.001**
Male	91±10	112±10	**0.001**
Female	98±7	110±12	**0.006**
GFR, mL/min	77±25	87±27	0.184
Fasting glucose, mg/dl	93±3	97±10	0.211
Total cholesterol, mg/dl	203±63	198±40	0.723
Fasting triglycerides, mg/dl	117±66	132±71	0.496
LDL-cholesterol, mg/dl	133±55	123±42	0.484
HDL-cholesterol, mg/dl	46±13	47±11	0.797
ADMA, µmol/L	3.1±1.8	5.4±3.3	**0.006**

GFR – glomerular filtration rate; LDL – low density lipoprotein; HDL – high density lipoprotein; ADMA – asymmetric dimethylarginine.

Statistical analyses

Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 13.0, SSPS Inc, Chicago, IL, USA). Parametric variables are expressed as the mean ± SD. Differences between parametric variables among the 2 groups were evaluated using 2-tailed unpaired *t* test or the Mann-Whitney *U* test. Categoric variables are presented as absolute values and comparisons were tested using the chi-square test. Spearman's rank correlation coefficient was used to demonstrate correlations between the data exhibiting parametric distribution. A *P* value <.05 was considered statistically significant.

Results

Baseline characteristics of the volunteers enrolled in the study are presented in Table 1. The mean body mass index

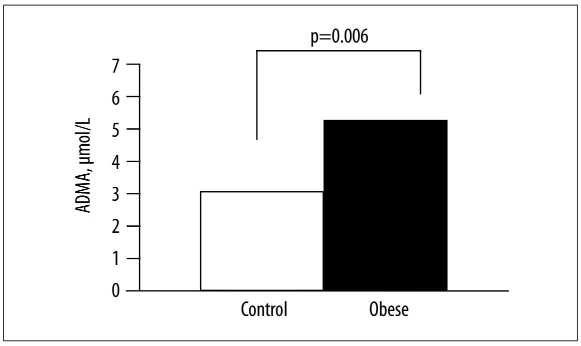

Figure 1. Serum ADMA levels in obese and control groups.

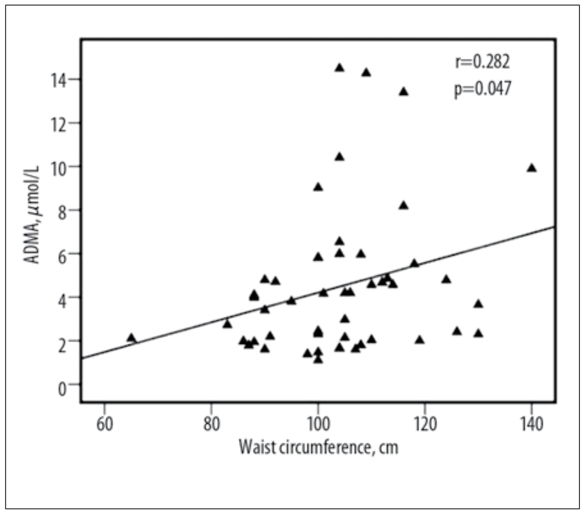

Figure 2. Correlation between ADMA with waist circumference in the study groups.

of the obese group was significantly higher than that of the control group (35±4 vs 26±3 kg/m^2; *P*=.001). The mean waist circumference of the obese subjects was significantly higher compared with the controls (111±11 vs 93±10 cm; *P*=.001). No significant difference was present with respect to age, sex, blood pressure, and biochemistry parameters.

Serum ADMA levels were significantly higher in obese individuals when compared to healthy controls (5.4±3.3 vs 3.1±1.8 µmol/L; *P*=.006) (Table 1, Figure 1). A significant correlation was found between serum ADMA levels and waist circumference (r=0.282; *P*=.047) (Figure 2).

Discussion

The present study demonstrates that serum ADMA levels of normotensive obese individuals were significantly higher than healthy controls. A weak but significant correlation was identified between serum ADMA concentration and the waist circumference.

The endothelium plays a substantial role in providing normal coronary blood flow and vascular tonus [12]. Endothelial dysfunction is one of the early abnormalities observed in the pathogenesis of atherosclerosis [13]. Inhibition of NO synthesis by ADMA leads to impairment of endothelium-dependent vasodilatation [14]. Sen and associates [15] investigated the relation between ADMA concentrations and carotid artery intima-media thickness in cardiac syndrome X patients, regarded to have endothelial dysfunction as the underlying mechanism. The ADMA concentration was higher in cardiac syndrome X patients, and a positive correlation was found with carotid artery intima-media thickness. In the study conducted by Furuki and associates [16], besides a correlation between the ADMA concentration and carotid artery intima-media thickness, ADMA was found to be a predictive factor for the progression of carotid artery intima-media thickness. Elevated ADMA levels have been suggested as having a role in cardiovascular system disorders, diabetes mellitus, and in the pathogenesis of hypertension [13]. Stuhlinger and associates [17] demonstrated that ADMA levels, independent of the other risk factors, had a relation with insulin resistance. Eid and associates [13] observed that ADMA concentrations were higher in obese and overweight individuals compared with control subjects, and that there was a relation between body mass index and ADMA concentrations; however, the mean blood pressure values of the patients were above the normal limits in this study. On the other hand, Onat and associates [5] demonstrated that there was a relation between ADMA concentrations and waist circumference. Previous studies have reported a relation between obesity and glucose intolerance, hyperinsulinemia, dyslipidemia, and high levels of C-reactive protein [18]. Obesity decreases insulin sensitivity, and increases the development and progression of coronary artery disease by promoting systemic inflammation [19]. The American Heart Association and American College of Cardiology consider obesity as the major modifiable risk factor for coronary artery disease [20]. In the study conducted by Teplan and associates [21], levels of ADMA were shown to be increased in obese renal transplant recipients. Additionally, these authors demonstrated a significant negative correlation between ADMA concentrations with body mass index and waist circumference [21]. We also demonstrated that ADMA concentrations were significantly higher in obese normotensive patients compared with healthy controls. Furthermore, a weak but significant negative correlation was observed between ADMA concentrations and waist circumference.

Conclusions

The individuals enrolled in our study had normal blood pressure levels and they were not diabetic. However, increased ADMA concentrations observed only in the obese group were deemed to be important in future cardiovascular disease.

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