Relationship between plasma asymmetric dimethylarginine level and autonomic dysfunction in diabetic patients

Diyabetli hastalarda plazma asimetrik dimetilarjinin düzeyi ile otonomik disfonksiyon arasındaki ilişki

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ABSTRACT

Objectives: We aimed to investigate the relationship between plasma asymmetric dimethylarginine (ADMA) levels and heart rate variability (HRV) in diabetic patients.

Study design: The study included 100 patients (44 men, 56 women) with type 2 diabetes mellitus. The patients were divided into two groups based on the use of oral antidiabetics (n=67; mean age 54.6±7.8 years) or insulin (n=33; mean age 51.6±8.8 years). Plasma ADMA levels were measured and HRV parameters were calculated from 24-hour Holter EKG recordings. The findings were compared with those of a control group consisting of 42 nondiabetic individuals (mean age 52.8±6.2 years).

Results: Compared to the control group, plasma ADMA levels were significantly higher (p=0.007) and all HRV parameters were significantly reduced in both diabetic groups. However, ADMA levels and HRV parameters were similar in the two diabetic groups (p>0.05). Correlation analysis showed no significant relationship between plasma ADMA levels and HRV parameters.

Conclusion: Our findings show that plasma ADMA levels are increased and HRV is reduced in diabetic patients, indicating that these patients have both endothelial dysfunction and autonomic dysfunction, but plasma ADMA levels cannot be used to evaluate autonomic dysfunction.

ÖZET

Amaç: Diyabetli hastalarda plazma asimetrik dimetilarjinin (ADMA) düzeyi ile kalp hızı değişkenliği (KHD) arasındaki ilişki araştırıldı.

Çalışma planı: Çalışmaya tip 2 diyabeti olan 100 hasta (44 erkek, 56 kadın) alındı. Hastalar, oral antidiyabetik ilaç kullanan 67 hasta (ort. yaş 54.6±7.8) ve insülin kullanan 33 hasta (ort. yaş 51.6±8.8) olmak üzere iki gruba ayrıldı. Tüm hastalarda plazma ADMA düzeyleri ölçüldü ve 24 saatlik Holter EKG kayıtlarından KHD parametreleri hesaplandı. Sonuçlar, diyabetli olmayan 42 kişiden oluşan (ort. yaş 52.8±6.2) kontrol grubuyla karşılaştırıldı.

Bulgular: Kontrol grubuyla karşılaştırıldığında, her iki diyabet grubunda plazma ADMA düzeyleri anlamlı derecede daha yüksek (p=0.007), KHD parametreleri ise anlamlı derecede azalmış bulundu. İki diyabet grubu arasında ise ADMA ve KHD parametreleri açısından anlamlı farklılık yoktu (p>0.05). Korelasyon analizinde plazma ADMA düzeyleri ile KHD parametreleri arasında anlamlı ilişki görülmedi.

Sonuç: Bulgularımız, diyabetik hastalarda plazma ADMA düzeylerinin arttığını, KHD'nin azaldığını; böylece, bu hastalarda hem endotel disfonksiyonunun hem de otonomik disfonksiyonun varlığını göstermektedir; ancak, plazma ADMA düzeyi otonomik disfonksiyonun değerlendirilebileceği bir belirteç değildir.

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Diabetes mellitus is a highly prevalent disease that is closely related with cardiovascular diseases. Its microvascular and macrovascular complications are the leading causes of death. Endothelial dysfunction has a substantial role in the development and progression of these complications.[1] Nitric oxide is one of the major determinants of endothelial function and vascular health.[2] Asymmetric dimethylarginine inhibits nitric oxide synthesis. High levels of ADMA have been shown to be closely related with atherogenesis, endothelial dysfunction, and complications of diabetes.[3-5]

Autonomic dysfunction is another aspect of DM and it is one of the major determinants of prognosis. In a meta-analysis, it was shown that cardiac autonomic dysfunction doubled silent myocardial ischemia and mortality.[6] Heart rate variability is one of the most widely used methods in the diagnosis of cardiac autonomic dysfunction.[7] It has been suggested that decreased HRV is one of the earliest findings of autonomic dysfunction and low HRV can present even in asymptomatic patients.[8]

There are some clues about the relationship between endothelial dysfunction and autonomic dysfunction. Levels of norepinephrine, as a marker of sympathetic activity, have been shown to be correlated with ADMA levels in end-stage renal disease.[9] Gautier et al.[10] found a significant relationship between carotid atherosclerosis and low HRV. The results of the ARIC study (Atherosclerosis Risk In Communities) also provided supportive data on the relationship between atherosclerosis and HRV.[11]

In the present study, we sought to examine whether there was any relationship between the levels of plasma ADMA (as a marker of endothelial dysfunction) and HRV (as a marker of autonomic dysfunction). In this case, plasma ADMA levels can be used to determine autonomic dysfunction, as well.

PATIENTS AND METHODS

A total of 142 individuals were recruited to the study from cardiology and endocrinology outpatient clinics to form three groups: two diabetic groups (n=100), and one control group (n=42). Type II DM was the inclusion criterion for the two diabetic groups. The control group included subjects who did not have any disease other than hypertension (42 subjects). Exclusion criteria from the study were the same for both diabetic groups and control group and included the following: chronic renal disease/failure, history of heart failure (systolic or diastolic), severe or moderate valvular heart disease, history of arrhythmia (e.g., atrial fibrillation) or pacemaker use, active and/or chronic infectious disease, malignancy, documented coronary artery disease, rheumatic diseases, endocrinologic diseases, chronic obstructive lung disease, and obstructive sleep apnea.

Abbreviations:

ADMA *Asymmetric dimethylarginine*
DM *Diabetes mellitus*
HRV *Heart rate variability*

We divided the diabetic patients into two groups, considering the literature data on the effect of insulin on ADMA levels. Group I was composed of 67 patients that were using oral antidiabetic drugs and group II was composed of 33 patients that were using insulin as an antidiabetic agent. Baseline characteristics of the patients were also recorded. All patients gave informed consent and the study was approved by the local ethics committee.

Blood sampling

After at least eight hours of fasting, blood samples were taken for fasting blood glucose, hemogram, biochemistry panel, HbA_{1c}, lipid panel, and plasma ADMA. Blood samples for ADMA were immediately centrifuged at 3,000 bpm/min and plasma samples were stored below -70°C. Plasma ADMA levels were studied with commercially available ELISA kits (Immundiagnostik AG, Bensheim, Germany).

24-hour Holter monitoring

Twenty-four-hour Holter EKG recordings were obtained with a three-channel digital recorder (Del Mar Reynolds Medical Ltd, Hertford, UK). The recordings were manually processed before data analysis. Recordings that lasted at least 18 hours and of sufficient quality for evaluation were included in the analysis. Insufficient or inappropriate recordings were repeated. The time domain HRV parameters were calculated by the help of statistical and geometrical methods. By using statistical methods, standard deviation of all RR intervals (SDNN) in the entire recording, the mean of the standard deviations of all RR intervals for all 5-minute segments over the entire recording (SDNNi), standard deviation of the averaged normal RR intervals calculated for all 5-minute periods (SDANN), and the root-mean-square of the successive normal sinus RR interval difference (RMSDD) were calculated. By using geometrical methods, the total number of all RR intervals divided by the height of the histogram of all RR intervals measured on a discrete scale with bins of 7.8125 msec (1/128 sec) and triangular index (TI) were calculated. All HRV parameters were calculated in accordance with the established guidelines.[12]

Table 1. Baseline characteristics and heart rate variability parameters of the patients

	Group I (n=67)			Group II (n=33)			Control group (n=42)			
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			54.6±7.8			51.6±8.8			52.8±6.2	0.15
Sex										0.97
Male	29	43.3		15	45.5		19	45.2		
Female	38	56.7		18	54.6		23	54.8		
Duration of diabetes mellitus (years)			4.6±3.1			6.0±3.1			–	**0.046**
Body mass index (kg/m^2)			25.8±6.8			25.2±2.9			21.8±6.5	**0.04**
Hypertension	40	59.7		20	60.6		24	57.1		0.94
Creatinine (mg/dl)			0.8±0.1			0.8±0.1			0.7±0.1	0.42
Total cholesterol (mg/dl)			192±37			187±41			181±35	0.33
HDL cholesterol (mg/dl)			45±11			42±10			47±11	0.13
LDL cholesterol (mg/dl)			115±35			112±32			110±31	0.79
Triglyceride (mg/dl)			176±115			162±65			106±42	**0.01**
Fasting blood glucose (mg/dl)			141±50			158±56			90±7	**<0.01**
Postprandial glucose (mg/dl)			178±94			228±142			–	0.08
HbA_{1c} (%)			6.4±1.2			7.2±1.9			–	**0.01**
Medications										
Angiotensin-converting enzyme inhibitor	19	28.4		11	33.3		10	23.8		0.60
Angiotensin receptor blocker	23	34.3		7	21.2		11	26.2		0.35
Beta-blocker	10	14.9		4	12.1		5	11.9		0.87
Calcium channel blocker	10	14.9		4	12.1		5	11.9		0.87
Antihyperlipidemic drugs	22	32.8		8	24.2		1	2.4		**0.001**
Heart rate variability										
SDNN (msec)			119±27			103±27			130±30	**<0.01**
SDNNi (msec)			43±11			37±11			48±12	**0.001**
SDANN (msec)			110±27			96±27			121±30	**0.001**
RMSDD (msec)			42±25			33±18			67±20	**0.001**
Triangular index			42±35			33±27			67±31	**0.001**

Group I: Diabetic patients using oral antidiabetic drugs; Group II: Diabetic patients using insulin; SDNN: Standard deviation of all RR intervals; SDNNi: Mean of the standard deviations of all RR intervals for all 5-minute segments over the entire recording; SDANN: Standard deviation of the averaged normal RR intervals calculated for all 5-minute periods; RMSDD: Root-mean-square of the successive normal sinus RR interval difference.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences 15.0 for Windows. Continuous variables were given as mean±SD, and categorical variables as percentages. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Descriptive statistics were applied accordingly. Data were analyzed by the ANOVA test for multiple comparisons and *post hoc* analysis between groups were evaluated by the Tukey test. Pearson correlation coefficients were used to test relationship between plasma ADMA levels and HRV parameters. The statistical significance was considered to be $p<0.05$.

RESULTS

Baseline characteristics and HRV parameters of the study groups are summarized in Table 1. There was no significant difference in the prevalence of hypertension between the three groups ($p>0.05$).

Table 2. Correlation analysis for the relationship between plasma ADMA levels and heart rate variability parameters

	Control group		Group I		Group II	
	r	*p*	r	*p*	r	*p*
SDNN	0.049	0.75	0.151	0.22	0.218	0.22
SDNNi	0.063	0.69	0.106	0.39	-0.013	0.94
SDANN	0.016	0.92	0.158	0.20	0.236	0.18
RMSDD	0.075	0.64	0.070	0.57	0.206	0.25
Triangular index	0.005	0.97	0.069	0.581	0.132	0.46

Group I: Diabetic patients using oral antidiabetic drugs; Group II: Diabetic patients using insulin; SDNN: Standard deviation of all RR intervals; SDNNi: Mean of the standard deviations of all RR intervals for all 5-minute segments over the entire recording; SDANN: Standard deviation of the averaged normal RR intervals calculated for all 5-minute periods; RMSDD: Root-mean-square of the successive normal sinus RR interval difference.

Plasma levels of ADMA were significantly higher in the two diabetic groups compared to the control group (Fig. 1) (0.7±0.09, 0.7±0.10, 0.64±0.10 μmol/l, respectively; p=0.007), but the two diabetic groups did not differ significantly in this respect (p=0.94).

All HRV parameters were significantly reduced in both diabetic groups compared to the control group.

In correlation analysis, no significant relationship was found between plasma ADMA levels and HRV parameters (Table 2). The only parameter that was significantly correlated with plasma ADMA levels was body mass index and the only parameter that was significantly correlated with HRV parameters was the duration of diabetes (Table 3).

We also compared plasma ADMA levels in antihypertensive drug users and non-users, but found no significant difference in plasma ADMA levels between antihypertensive drug users and non-users.

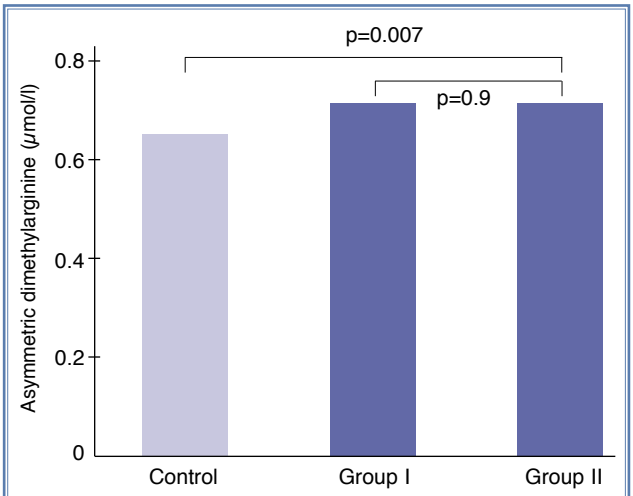

Figure 1. Plasma ADMA levels. Group I: Diabetic patients using oral antidiabetic drugs; Group II: Diabetic patients using insulin.

DISCUSSION

In the present study, our aim was to investigate the relationship between plasma ADMA levels (as a marker of endothelial dysfunction) and HRV parameters (as a marker of autonomic dysfunction). We showed that, despite increased plasma ADMA levels and reduced HRV, there was no significant relationship between plasma ADMA levels and HRV in diabetic patients.

Our study showed that time domain HRV parameters were significantly reduced in diabetic patients and these changes were well-correlated with the duration of DM, suggesting that autonomic dysfunction is much more prevalent in diabetic patients compared to nondiabetics. Although our diabetic patients were not only free from coronary artery disease, cerebrovascular disease, or peripheral artery disease, but also were asymptomatic and had a relatively low risk, their HRV

Table 3. Correlation analysis for the relationship of plasma ADMA and heart rate variability parameters with body mass index and duration of diabetes

	Body mass index		Duration of diabetes	
	r	*p*	r	*p*
ADMA	0.566	**<0.01**	-0.248	0.123
SDNN	0.055	0.683	-0.728	**<0.01**
SDNNi	-0.003	0.982	-0.763	**<0.01**
SDANN	0.029	0.831	-0.682	**<0.01**
RMSDD	-0.033	0.808	-0.462	**<0.01**
Triangular index	0.125	0.350	-0.717	**<0.01**

SDNN: Standard deviation of all RR intervals; SDNNi: Mean of the standard deviations of all RR intervals for all 5-minute segments over the entire recording; SDANN: Standard deviation of the averaged normal RR intervals calculated for all 5-minute periods; RMSDD: Root-mean-square of the successive normal sinus RR interval difference.

values were reduced, suggesting that autonomic dysfunction can be present even in asymptomatic diabetic patients. These findings were compatible with previous reports in the literature. It is well-known that there is a relationship between impaired glucose tolerance or DM and reduced HRV.[8] Ziegler et al.[13] showed that autonomic dysfunction, as evaluated by HRV, was relatively frequent in diabetic patients with a prevalence of 25.3% in type I DM and 34.3% in type II DM. Min et al.[14] evaluated 1041 patients with metabolic syndrome and found that there was a negative correlation between diabetes and HRV parameters. It was also shown in the ARIC study that there was an independent relationship between DM and reduced HRV.[15]

Another finding of our study was that plasma ADMA levels were increased in diabetic patients compared to the nondiabetic group. Levels of ADMA in diabetic patients were investigated previously, and endothelial dysfunction was found to be much more prevalent with higher plasma ADMA levels in diabetic patients compared to nondiabetic individuals.[16,17] In another study, it was shown that plasma ADMA levels were significantly increased in type I DM patients even before the development of complications of diabetes.[17] Because high plasma ADMA levels were independent from diabetes duration in our study, it can be interpreted that elevations in plasma ADMA levels can occur even in the early stages of DM. This makes ADMA a marker of vascular health. There is controversy about the effect of insulin on ADMA levels. Although insulin may decrease plasma ADMA levels, cause-effect relationship is still not known. In our study, there was no significant difference in ADMA levels between oral antidiabetic users and insulin users, suggesting that insulin-ADMA relationship may be dependent on the glucose regulatory mechanism of insulin; thus, ADMA levels may be more dependent on glucose regulation rather than insulin.

The effects of DM duration on autonomic dysfunction and ADMA levels were also examined in our study. Although DM duration showed no significant relationship with plasma ADMA levels, it did show a significant relationship with HRV. Longer duration of DM was associated with reduced HRV parameters, indicating the presence of autonomic dysfunction. The same relationship was shown previously with similar results.[18]

Previously, it was proposed that there might be a relationship between nitric oxide inhibition and norepinephrine, which is one of the important hormones of the sympathetic system. In one study, a significant relationship was found between ADMA and plasma norepinephrine levels in patients with end-stage renal disease.[9] In an animal study, it was shown that increased endogenous nitric oxide synthase inhibitors like N-nitro-L-arginine methyl ester (L-NAME) and ADMA were associated with increased sympathetic neural activation.[19] Aside from these findings, there are also some studies showing a relationship between atherosclerosis and autonomic dysfunction. The ARIC study showed the relationship between atherosclerosis and HRV.[15] Gautier et al.[10] showed that carotid atherosclerosis was related with reduced HRV. Since ADMA is a crucial molecule for endothelial dysfunction and atherosclerosis, we thought that this molecule might also have relationship with HRV. However, we found no significant relationship between plasma ADMA levels and HRV parameters in our low-risk diabetic patient group. As there are many factors that can impair autonomic dysfunction and endothelial dysfunction in diabetic patients, it is not convenient to exclude a relationship between these two conditions. Rather, we simply found no correlation between plasma ADMA levels and HRV parameters.

Schwarz et al.[20] investigated the effect of nitric oxide on rat heart sympathetic nerves. They used N^G-nitro-L-arginine (L-NNA) and N^G-methyl-L-arginine as nitric oxide synthase inhibitors and both molecules increased norepinephrine levels. It was also observed that there were no changes in cardiac contractility and cardiac rhythm with the inhibition of endogenous nitric oxide. When these findings are evaluated together with our results, it can be speculated that nitric oxide may be related with the autonomic system causing norepinephrine elevation, but this relationship may be at an autocrine/paracrine level, which does not have a direct effect on cardiac rhythm. This can also explain why ADMA is not related with HRV parameters. Thus, ADMA may cause elevation in norepinephrine levels without any effect on cardiac functions. The β1-receptor functions may have a crucial role in this process.

There are some studies suggesting the possible effects of antihypertensive drugs like renin-angiotensin-aldosterone system blockers on plasma ADMA levels.[21,22] Thus, antihypertensive drugs might influence plasma ADMA levels and interfere with the relationship between ADMA and HRV. For this reason, we compared plasma ADMA levels in antihypertensive drug users and non-users and found no effect of antihypertensive drug use on plasma ADMA levels.

There are some limitations in our study. A larger sample size might provide more information. Hypertension was not considered among the exclusion criteria, though comparison of patients with and without hypertension yielded no significant differences in plasma ADMA levels. Another limitation may be that we did not measure blood norepinephrine levels.

In conclusion, plasma ADMA levels are increased and HRV is reduced in diabetic patients, indicating that these patients have both endothelial dysfunction and autonomic dysfunction. However, this coexistence lacks a significant relationship between plasma ADMA levels and HRV parameters. Therefore, plasma ADMA levels can be used as a marker for endothelial dysfunction, but not for autonomic dysfunction in diabetic patients.

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Key words: Arginine; autonomic nervous system; biological markers; diabetes mellitus, type 2; endothelium, vascular; heart rate.

Anahtar sözcükler: Arginin; otonomik sinir sistemi; biyolojik belirteç; diabetes mellitus, tip 2; endotel, vasküler; kalp hızı.