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Uncomplicated Type 1 Diabetes Is Associated with Increased Asymmetric Dimethylarginine Concentrations

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Context: Asymmetric dimethylarginine (ADMA) has recently emerged as an independent risk marker for cardiovascular disease, but studies investigating the ADMA levels in type 1 diabetes mellitus (DM) are scarce.

Objective: We aimed to evaluate plasma ADMA, L-arginine concentrations, and L-arginine to ADMA ratio in uncomplicated type 1 diabetic patients and controls.

Design and Subjects: Forty patients with type 1 DM who did not have clinical evidence of vascular complications and 35 healthy controls were included in the study.

Results: Plasma ADMA concentrations were higher (2.6 ± 1.9 *vs.* 1.7 ± 0.7 μmol/liter, $P < 0.01$), and L-arginine levels were lower (79.3 ± 22.6 *vs.* 89.6 ± 19.4 μmol/liter, $P < 0.05$) in the diabetic group, compared with controls. The L-arginine to ADMA ratio was also lower in the diabetic group (38.7 ± 17.1 *vs.* 62.0 ± 27.9, $P < 0.0001$). In diabetic patients, logADMA correlated positively with body mass index (BMI) ($P = 0.01$), fasting blood glucose ($P = 0.006$), and low-density lipoprotein cholesterol (LDL-c) ($P = 0.01$) and negatively with high-density lipoprotein cholesterol ($P = 0.03$). L-Arginine to ADMA ratio correlated negatively with BMI ($P = 0.004$), fasting blood glucose ($P = 0.02$), and LDL-c ($P = 0.01$) and positively with high-density lipoprotein cholesterol ($P = 0.04$). In controls, logADMA and L-arginine to ADMA ratio correlated with BMI and LDL-c ($P < 0.05$). In regression analysis, BMI predicted 15% variance of ADMA levels ($P = 0.02$).

Conclusions: We demonstrated that ADMA increases and L-arginine to ADMA ratio decreases, even before the development of vascular complications in type 1 DM. **(*J Clin Endocrinol Metab* 92: 1881–1885, 2007)**

NITRIC OXIDE (NO), synthesized from the amino acid precursor L-arginine by NO synthase (NOS), is a major endothelial-derived vasoactive mediator which is involved in the maintenance of vascular homeostasis (1, 2). There are two types of endogenous NOS inhibitors in circulation, NG-monomethyl-L-arginine and asymmetric N^G, N^G-dimethyl-L-arginine (ADMA) (3). ADMA is the major inhibitor of NOS by competing with L-arginine and metabolized by the enzyme dimethylarginine dimethylaminohydrolase (DDAH) (4). Because ADMA is eliminated from the body by renal excretion, accumulation of ADMA was first shown in patients with chronic renal failure (5). Elevated plasma ADMA levels have also been reported in hypercholesterolemia (6), hypertension (7), and insulin resistance syndrome (8). Besides, there is substantial evidence that high circulating ADMA levels are associated with endothelial dysfunction and increased risk of atherosclerosis (3, 9, 10). A previous prospective study has revealed that plasma ADMA concentrations act as an independent risk factor for cardiovascular mortality in patients with end-stage renal disease (11). In addition to ADMA, L-arginine to ADMA ratio has been suggested to be important for the regulation of endothelial NOS activity (12).

Endothelial dysfunction is the earliest feature for the vascular complications of diabetes mellitus (DM) and its underlying mechanisms are not fully established (13). Changes in NOS pathway associated with endothelial dysfunction has an important role in the course of type 1 DM (14). Chan *et al.* (15) reported previously impaired NO release in a study consisting of mostly uncomplicated type 1 diabetic patients. Another report has demonstrated a decrease in NO metabolite levels as an evidence of early endothelial dysfunction in type 1 diabetic patients without clinical evidence of microvascular disease (16).

Because ADMA is an endogenous competitive inhibitor of NOS, elevated ADMA levels may contribute to the impaired NOS pathway in patients with type 1 DM. There are few data regarding the association between elevated plasma ADMA levels and type 1 DM. The purpose of the present study was to investigate the circulating ADMA concentration and its relation to metabolic parameters in type 1 diabetic patients without vascular complications.

Subjects and Methods

We studied 40 patients with type 1 DM (21 women and 19 men) and 35 healthy subjects (24 women and 11 men) whose age, gender, and body mass index (BMI) were similar to those of patients. Mean ages were 28.0 ± 7.1 (19–45) yr for diabetic patients and 30.4 ± 9.4 (17–48) yr for healthy subjects. Some biochemical and demographic characteristics of the patients and controls are presented in Table 1. Diagnosis of type 1 DM was based on the American Diabetes Association criteria (17). Patients did not have hepatic or renal dysfunction, chronic inflammatory, and clinically significant infectious diseases. None of the patients were

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Abbreviations: ADMA, Asymmetric N^G, N^G-dimethyl-L-arginine; BMI, body mass index; DDAH, dimethylarginine dimethylaminohydrolase; DM, diabetes mellitus; HbA1c, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NO, nitric oxide; NOS, NO synthase; T-c, total cholesterol; Tg, triglyceride.

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TABLE 1. Biochemical and demographic characteristics of the patients and controls

	Type 1 diabetic patients (n = 40)	Controls (n = 35)
Age (yr)	28.0 ± 7.1	30.4 ± 9.4
Gender (F/M)	21/19	24/11
BMI (kg/m^2)	21.6 ± 2.6	22.4 ± 2.8
SBP (mm Hg)	114.3 ± 11.1	116.4 ± 9.8
DBP (mm Hg)	73.0 ± 6.6	73.2 ± 7.3
FBG (mg/dl)	200.3 ± 93.3	84.0 ± 7.6
HbA1c (%)	8.6 ± 2.2	
Insulin dose (U/kg·d)	0.8 ± 0.1	
Creatinine (mg/dl)	0.8 ± 0.1	0.7 ± 0.1
T-c (mg/dl)	175.2 ± 41.0	177.3 ± 40.1
LDL-c (mg/dl)	105.7 ± 36.0	106.8 ± 33.0
HDL-c (mg/dl)	51.7 ± 11.9	51.3 ± 7.8
Tg (mg/dl)	92.0 ± 48.7	77.3 ± 30.2
ADMA (μmol/liter)	2.6 ± 1.9[a]	1.7 ± 0.7
L-Arginine (μmol/liter)	79.3 ± 22.6[b]	89.6 ± 19.4
L-Arginine to ADMA ratio	38.7 ± 17.1[c]	62.0 ± 27.9

Data are expressed as mean ± SD. SBP, Systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose.

[a] $P < 0.01$.

[b] $P < 0.05$.

[c] $P < 0.0001$.

taking any medication other than insulin. Cardiovascular disease was defined as a positive medical history for myocardial infarction, angina, coronary artery bypass graft and stroke, and ischemic changes in electrocardiogram. Diabetic nephropathy was defined as having persistent microalbuminuria (30–300 mg/d) or macroalbuminuria (>300 mg/d) in at least two of three samples collected in 24 h in the presence of retinopathy. Diabetic retinopathy was diagnosed by an ophthalmologist in the presence of background, preproliferative, or proliferative retinopathy during examination of fundus. Diabetic neuropathy was diagnosed in the presence of typical neuropathic symptoms and positive findings related to neuropathy in neurological examination. Patients who had clinical signs or symptoms of cardiovascular disease, nephropathy (including microalbuminuria), retinopathy, or neuropathy were excluded.

Height, weight, BMI, blood pressure, ADMA, L-arginine, fasting glucose, creatinine, total cholesterol (T-c), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and triglycerides (Tg) were measured in all subjects. Glycated hemoglobin (HbA1c) was measured in diabetic patients.

Venous blood samples were drawn after a 12-h overnight fast. Samples were separated and stored at −80 C until analysis. Serum levels of T-c, HDL-c, and Tg were measured using Abbott-Aeroset (Chicago, IL) autoanalyzer with original kits. LDL-c levels were calculated using Friedewald equation. HbA1c was done by HPLC-UV detector. ADMA measurements was done by HPLC-fluorescence detector by the method of Chen *et al.* (18).

The study was approved by the local ethics committee of the University of Gazi Faculty of Medicine. All subjects gave informed consent to participation.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (Statistical Package for Social Science, version 11.5; Chicago, IL). Continuous variables were shown as arithmetic mean ± SD. All data were tested for normal distribution using the Kolmogorov-Smirnov test. χ^2 test was used to investigate the difference between the groups regarding the gender. Comparisons of the groups were examined by Student's t test for normally distributed data and the Mann Whitney U test for nonparametric data. Because plasma ADMA concentrations did not follow a normal distribution, we used log transformation before analysis. Pearson correlation test was used to determine the relationships between continuous variables. Linear multivariate regression analysis were performed to find which variables predicted ADMA levels. $P < 0.05$ was considered statistically significant for all analyses.

Results

No differences were found between diabetic group and controls with respect to age, gender, and BMI ($P > 0.05$). In the diabetic group, duration of diabetes ranged between 1 month and 23 yr (7.9 ± 6.2 yr) and insulin dose from 0.3 to 1.2 U/kg·d (0.8 ± 0.1 U/kg·d). Mean HbA1c level was 8.6 ± 2.2%. Plasma ADMA concentrations were increased (2.6 ± 1.9 *vs.* 1.7 ± 0.7 μmol/liter, $P < 0.01$), whereas L-arginine levels were decreased (79.3 ± 22.6 *vs.* 89.6 ± 19.4 μmol/liter, $P < 0.05$) and L-arginine to ADMA ratio was also decreased (38.7 ± 17.1 *vs.* 62.0 ± 27.9, $P < 0.0001$) in the diabetic group, compared with controls. There were no differences between plasma ADMA levels and L-arginine to ADMA ratio of diabetic women and those of diabetic men (2.2 ± 1.3 *vs.* 3.0 ± 2.0 μmol/liter and 44.4 ± 32.9 *vs.* 39.2 ± 16.9, respectively, $P > 0.05$). There were no significant differences between smoker and nonsmoker diabetic patients with respect to ADMA and L-arginine to ADMA ratio ($P > 0.05$).

When diabetic patients were further divided into two subgroups as having poor or good glycemic control (HbA1c > 7 and HbA1c ≤ 7, respectively), ADMA levels of poorly controlled diabetic patients were comparable with well-controlled diabetic patients (2.3 ± 1.0 *vs.* 3.0 ± 2.4 μmol/liter, $P > 0.05$). L-Arginine to ADMA ratio was also similar between poorly and well-controlled diabetic patients (40.7 ± 15.8 *vs.* 36.1 ± 17.6, $P > 0.05$).

As shown in Table 2, in diabetic patients, logADMA correlated positively with BMI (r = 0.43, $P = 0.01$) (Fig. 1A), fasting blood glucose (r = 0.45, $P = 0.006$) (Fig. 1B), LDL-c (r = 0.40, $P = 0.01$) and negatively with HDL-c (r = −0.40, $P = 0.03$). There were also significant correlations between L-arginine to ADMA ratio and BMI (r = −0.49, $P = 0.004$), fasting blood glucose (r = −0.37, $P = 0.02$), LDL-c (r = −0.42, $P = 0.01$), and HDL-c (r = 0.33, $P = 0.04$) in diabetic patients. In controls, logADMA correlated positively with LDL-c (r = 0.40, $P = 0.01$) and BMI (r = 0.35, $P = 0.04$), and L-arginine to ADMA ratio correlated negatively with LDL-c (r = −0.34, $P = 0.04$) and BMI (r = −0.36, $P = 0.03$). Linear multivariate regression analysis demonstrated that BMI predicted 15% variance of ADMA (Table 3).

TABLE 2. Association between ADMA and L-arginine to ADMA ratio and clinical and biochemical variables in type 1 diabetic patients

	LogADMA		L-Arginine to ADMA ratio	
	r	*P*	r	*P*
Age (yr)	−0.03	0.85	−0.19	0.23
Duration of diabetes (yr)	0.11	0.53	−0.21	0.22
FBG (mg/dl)	0.45	0.006	−0.37	0.02
HBA1c (%)	−0.21	0.23	0.12	0.52
BMI (kg/m^2)	0.43	0.01	−0.49	0.004
SBP (mm Hg)	0.28	0.14	−0.17	0.39
DBP (mm Hg)	−0.12	0.52	0.26	0.18
T-c (mg/dl)	−0.06	0.75	−0.07	0.71
LDL-c (mg/dl)	0.40	0.01	−0.42	0.01
HDL-c (mg/dl)	−0.40	0.03	0.33	0.04
Tg (mg/dl)	0.03	0.86	0.04	0.79

LogADMA, Log transformed ADMA; FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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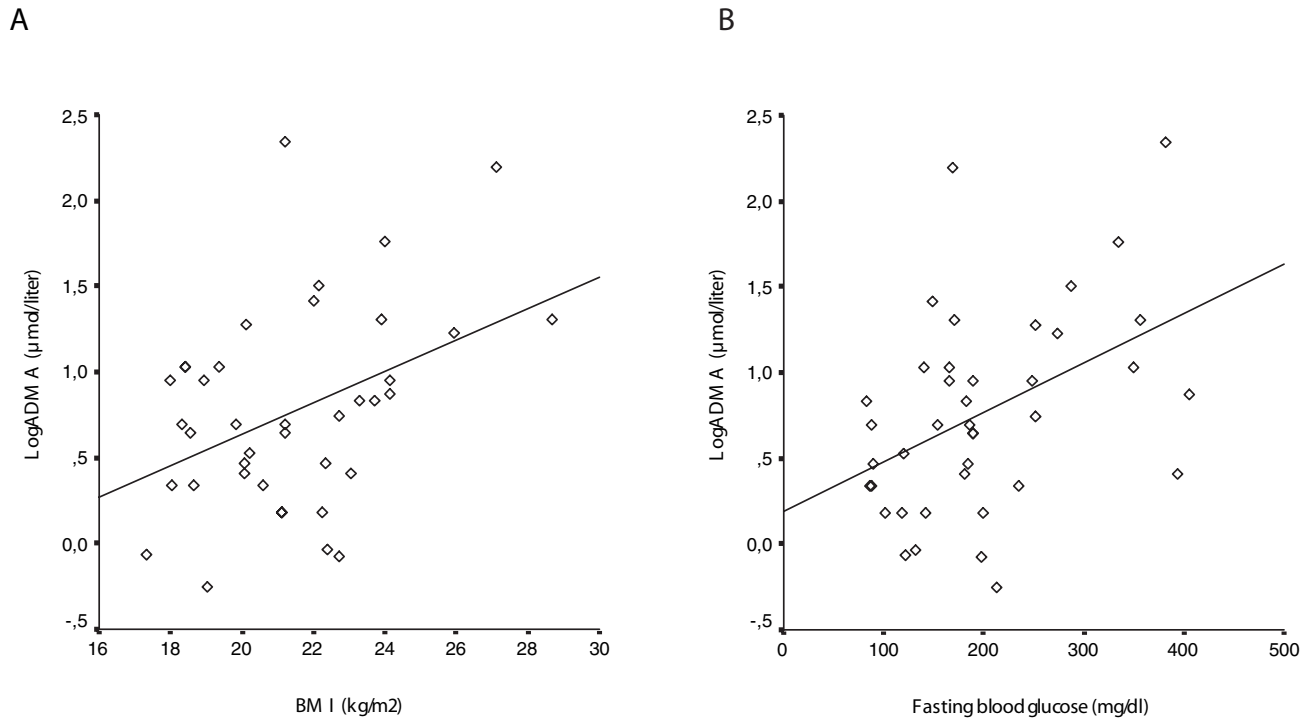


FIG. 1. Relations of logADMA to BMI (r = 0.43, $P = 0.01$) (A) and fasting blood glucose (r = 0.45, $P = 0.006$) (B) in diabetic patients.

Discussion

The major finding of the present study is that increased ADMA concentrations and decreased L-arginine to ADMA ratio are associated with uncomplicated type 1 DM. Also, ADMA level and L-arginine to ADMA ratio are strongly correlated with the metabolic parameters in type 1 diabetic patients. Data from recent studies have shown that the ratio between the concentration of L-arginine and that of ADMA modulates NOS activity and elevation of ADMA levels may cause relative L-arginine deficiency (4). Thus, our result that decreased levels of L-arginine as well as decreased levels of L-arginine to ADMA ratio found in diabetic group supports the elevation of ADMA levels in these patients. Most studies in literature have not evaluated these parameters together. Our finding that increased ADMA and decreased L-arginine to ADMA ratio in uncomplicated type 1 diabetic subjects is significant because endothelial dysfunction associated with increased ADMA concentrations seems to begin before the detectable vascular damage in type 1 diabetic patients. Additionally, type 1 diabetic patients had increased levels of ADMA leading to endothelial damage, even if hypertension or hyperlipidemia does not exist. Measurement of ADMA and L-arginine to ADMA as markers of endothelial dysfunction may provide an opportunity for the prevention of irreversible endothelial damage in these patients.

TABLE 3. Multivariate regression analysis of logarithmic ADMA levels in type 1 diabetic patients

Parameters	Beta	*P*
Age	−0.10	0.56
Gender	0.14	0.42
BMI	0.40	0.02
LDL-c	0.32	0.05
HDL-c	−0.31	0.07
HbA1c	−0.08	0.63
FBG	0.25	0.14

FBG, Fasting blood glucose.

With regard to the association between ADMA and type 1 DM, Tarnow *et al.* (19) reported that circulating ADMA levels were higher in type 1 diabetic patients with early diabetic nephropathy, and ADMA levels were negatively correlated with glomerular filtration rate. In another previous study (20), in 11 patients with type 1 diabetes, higher ADMA levels and unchanged L-arginine, L-arginine to ADMA ratio were determined before the exercise when compared with controls. In contrast to our study group, some of the diabetic patients had microvascular complications in that study. Mean plasma ADMA concentrations in our diabetic patients were 2.6 ± 1.9 μmol/liter. ADMA levels found in this study were higher than the levels found in the study by Tarnow *et al.* (0.46 ± 0.08 μmol/liter) (19) and the study by Mittermayer *et al.* (0.54 ± 0.02 μmol/liter) (20) but lower than those in the study by Yasuda *et al.* (4.8 ± 1.5 μmol/liter) (21). These studies included patients with either type 1 or type 2 DM, which might be the reason of this difference. Also, this discrepancy may be due to the different reference methods used in HPLC assay.

There are controversial data from the studies investigating ADMA levels in type 2 DM. Krzyzanowska *et al.* (22) reported increased ADMA concentration and its relation with macrovascular complications in type 2 DM. In contrast, Paiva *et al.* (23) showed decreased ADMA levels in type 2 diabetic patients. A high glomerular filtration rate and poor glycemic control were suggested to be responsible for the decrease in ADMA levels in these patients, but the mechanism related

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the decrease of ADMA levels could not been clearly defined in their study.

We observed as an interesting finding, that fasting blood glucose concentrations of diabetic patients were correlated with ADMA and L-arginine to ADMA ratio, in this study. Fasting blood glucose levels depend in part on the amount of insulin that the subjects receive as well as on the intake of food on the evening before the blood draw. It is possible that it is relative insulin deficiency and not elevated blood glucose levels that might explain the elevated ADMA levels. Therefore, we investigated whether ADMA levels and L-arginine to ADMA ratio correlate with insulin dose that the patients received and no relationship was found. In the present study, neither ADMA nor L-arginine to ADMA ratio were correlated with HbA1c, which shows long-term glycemic control. Inconsistent with our data, Tarnow *et al.* (19) reported no association between ADMA and HbA1c in type 1 diabetic patients. But they also found no relationship between ADMA and fasting blood glucose concentrations. A negative relationship between ADMA and HbA1c was reported in another previous study covering type 2 diabetic patients (23). Besides, Yasuda *et al.* (21) reported that intensive control of blood glucose levels led to a decrease in ADMA level in hospitalized patients with type 2 DM.

There are some explanations about the interaction between hyperglycemia and the L-arginine-NO system. Hyperglycemia-induced activation of protein kinase C, increased superoxide anion production from glucose autoxidation and accumulation of advanced glycation end product due to nonenzymatic cross-linking of proteins via oxidative stress can reduce the bioavailability of NO and activation of the polyol pathway, which increases the use of nicotinamide-adenine dinucleotide phosphate can reduce the biosynthesis of NO (8). However, the exact mechanism of how hyperglycemia influences circulating ADMA concentrations in DM is not fully known. One possible mechanism has been suggested in an animal study that hyperglycemia-induced oxidative stress increases ADMA by impairing the enzyme DDAH, which is involved in the metabolic degradation of ADMA (24). Furthermore, Sorrenti *et al.* (25) recently reported that exposure to high glucose in endothelial cells increases oxidative stress, reduces DDAH-2, and leads to a NOS imbalance. Although renal clearance is the first mechanism for the elimination of ADMA (11), enzymatic degradation of ADMA by DDAH has recently gained substantial importance. DDAH degrades ADMA to dimethylamine, and L-citrulline and DDAH activity is found in almost all tissues, especially in kidney and liver (26). One of the allelic isoforms of this enzyme, DDAH-2, is mainly present in vascular tissues that coexpress endothelial NOS (27). Another mechanism for the increase in ADMA concentrations in hyperglycemic media may be associated with the enzyme arginine methyltransferase, which synthesizes ADMA, because hyperglycemia-induced oxidative stress up-regulates the expression of arginine methyltransferases (28).

In our study, we have shown a strong positive relationship between ADMA levels and BMI in both univariate and multivariate analyses. Supporting our results, Eid *et al.* (29) also showed this kind of relationship between ADMA and BMI in an overweight elderly population. They also suggested that ADMA was correlated with BMI independent from several metabolic risk factors such as blood pressure, LDL-c, and HDL-c. Our finding about the association between ADMA and BMI indicates that BMI and gaining weight may have an importance for ADMA levels, even in type 1 diabetic patients.

To our knowledge, our study is also the first report that plasma concentrations of ADMA are related with both HDL-c and LDL-c in diabetes. Elevated concentrations of ADMA have been shown in patients with hypercholesterolemia (6). Enhancing of methyltransferase activity by LDL-c has been suggested to be a mechanism for the elevated ADMA levels in hypercholesterolemia (30). A previous *in vitro* study revealed that one of the components of oxidized LDL-c may increase the circulating ADMA concentrations via the reduction of DDAH activity in endothelial cells (31). Besides, in patients with acute myocardial infarction or unstable angina pectoris, plasma ADMA concentrations have been observed to be correlated significantly with HDL-c levels (32). However, other studies showed that ADMA levels were not associated with lipid parameters including HDL-c and LDL-c in patients with type 2 DM (22, 23). Furthermore, one study evaluating hypercholesterolemic men and patients with well-controlled type 1 DM with respect to the effect of hypolipidemic therapy on ADMA levels reported significant reduction in LDL-c levels but no change in the levels of ADMA after treatment (33).

We observed that our diabetic patients did not show a good glycemic control. Therefore, the limitation of the present study may be the lack of plasma ADMA and L-arginine to ADMA ratio after achieving a good control in these patients. Nevertheless, it is unlikely to be a major effect of tight blood glucose control on increased plasma ADMA concentrations because of the lack of a correlation between ADMA and HbA1c levels and similar ADMA levels between poorly and well-controlled diabetic patients in our study group.

In conclusion, in the present study, increased ADMA concentrations have been demonstrated in type 1 diabetic patients who do not suffer from diabetic vascular complications. Further studies would be required to clearly establish the utility of decreasing ADMA levels or normalizing the L-arginine to ADMA ratio in the treatment of type 1 diabetic patients.

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