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ORIGINAL ARTICLE – OPEN ACCESS

Relationship Between the Flow-Mediated Dilatation of the Human Brachial Artery and Blood Biomarkers Related to the Endothelial Function in Cardiovascular Diseases

Suzan Emel Usanmaz[1], İnci Aslı Atar[2], Ayşen Aksöyek[3], Muharrem Tola[4], Emre Kubat[5], Tuğba Kayhan Altuner[6], Hüseyin Bozbaş[6], Utkan Sevük[7], Mehmet Emin Korkmaz[6], Emine Demirel Yılmaz[1]

ABSTRACT

Objective: Endothelial dysfunction plays an important role in the development of heart diseases. Although several markers have been examined, a definitive biomarker for monitoring endothelial function has not yet been established. The flow-mediated dilatation (FMD) of the brachial artery enables non-invasive assessment of endothelial function. This study investigated plasma levels of nitric oxide (NO), asymmetric dimethylarginine (ADMA), total antioxidant capacity (TAC), and hydrogen sulfide (H_2S) as biomarkers of endothelial function. This study aimed to investigate any correlation between FMD and these blood biomarkers in patients with diabetes mellitus (DM), prediabetes (preDM), coronary artery disease (CAD), and valvular heart disease (VD).

Materials and Methods: Prospective evaluation was made within five groups of patients with preDM, DM, CAD, VD, and healthy controls. The FMD of the brachial artery was examined using Doppler imaging, and biomarker levels in plasma were measured by spectrophotometry.

Results: The FMD of the VD group was significantly higher than that of DM and CAD groups. Plasma NO levels of CAD and VD groups were significantly lower than those of the control group. ADMA levels were lower in the CAD group. TAC and H_2S levels were comparable in all groups. The FMD of the brachial artery was negatively correlated with plasma NO and cholesterol levels in all groups.

Conclusion: These results suggested that the correlation of FMD with blood biomarkers related to endothelial function was altered in cardiovascular diseases and would be affected by the patient's clinical state and treatment.

Keywords: Flow-mediated dilatation, endothelial function, nitric oxide, ADMA, cardiovascular diseases

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[1]Department of Medical Pharmacology, Ankara University Faculty of Medicine, Ankara, Turkey
[2]Department of Cardiology, Ministry of Health Ankara City Hospital, Ankara, Turkey
[3]Department of Cardiovascular Surgery, Ministry of Health Ankara City Hospital, Ankara, Turkey
[4]Department of Radiology, Ministry of Health Ankara City Hospital, Ankara, Turkey
[5]Department of Cardiovascular Surgery, Gülhane Training and Research Hospital, Ankara, Turkey
[6]Department of Cardiology, Güven Hospital, Ankara, Turkey
[7]Department of Cardiovascular Surgery, Dicle University Faculty of Medicine, Diyarbakır, Turkey

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Correspondence Suzan Emel Usanmaz, Ankara University Faculty of Medicine, Department of Medical Pharmacology, Ankara, Turkey
Phone: +90 312 595 82 60
e-mail: usanmaz@medicine.ankara.edu.tr

INTRODUCTION

Cardiovascular diseases are the number one cause of death worldwide. Their most common risk factors are diabetes mellitus (DM) and atherosclerosis, which are both characterized by impaired endothelial function of the vessels (1).

By secreting various vasoactive substances, vascular endothelium has the principal control of vascular function and structure (2). Of these vasoactive substances, nitric oxide (NO) plays a leading role in vascular tone regulation, platelet aggregation, and immune reactions in various physiological and pathological situations (3). Endothelial NO synthase (eNOS)-mediated NO release, in physiological conditions, is relatively low compared with the high amounts of NO generated by the inducible form of NO synthase (iNOS) in response to pathological stimulations.

Decreased bioavailability of NO, due to the inhibition of endothelium-derived NO synthesis and scavenging of NO by overproduction of superoxide anion, is related to endothelial dysfunction (3). The levels of antioxidant components of plasma are very important for the continuity of endothelial function, since reactive oxygen species (ROS) can damage cells. Therefore, the total antioxidant capacity (TAC) of plasma is critical for a durable endothelial function. In addition, endothelial dysfunction in cardiovascular events has been attributed to the increased plasma level of asymmetric dimethyl arginine (ADMA), an endogenous NOS inhibitor (3).

Hydrogen sulfide (H_2S) is an endogenous gaseous transmitter and has many biological effects, such as vasodilatation, antioxidation, anti-inflammation, metabolic modulation, and angiogenesis. Interactions with NO metabolism result in various physiological and pathological situations. H_2S can ameliorate endothelial dysfunction (4).

Endothelial function can be assessed reliably with the measurement of the flow-mediated dilatation (FMD) of the brachial artery, which a non-invasive ultrasonographic test (5). In individuals at risk of cardiovascular disease, the correlation of FMD and endothelial biomarkers may be useful for the determination of the pathological status of the disease and for monitoring of the progress of therapy or prevention.

Table 1. Demographic characteristics and clinical findings of the study population

	Control		preDM		DM		CAD		VD	
	n	%	n	%	n	%	n	%	n	%
Number of groups	23		25		49		31		21	
Male	11	47.8	5	20	12	24.5	22	71	6	28.6
Female	12	52.2	20	80	37	75.5	9	29	15	71.4
Smoking	6	26.1	7	28	7	14.3	16	51.6	3	14.3
Hypertension	12	52.2	16	64	37	75.5	18	58.1	4	19
Drugs										
Aspirin	1	4.3	3	12	5	10.2	13	41.9	3	14.3
Beta-blockers	2	8.7	5	20	9	18.4	25	80.6	12	57.1
CCB	3	13	1	4	3	6.1	1	3.2	1	4.8
ACEI	2	8.7	1	4	5	10.2	12	38.7	4	19
ARB	2	8.7	7	28	17	34.7	4	12.9	3	14.3
Statin	3	13	2	8	7	14.3	19	61.3	3	14.3

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CAD: Coronary artery disease; CCB: Calcium channel blockers; DM: Diabetes mellitus; preDM: Prediabetes mellitus; VD: Valvular disease

This study explored the correlation of the FMD of the brachial artery with the plasma levels of NO, ADMA, TAC, and H_2S, as biomarkers of endothelial functions, in patients with prediabetes (preDM), DM, coronary artery disease (CAD), valvular heart disease (VD), and healthy individuals.

MATERIALS and METHODS

Study Design

This prospective study was carried out according to the ethical guidelines of the Declaration of Helsinki. Informed consent was obtained from all participants, and the study protocol was approved by the Ethics Committee of Türkiye Yüksek İhtisas Teaching and Research Hospital, Ankara, Turkey (26.12.2008/217).

This study enrolled a total of 149 patients, which were evaluated in the cardiology and cardiovascular surgery outpatient clinics, either with preDM, DM, CAD, and VD. These patients were divided into four patient groups and a control group. The control group (n=23) was composed of patients who presented to the cardiology outpatient clinic, whose coronary artery findings were normal on conventional or computed tomography coronary angiography and fasting plasma glucose (FPG) levels were normal (100 mg/dl). Coronary arteries with no lesions were defined as normal. Patients with DM and preDM were diagnosed according to the criteria of American Diabetes Association (6). In each participant, blood glucose level was measured in the morning, after fasting for 8 h. Patients with FPG level of 126 mg/dl or patients on antidiabetic therapy constituted the DM group (n=49). Patients with FPG levels between 100 and 125 mg/dl and plasma glucose level between 140 and 199 mg/dl 2 h after a 75-g oral glucose challenge comprised the preDM group (n=25). Prior to the study, none of the patients of the DM and preDM groups had CAD, atrial fibrillation, mitral or aortic stenosis, mild mitral or aortic regurgitation, hypertrophic cardiomyopathy, uncontrolled hypertension, hepatic or renal dysfunction, asthma, rheumatological disease, or malignancy. The CAD group (n=31) was composed of patients with >70% diameter narrowing of at least one vessel, and the diameter of the nearest normally appearing region was used as the reference. Coronary artery stenosis was measured quantitatively by an interventional cardiologist and cardiovascular surgeon, using a hand-held electronic caliper. All the aforementioned exclusion criteria for the control, DM, and preDM groups also applied to the CAD group. The VD group (n=21) was composed of patients who underwent surgery for either aortic or mitral valve disease and had the same exclusion criteria, except for the presence of VD requiring open-heart surgery. Twelve patients who had predominant mitral valve disease (stenosis, n=7; regurgitation, n=5), four patients with aortic valve disease (regurgitation, n=3; stenosis, n=2), and four patients who had regurgitation of both leaflets underwent double valve replacement. Tricuspid valve regurgitation was accompanied with lesions in seven patients. Patients receiving antihypertensive therapy or having a systolic/diastolic blood pressure ≥140/90 mmHg were considered hypertensive.

Measurement of FMD

Patients abstained from smoking and taking food or beverages containing caffeine for at least 24 h before the study. Vasoactive medications were discontinued 12 h before FMD measurement, which was performed in the morning after 8 h of fasting (7). The study was performed in a quiet, temperature-controlled room by an investigator experienced in vascular ultrasonography using Acuson CV70 Mountain View (CA, USA) and Logic 7 system (GE Healthcare, Tokyo, Japan) ultrasound systems with 7-MHz linear array transducers. For imaging of the brachial artery, the participant was positioned supine with the arm in a comfortable position. The brachial artery was visualized above the antecubital fossa. A sphygmomanometer cuff was placed in the upper arm, above the antecubital fossa. Before the flow measurement, a baseline image was acquired. Then, the cuff was inflated to 250 mmHg or at least

50 mmHg above the systolic pressure to cease blood flow and create arterial occlusion. After 5 min, the cuff was deflated, and the longitudinal image of the artery was recorded continuously for 5 min after cuff deflation. A pulsed Doppler signal was obtained from the mid-arterial segment immediately after cuff release and then every minute; the highest flow-hyperemic response velocity was then assessed and recorded. On the release of the cuff, an increase in flow or shear stress occurs, followed by dilatation of the vessel, in which the principal mediator is NO. Thus, the FMD of the vessel depends on the NO-secreting capacity of the endothelium. FMD was calculated using the following formula:

FMD (%)=[(peak diameter−baseline diameter)/baseline diameter)] ×100

Measurements of Biomarkers

As an indicator of NO production, plasma nitrite levels were measured. For the measurement of nitrite level, a Griess reaction-based spectrophotometric method was employed (8). In our laboratories, we modified the method for 96-well plates. TAC levels were measured by spectrophotometry (9). In this method, Cu^{+2} was reduced to Cu^{+} by the antioxidants of the plasma, and the resultant color was measured at 455 nm. H_2S levels were measured at 670 nm by spectrophotometry (10). This method was modified for 96-well plates in our laboratories. Plasma ADMA levels were measured with a commercially available enzyme-linked immunosorbent assay kit (Immunodiagnostic A.G., Germany).

Statistical Analysis

All statistical analyses were evaluated using Sigmaplot version 11 for Windows (Systat Software Inc., USA). The suitability of data to a normal distribution was evaluated using the Shapiro–Wilk test. One-way analysis of variance test was used to identify differences among five groups for normally distributed variables, and values were expressed as mean±standard deviation. Kruskal–Wallis test was used for variables without normal distribution, and values were expressed as median (25%–75%). At a level of $p<0.05$, values were accepted as statistically significant. When the p value was statistically significant, post-hoc Dunn's multiple comparison tests were used to identify significant pairs. Pearson product moment was used to test correlations. To eliminate the possible effect of age, body mass index (BMI), waist-to-hip ratio, systolic and diastolic blood pressures, and FPG on the comparison of groups in terms of FMD, analysis of covariance was performed for each variable separately.

RESULTS

Demographic and some clinical properties of the groups are shown in Table 1. In addition, clinical and laboratory findings are shown in Table 2. The mean age of the DM group was higher than that of the control group ($p<0.001$). The median BMI of the VD group was significantly lower than that of the control group ($p<0.005$). The CAD group had the highest waist-to-hip ratio among the groups ($p<0.001$). While both systolic and diastolic blood pressures of the DM group were the highest among the groups, the VD group had the lowest blood pressure levels ($p<0.001$). The FPG levels of preDM, DM, and CAD groups were significantly different from those of the control group ($p<0.001$).

Table 2. Clinical and laboratory findings of the study population

	Control	preDM	DM	CAD	VD	P
Age	48.87±9.56	53.04±9.18	58.59±8.60*	53.16±7.86	49.71±6.59	0.001
BMI	29.32 (24.16–36.49)	28.98 (26.78–33.02)	30.01 (27.63–32.90)	28.39 (25.66–32.42)	25.51 (22.47–29.94)*	0.005
Waist (cm)	104.17±14.17	99.92±17.77	103.07±9.77	98.55±9.31	86.14±10.24*	0.001
Hip (cm)	116.07±15.34	118.04 ±15.86	117.46±11.54	100.74±9.68*	95.23±9.60*	0.001
Waist-to-hip ratio	0.92 (0.85–0.95)	0.84 (0.81–0.89)	0.88 (0.84–0.91)	1.00 (0.93–1.01)*	0.90 (0.86–0.94)	0.001
Systolic BP	125.00 (110.00–136.25)	127.50 (120.00–138.75)	140.00 (130.00–152.50)*	125.00 (120.00–130.00)	110.00 (110.00–120.00)*	0.001
Diastolic BP	77.27±7.19	80.00±9.21	84.89±7.11*	82.42±5.90*	63.81±9.86*	0.001
FPG (mg/dl)	92.00 (88.25–96.25)	104.00 (100.00–109.00)*	136.00 (109.50–203.00)*	99.00 (92.00–114.00)*	99.00 (91.00–111.50)	0.001
Uric acid (mg/dl)	5.50 (4.25–7.20)	5.50 (3.95–6.20)	4.65 (3.90–5.78)	5.00 (4.25–5.88)	5.60 (4.30–6.75)	0.621

BMI: Body mass index; BP: Blood pressure in mmHg; FPG: Fasting plasma glucose level; *: Significantly different than the control group. Values are mean±standard deviation or median (25%–75%)

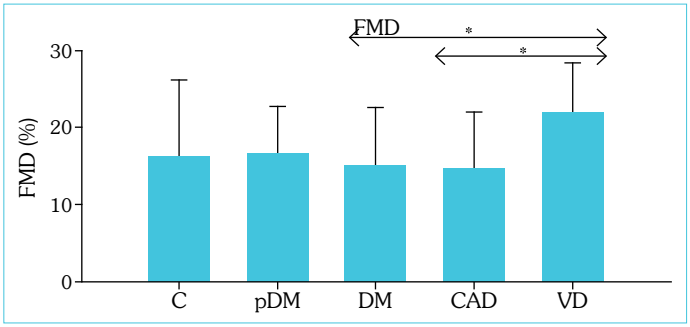

Figure 1. Flow-mediated dilatation (FMD) of the patient population. FMD differed significantly among the groups. In the valvular disease (VD) group, FMD was the highest and significantly different from that of the coronary artery disease (CAD) and diabetes mellitus (DM) groups (p<0.05) (*). Values were expressed as mean±SD

The highest FMD occurred in the VD group, while the lowest FMD was observed in the CAD group. The FMD of the DM and CAD groups were significantly lower than that of the VD group (p<0.05) (Fig. 1). Analysis of covariance was performed to examine the possible effect of different variables (Table 2) on FMD. Age, BMI, waist-to-hip ratio, systolic/diastolic blood pressures, and FPG did not demonstrate significant effects on the comparison of groups in terms of the FMD.

Plasma NO levels were significantly lower in CAD and VD groups than in the control group (p<0.001) (Fig. 2). Plasma ADMA levels were significantly lower in the CAD group than in the control group (p<0.001) (Fig. 2). Plasma TAC levels of the groups were significantly different (p<0.013), but the plasma TAC levels of any group were not different from that of the control group. Only TAC level of the VD group was significantly higher than that of the DM group. Plasma H_2S levels were comparable in all groups.

The correlation of the FMD with plasma biomarkers is shown in Figure 3. Only the plasma NO levels were significantly, but negatively, associated with the FMD of the brachial artery (p<0.0127).

The lipid profiles of the patients are shown in Figure 4. The levels of high-density lipoprotein (HDL) of the CAD group were significantly different from those of the preDM, DM, and VD groups (p<0.002).

The correlation of FMD with plasma lipids is shown in Figure 5. The FMD of the brachial artery was significantly, but negatively, associated with blood levels of the total cholesterol (p<0.0209).

DISCUSSION

The results of this study suggest that endothelium-dependent relaxation of vessels and blood levels of biomarkers related to endothelial function were affected differently in various cardiovascular diseases. In addition, a negative correlation was observed between the FMD of the brachial artery and blood levels of NO and cholesterol.

Substantial evidence suggests that endothelial dysfunction is the cause/result of cardiovascular diseases (11). The FMD of the brachial artery is widely used for non-invasive determination of the functional integrity of the endothelium (5). In this study, the FMD of the brachial artery was explored in two different cardiovascular

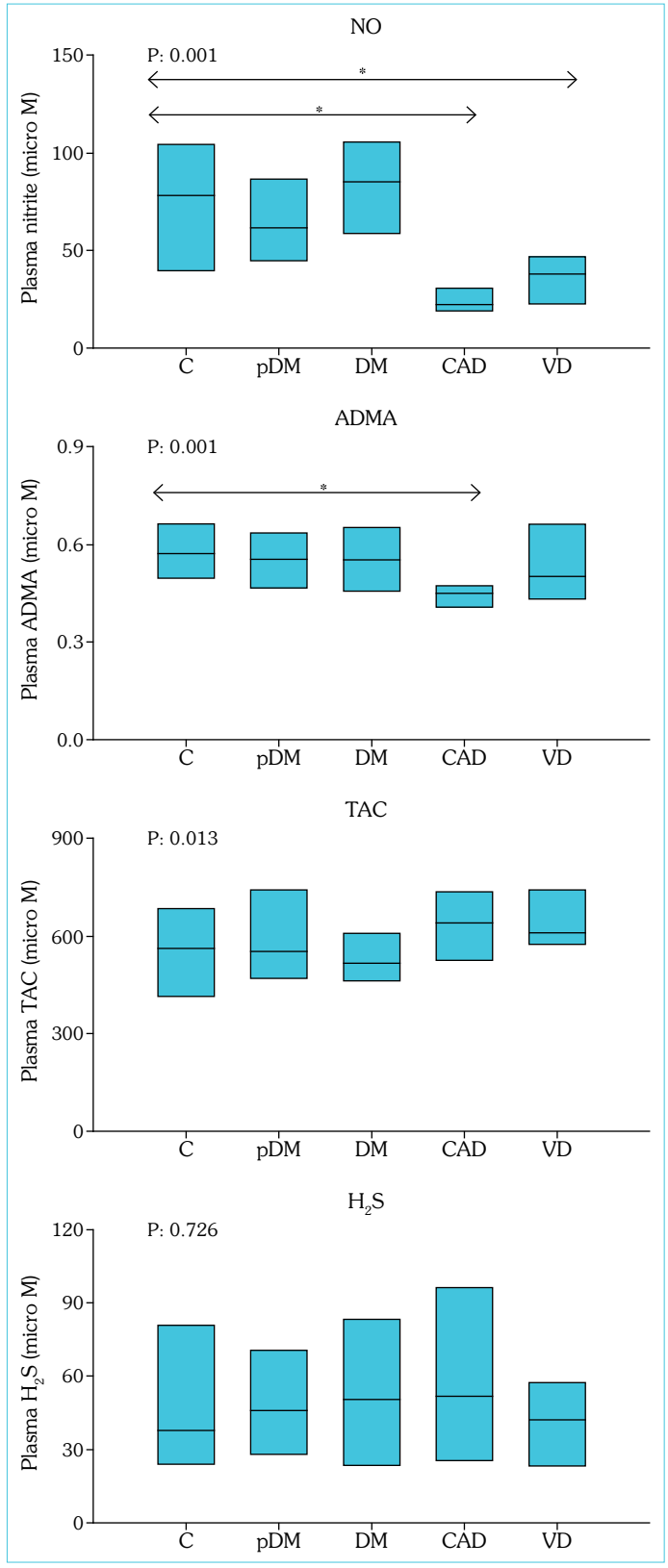

Figure 2. Plasma NO, ADMA, TAC, and H2S levels in the patient population. Plasma levels of NO and ADMA in some groups differ significantly from those of the control group (p<0.05) (*). Values were expressed as median (25%–75%)

NO: Nitric oxide; ADMA: Asymmetric dimethylarginine; TAC: Total antioxidant capacity; H_2S: Hydrogen sulfide

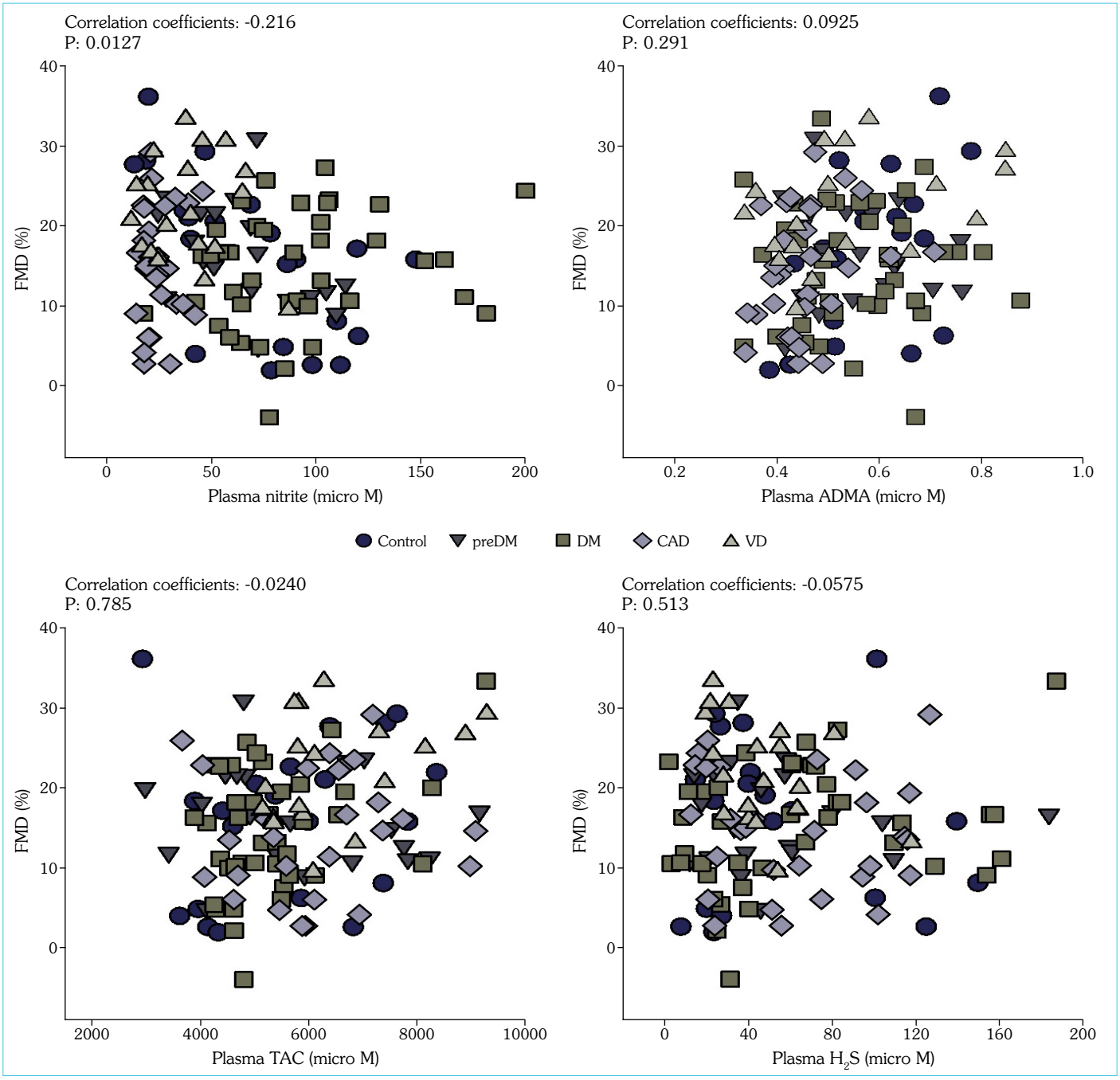

Figure 3. Correlation of endothelium-related biomarkers with flow-mediated dilatation (FMD). Only plasma nitric oxide levels were significantly correlated with FMD in all study population ($p<0.05$)

diseases (CAD and VD) and two stages of metabolic diseases (DM and preDM) as risk factors for cardiovascular disease. In this study, the highest FMD was measured in the VD group, the lowest FMD of the brachial artery was observed in CAD and DM groups, and the results were consistent with those of other previously published studies, regarding patients with CAD and DM (12, 13).

The endothelial dysfunction in cardiovascular diseases was caused by the interrupted release of endothelial substances (1). Endothelium-derived potent bioactive substances regulate the activity of vascular smooth muscle cells and blood cells (2). The bioavailability of the endothelium-derived NO reflects the functional integrity of the endothelium. The relaxation of the vascular smooth muscles and the inhibition of platelet aggregation are regulated by endothelium-derived NO under physiological conditions. However, large amounts of NO released from inflammatory cells may cause nitrosative stress under pathological conditions (14). Alterations in FMD and blood NO levels have been examined in patients with CAD (15, 16) and DM (17). Schumm et al. (18) found a positive correlation between peak aortic jet velocity and FMD in patients with aortic stenosis. Although circulating NO levels were not evaluated, they have discussed that NO released from red blood cells due to turbulent post-stenotic blood flow may account for the higher FMD observed

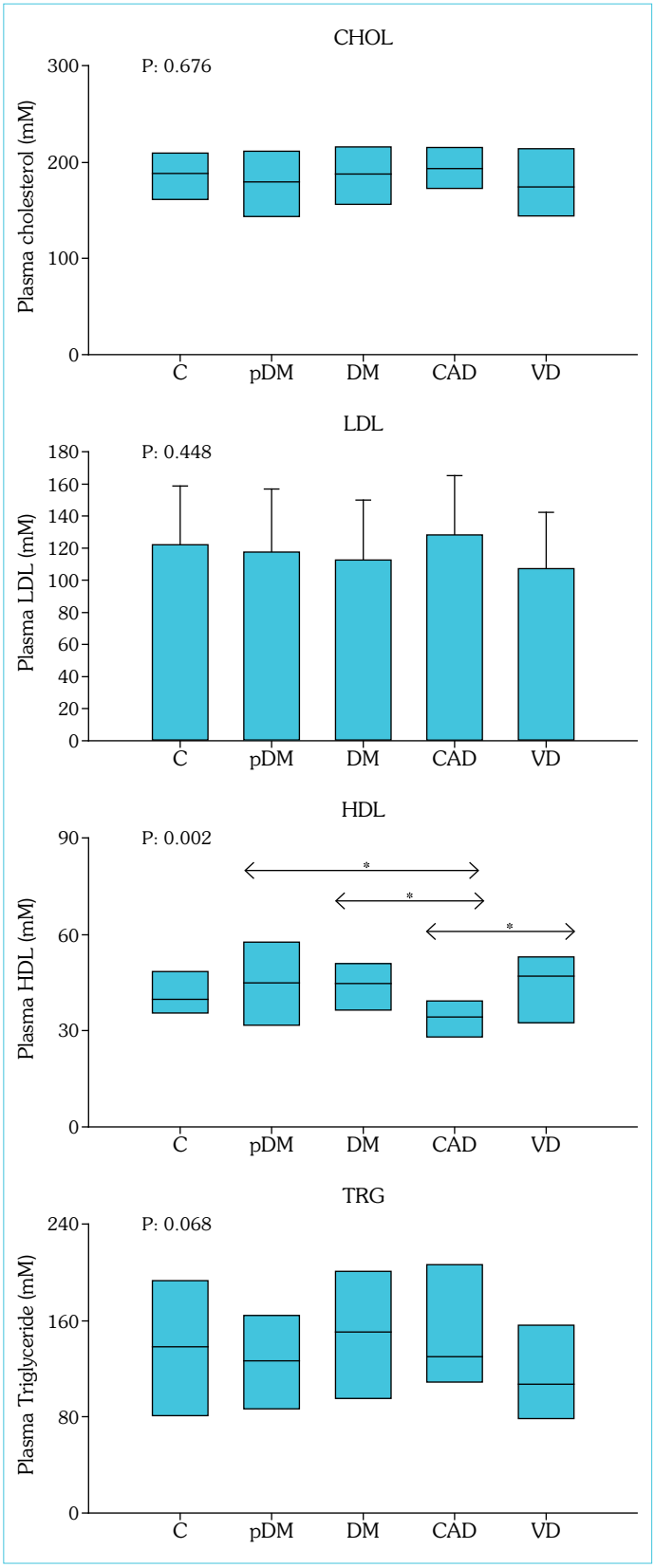

Figure 4. Blood cholesterol, LDL, HDL, and triglyceride levels in the patient population. Plasma levels of HDL were significantly different among the groups ($p<0.05$) (*). Values were expressed as mean±SD or median (25%–75%)

HDL: High-density lipoprotein; LDL: low-density lipoprotein

in their patients. Another study reported that VD was associated with higher levels of circulating microparticles, decreased NO production, and increased superoxide anion generation by uncoupling eNOS (19). However, the correlation of plasma NO levels with FMD of the artery has not been explored in different cardiovascular diseases. The present study showed that the plasma NO levels in CAD and VD groups were significantly lower than those of the control group. In addition, the plasma NO levels of the whole study population was negatively correlated with the FMD of the brachial artery. Thus, low plasma levels of NO under physiological conditions would correspond to the functional integrity of the vessel, and increased levels of NO under pathological conditions are associated with the failure of the endothelium-dependent arterial dilatation.

On the contrary, competitive inhibition of NO synthase by endogenous ADMA has been related to endothelial dysfunction in cardiovascular diseases. An increased blood level of ADMA in CAD and DM has been reported (20). In the present study, ADMA levels were not increased in any patient groups; moreover, in the CAD group, ADMA levels were significantly lower than those of the control group. This discrepancy can be attributed to the heterogeneity of the groups with respect to medications. A study reported that some drugs such as angiotensin-converting enzyme inhibitors, statins, and beta-blockers caused a decrease in ADMA levels in the circulation (21). In the present study, the lower ADMA level in the CAD group can be explained by the high percent usage of these drugs. The CAD group also had the highest waist-to-hip ratio and lowest FMD and NO and HDL blood levels. The blood ADMA levels of the whole study population were not correlated with the FMD of the brachial artery. Further studies in more homogeneous subgroups are needed for better understanding of the relationship of ADMA and FMD.

Increased ROS-induced oxidative stress in the vasculature is a major contributor to endothelial dysfunction in cardiovascular diseases (3). Oxidative stress may cause a reduction in NO bioavailability, because of the scavenging of NO by overproduced superoxide anion and decreasing NO synthesis or release from endothelium. In addition, oxidative stress promotes atherogenesis due to the activation of transcription factors and induction of protein oxidation, lipid peroxidation, and DNA damage. TAC levels represent the redox state of the medium. Although the plasma TAC levels of the groups were significantly different in the present study, none of the values in the patient groups were not different from those of the control group. Only the plasma TAC levels of the DM group were lower than those of the VD group. A negative correlation between FMD and oxidative stress had been reported in DM and preDM in a previous study (22). However, the plasma TAC levels of the present study were not correlated with the FMD of the brachial artery. This discrepancy is probably due to the selection of different biomarkers. The characterization of oxidative stress can be quite difficult in some situations, and a biomarker may not necessarily be better than others (23). In addition, it is unclear whether a plasma redox status would represent cellular oxidative stress. The vast diversity of oxidative stress, between diseases and conditions, should be considered. Further studies are needed to identify the exact mechanisms of the tissue oxidative stress and plasma redox status in cardiovascular diseases.

H_2S is a new gaseous mediator crucial in various physiological functions (4). Decreased bioavailability of H_2S is associated with endothelial dysfunction. Increased plasma H_2S levels in patients

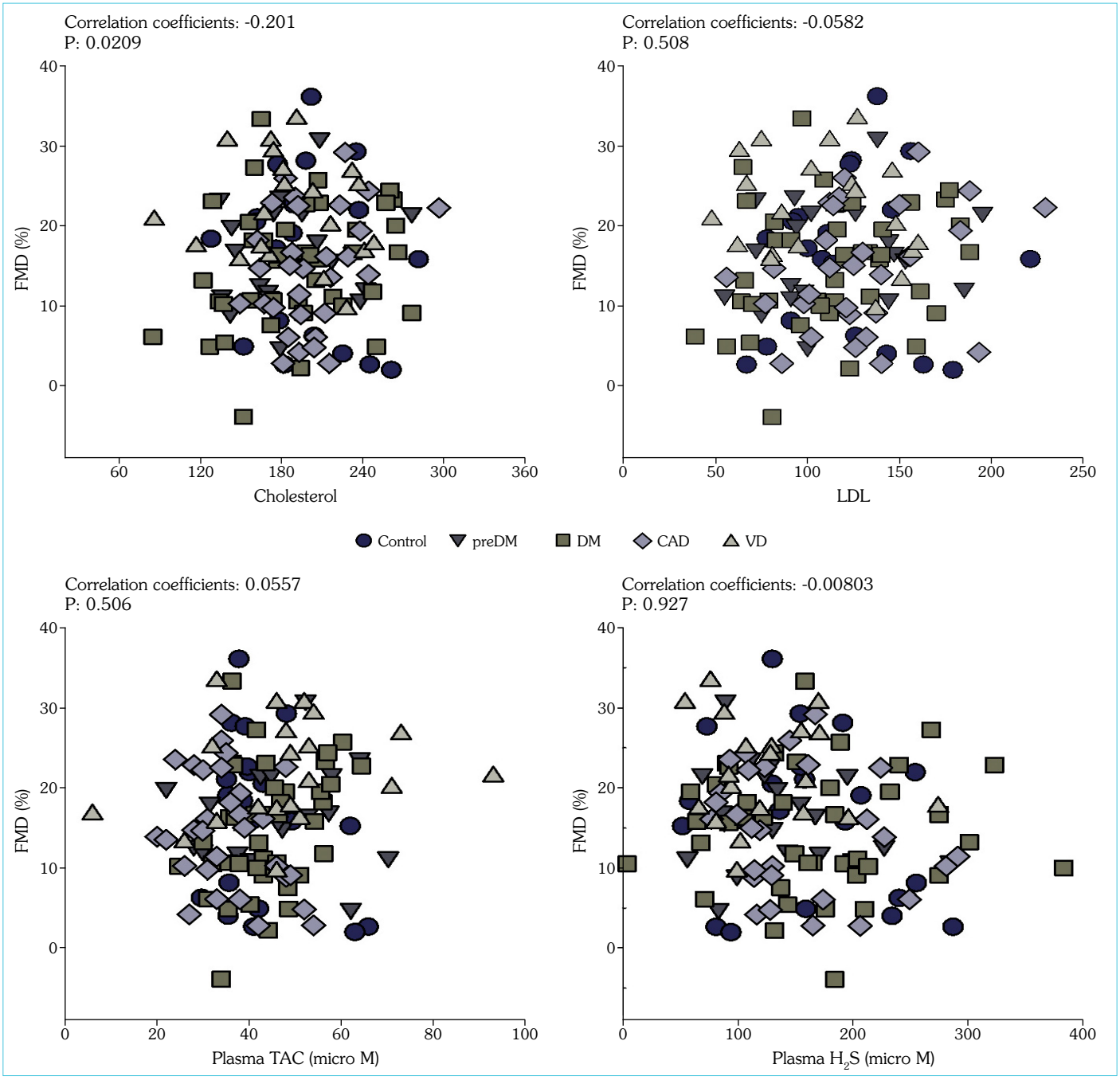

Figure 5. Correlation of blood biochemicals with flow-mediated dilatation (FMD). Only blood cholesterol levels significantly correlated with FMD in all study population (p<0.05)

with CAD (24) and decreased/increased H_2S levels in patients with DM (25) have been reported. In the present study, the plasma H_2S levels in all groups were not different. It is difficult to compare these data to other studies, because of differences in experimental methods and disease states. Further studies are needed to analyze blood H_2S levels using similar methods and standardized subgroups of patients. To the best of our knowledge, the present study is the first to demonstrate that plasma H_2S levels were not correlated with FMD in different cardiovascular diseases.

In cardiovascular diseases, for the diagnosis of the disease severity, monitoring disease course, and evaluation of therapeutic approaches, various biomarkers have been evaluated. However, a specific biomarker to assess the functional state of the endothelium in the cardiovascular diseases is not yet established.

CONCLUSION

The results of this study indicated that the FMD of the brachial artery correlates negatively with plasma levels of NO and cholesterol. These findings may contribute for the consideration of the predictive, preventive, diagnostic, or therapeutic approaches in cardiovascular diseases.

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Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Türkiye Yüksek İhtisas Teaching and Research Hospital, Ankara, Turkey (26.12.2008/217).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – AA, EDY, MEK; Design – AA, EDY, MEK; Supervision – EDY, AA, MEK; Resource – SEU, İAT, AA, MT, EK, TKA, HB, US, MEK, EDY; Materials – IAA, AA, MT, EK, TKA, HB, US, MEK; Data Collection and/or Processing – SEU, İAT, AA, MT, EK, TKA, HB, US, MEK, EDY; Analysis and/or Interpretation – SEU, İAT, AA, MT, EK, TKA, HB, US, MEK, EDY; Literature Search – SEU, EDY, AA; Writing – EDY, AA, SEU; Critical Reviews – SEU, İAT, AA, MT, EK, TKA, HB, US, MEK, EDY.

Conflict of Interest: The authors have no conflict of interest to declare.

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