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Original Article

Association between Newly Diagnosed Essential Hypertension, Smoking, Assymetric Dimethylarginine and ischemia-Modified Albumin

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Abstract

Objective: This study aimed to investigate the relationship between increasing levels of assymetric dimethylarginine (ADMA)and ischemia-modified albumin (IMA) in people with early diagnosis of hypertension (HT) and smoking history.

Methods: The study included 95 outpatients who visited our hospital. Patients were classified into three groups: group 1, healthy and non-smokers (n=25); group 2, no smoker patients with newly diagnosed essential HT with LVH (left ventricle hypertrophia) (n=35); group 3, smoking patients with a LVH accompanying newly diagnosed essential HT (n=35). 51% of patients are females; 49% of them are males.The trial was approved by the local ethics committee. Blood samples were analyzed, which were taken after 8 h of fasting. Biochemical parameters such as, C reactive protein (CRP), ADMA, IMA values were recorded. Using echocardiography, cardiac values were recorded.

Results: In this study, the first group consisted of 25 patients and second and third group of 35 patients. There were 49 females and 46 males; 70 patients were hypertensive and 6 diabetic. Comparing groups 1 and 2, a significant increase in ADMA was found in group 2. A significant difference was available regarding red cell distribution widht(RDW) and neutrophil lymphocyte ratio (N/L) ratio. Both parameters have increased. Significant differences were found between groups 2 and 3 in terms of ADMA, arginine, albumin, and WBC. While ADMA, white blood cell(WBC), and albumin increased and arginine decreases in group 3.

Conclusion: There is an association between ADMA level, smoking, and HT. Patients with HT and smoking history showed increased ADMA level compared with normal. Hypertension and smoking are the causes of increased ADMA, but decreased NO level.

Keywords: Hypertension, assymetric dimethylarginine, smoking

Introduction

Essential hypertension (HT) is one of the major reasons for admission to hospitals worldwide; it is a preventable and curable disease. In case of long-term exposure, clinical pictures such as renal failure, heart failure, and blindness can occur (1).

Because the endothelium is a vascular layer that has very important roles in the maintenance of normal vascular functions, its dysfunction leads to many diseases of the cardiovascular system. One of the important molecules that regulate endothelial functions is nitric oxide (NO). NO deficiency can cause endothelial dysfunction and many diseases, particularly cardiovascular disease (2). Asymmetric dimethylarginine (ADMA) is an endogenous NO synthase (NOS) inhibitor. It inhibits local NO synthesis and causes endothelial dysfunction. It is considered as a risk factor for the development of coronary artery disease and essential HT (3).

Ischemia-modified albumin (IMA) is a molecule that emerges due to a series of structural changes in the amino-terminal end binding metals in serum albumin (4). Its level increases due to oxidative stress, and one of the reasons for this increase is acute coronary syndrome (5).

Smoking triggers many inflammatory disorders, particularly pulmonary diseases characterized by a progressive restriction in the airways. Although this process has not been clearly explained yet, it affects the extrapulmonary system (6).

This study aimed to investigate the relationship between oxidative stress and increasing ADMA and IMA levels in patients with newly diagnosed HT and a history of smoking.

Methods

This study included 95 consecutive patients who presented to the outpatient clinic for any reason. The patients were divided into three groups: those who were healthy and non-smokers (Group 1, n=25), those who had left ventricular hypertrophy (LVH) accompanying newly diagnosed HT and were smokers (Group 2, n=35), and those who had LVH accompanying newly diagnosed HT

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and were smokers (Group 3, n=35). Among the patients, 49 were females (51%) and 46 were males (49%).

The exclusion criteria were a history of chronic or acute heart failure, kidney or liver failure, coronary artery disease, severe valvular heart disease, and malignancy. Ethical approval for the study was received from the local ethics committee. Written informed consent was obtained from the patients after informing them about the study.

Blood samples were taken from the patients after 8 h of fasting. From the samples, the levels of glucose, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides were measured with a colorimetric assay (BS-2000, Mindray, Shenzhen, China), the levels of C-reactive protein were measured with the nephelometric method (Immage 800 Rate Nephelometer, Beckman Coulter Inc. Brea, CA, USA), and the level of IMA was measured with the spectrophotometric albumin cobalt-binding assay (Bar-Or D. 2000). The albumin cobalt binding assay is a method that measures the decrease in the albumin cobalt binding capacity and indirectly detects IMA. When a certain amount of cobalt ions is added to a patient's serum sample, it is held by albumin at normal rate of albumin and it is released at the rate of IMA in blood. Unbound cobalt was colored with dithiothreitol and identified spectrophotometrically (Sigma Aldrich, Missouri, USA). In this method, because the amount of unbound cobalt decreases in patients with high levels of albumin, IMA levels are measured as low. Therefore, for preventing changes in the levels of albumin to affect the levels of IMA, the albumin-adjusted IMA index (albumin level×23+IMA level−100) was calculated.

ADMA, symmetric dimethylarginine (SDMA), and L-arginine levels were measured with the HPLC system (LC-20AT, Shimadzu, Kyoto, Japan), and the complete blood count was determined (Coulter LH 780, Beckman Coulter Inc. Brea, CA, USA).

In all patients, the left and right cardiac cavity diameters, wall thickness, valve insufficiency degree, ejection fraction, and systolic pulmonary artery pressure were evaluated using a Vivid 3 echocardiography device (Vivid-3, General Electric, Milwaukee, Wisconsin, USA) and a 2.5 MHz transducer and were recorded.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences 20.0 for Windows (Armonk, New York, USA). Descriptive statistical methods (mean and standard deviation) were used for evaluating data. Student's t-test, non-parametric tests, Mann–Whitney U test, and Wilcoxon test were used.

Results

Among the patients admitted to the outpatient clinic, 25 were included in the normal group, 35 in the group with LVH accompanying newly diagnosed HT, and 35 in the group with LVH accompanying newly diagnosed HT and a history of smoking. Forty-nine were females and 46 were males. Seventy patients were hypertensive and 6 were diabetic. Other findings are summarized in Table 1.

A significant difference was found between Group 2 and Group 3 in terms of ADMA, arginine, and albumin levels and white blood

Table 1. Parametric values among all patients and groups

Characteristic	All patients	Group 1	Group 2	Group 3
Age (years)	57.02±12.489	51.04±10.753	60.41±12.371	58.09±12.874
Total cholesterol (mg/dL)	194.957±44.320	198.64±36.541	191.74±37.761	196.45±55.223
LDL (mg/dL)	115.598±32.01	117.24±34.268	118.38±28.911	112.45±34.249
HDL (mg/dL)	44.147±12.753	51.04±15.073	42.571±10.74	40.80±11.171
Triglyceride (mg/dL)	175.978±141.308	157.08±86.103	162.97±101.399	209.21±200.254
Fasting blood glucose (mg/dL)	113.357±57.115	92.04±7.61	109.571±28.84	132.371±86.16
Sodium(mmol/L)	140.0.31±2.58	140.08±2.197	140.82±2.779	139.03±2.338
Potassium(mmol/L)	4.20±0.354	4.148±0.250	4.181±0.411	4.252±0.334
Platelet count	257.684±67.071	266.84±50.084	260.44±71.101	245.09±72.766
MPV (fl)	9.034±1.72	9.868±0.988	9.009±1.361	8.443±1.104
IMA absorbance	339.66±79.998	332.48±71.319	334±75.571	350.46±90.559
IMA index	342.856±78.388	335.824±70.63	338.1±72.577	356.910±89.25104
ADMA	0.464±0.316	0.367±0.101	0.434±0.70	0.5464±0.315
SDMA	0.336±0.162	0.233±0.154	0.134±0.0907	0.647±0.275
Arginine	56.72±50.05	64.08±16.965	57.09±18.273	51.09±22.41
CRP(mg/dL)	0.460±0.290	0.403±0.228	0.509±0.364	0.452±0.242
Albumin (mg/dL)	4.47±0.332	4.462±0.256	4.48±0.260	4.516±0.412
White blood cell count (103/mL)	7.746±1.728	7.544±1.463	7.320±1.95	8.317±1.540
RDW(fl)	14.254	13.428±1.158	14.906±2.492	14.191±0.822
Neutrophil/lymphocyte ratio (N/L)	2.535±1.552	1.833±0.759	2.866±1.132	2.704±2.113

LDL: low-density lipoprotein; HDL: high-density lipoprotein; MPV: mean platelet volume; IMA: ischemia-modified albumin; ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; CRP: C-reactive protein; RDW: reticulocyte distribution width

Table 2. Comparison between Group 2 and Group 3

	ADMA	SDMA	Arginine	White blood cell count	Albumin	RDW	N/L
p	0.03	0.154	0.027	0.017	0.027	0.769	0.043

ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; RDW: reticulocyte distribution width; N/L: neutrophil/lymphocyte ratio
The P-value was determined using Student's t-test

Table 3. Comparison between Group 1 and Group 2

	SDMA	MPV	ADMA	Arginine	RDW	N/L
P	0.019	0.003	0.042	0.069	0.006	0.000

ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; RDW: reticulocyte distribution width; N/L: neutrophil/lymphocyte ratio; MPV: mean platelet volume
The P-value was determined using Student's t-test

Table 4. Comparison between Group 1 and Group 3

	MPV	HDL	ADMA	Arginine	SDMA	RDW	N/L
p	0.000	0.002	0.002	0.027	0.244	0.000	0.089

ADMA: asymmetric dimethylarginine; SDMA: symmetric dimethylarginine; RDW: reticulocyte distribution width; N/L: neutrophil/lymphocyte ratio; MPV: mean platelet volume
The P-value was determined using Student's t-test

cell count (P=0.03, 0.27, 0.027, and 0.017, respectively). In Group 3, while ADMA levels, white blood cell count, and albumin level increased, arginine levels decreased. While there was no statistically significant difference between two groups in terms of the reticulocyte distribution width (RDW), a significant difference was detected in terms of the neutrophil/lymphocyte (N/L) ratio (P=0.043). The N/L ratio increased in Group 3 (Table 2).

In the comparison between Group 1 and Group 2, the mean platelet volume (MPV) and SDMA levels were lower in Group 2 than in Group 1. A significant increase in ADMA levels was found in Group 2. Arginine levels were found to be near the significance value. Further, there was a significant difference in terms of the RDW and N/L ratio (P=0.006 and 0.00, respectively). In Group 2, an increase was observed in both parameters (Table 3).

In the comparison between Group 1 and Group 3, while the MPV and HDL and arginine levels showed a tendency to decrease, ADMA levels increased. Moreover, there was a statistically significant difference in terms of the RDW (P=0.000). An increase in the RDW was observed (Table 4).

Discussion

NO is an endogenous molecule that is secreted by the endothelium and exerts some effects such as vasodilation, decreased vascular resistance, and increased blood flow; it is synthesized by NOS. ADMA is an NO metabolite, and it inhibits NOS (7). This inhibition of ADMA causes hemodynamic changes (8).

In addition to the fact that platelet activation and aggregation are important parameters in the pathophysiology of atherosclerosis (9, 10), platelet function was found to be important for cardiovascular morbidity and mortality in hypertensive patients (11). Some studies have shown that antihypertensive therapy decreased the impairment of platelet function in hypertensive patients to a great extent (12, 13). Increased platelet activation is in parallel with increased MPV (14). In the present study, a significant difference was found between Group 1 and Group 2 in terms of the MPV (P=0.003). The MPV was higher in Group 1. Moreover, there was a significant difference between Group 1 and Group 3 in terms of the MPV (P=0.000). According to the results of the present study, the MPV was affected by smoking and HT and the MPV was lower in the HT group than in the normal group. A contrary result in terms of HT was found in some studies (15, 16). For smoking, similar results to ours were encountered (17). The MPV was lower in the smoking group than in the other two groups. Moreover, when the smoking and non-smoking hypertensive groups were compared in terms of the MPV, the MPV was found to be lower in the smoking group.

An increase in the level of ADMA is seen in cardiovascular disease and renal insufficiency. Similar findings are also seen in asthma and cystic fibrosis (18-25). Chronic obstructive pulmonary disease (COPD) is characterized by obstruction of the airways and progressive airway restriction (22). The levels of ADMA could also increase in COPD patients (26). In our study, increased ADMA levels were observed in smoking and HT patients than in normal patients. Similar results were detected in COPD patients and in animal models exposed to cigarette smoke (27, 28). Xia et al. (29) investigated the relationship between carotid intima-media thickness and ADMA levels and found an increase in the levels of ADMA. As the left ventricular mass index increased in hypertensive patients undergoing hemodialysis, ADMA levels also increased (30). Tain and Huang (31) also reported results similar to ours. In our study, the levels of ADMA were lower in the normal group than in the other two groups. The levels of ADMA were found to be higher in the smoking hypertensive group than in the non-smoking hypertensive group. Furthermore, a nearly significant difference was detected between Group 1 and Group 2 in terms of arginine levels. In the comparison between Group 2 and Group 3 and between Group 1 and Group 3, the levels of arginine were found to be lower in Group 3.

No significant difference was found among the groups in terms of IMA levels. In the present study, significant differences were revealed among the groups in terms of the RDW. The RDW was lower in the normal group than in the other groups. There was

no significant difference between Group 2 and Group 3. Kurtoğlu et al. (32) compared smoking and non-smoking groups and reported results that were consistent with those in our study. Chen et al. (33) compared two groups (patients with LVH and those without LVH) and detected an increase in the RDW in the LVH group. In our study, the normal group and the group with newly diagnosed LVH were compared and increased RDW was found in the hypertensive group. Similar results were observed in other studies (34). Accordingly, the RDW and N/L ratio may be associated with inflammation.

Limitations

The limitations are as follows: respiratory function tests were not performed, the stages of COPD were not investigated, and there were few patients.

Conclusion

A relationship was found between ADMA levels and HT and smoking. Increased ADMA levels were observed in the group with LVH and HT and in the group with LVH, HT, and a history of smoking compared to the normal group. HT and smoking cause an increase in ADMA levels and a decrease in NO levels. On the other hand, the RDW and MPV were found to be correlated with smoking and HT. In light of these findings, it can be concluded that high levels of ADMA underlies ischemic heart disease. Smoking may increase the levels of ADMA and increase this risk much more.

Ethics Committee Approval: Ethics committee approval was received for this study from local ethic committee.

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

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