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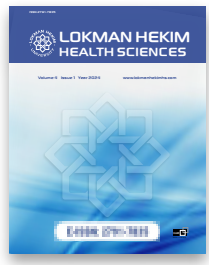

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ORIGINAL ARTICLE

Investigation of the Relationship Between Left Ventricular Hypertrophy and Endothelial Dysfunction in Patients with Primary Hypertension by ADMA and hsCRP

Esansiyel Hpertansiyonlu Hastalarda Sol Ventrikül Hipertrofisinin Endotel Disfonksiyonu ile İlişkisinin Serum ADMA ve hsCRP ile Araştırılması

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Abstract

Introduction: Hypertension targets many organs. This study investigates left ventricular hypertrophy (LVH), which can lead to conduction disorders, arrhythmias, and heart failure. Endothelial dysfunction (ED) was assessed using serum asymmetric dimethyl-arginine (ADMA) levels.

Methods: The study included a total of 90 voluntary participants: 30 patients with hypertension and left ventricular hypertrophy, 30 hypertensive patients without hypertrophy, and 30 normotensive healthy controls. Serum ADMA levels were used to detect endothelial dysfunction.

Results: The results showed that serum ADMA levels were significantly higher in the patient group compared to the control group. However, there was no significant difference in serum ADMA levels between the two subgroups of patients, with or without left ventricular hypertrophy (LVH). A correlation analysis was performed, revealing no correlation between serum ADMA levels and the left ventricular mass index (LVMI).

Discussion and Conclusion: There appears to be no direct relationship between LVH and endothelial dysfunction. Furthermore, inflammatory processes seem to contribute to the development of LVH rather than endothelial dysfunction. The duration of exposure to high blood pressure and the stage of hypertension are also believed to impact this process.

Keywords: Hypertension; Hypertrophy; Left ventricular hypertrophy; Inflammation

Hypertension (HT) is a significant public health problem with an increasing prevalence both in our country and worldwide, primarily due to the comorbidities and target organ damage it causes. HT ranks first in the etiology of diseases such as heart attack (MI), heart failure (HF), peripheral vascular disease (PAD), kidney failure (KF), and

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stroke, which are among the most common causes of death and disability (mortality and morbidity) in society. Treating HT can prevent these diseases and related disabilities.[1]

HT leads to atherosclerosis throughout the entire arterial system, particularly in the coronary arteries, by causing endothelial dysfunction (ED) and micro-inflammation in the vessels. When the entire vascular bed is affected, it implies that all organs are impacted. The first organs to be affected are the heart, kidneys, and brain.[2]

There are many methods for detecting ED. One of the most important and valuable non-invasive methods is flow-mediated dilation (FMD), which measures the elasticity of the endothelium exposed to ischemia. Additionally, blood levels of various markers have been found to correlate with ED, and asymmetric dimethyl-arginine (ADMA) is a frequently used and significant marker.[3–5]

Another significant target organ damage associated with HT is left ventricular hypertrophy (LVH). The presence of LVH has been found to increase the 5-year overall mortality rate by 5.6 times in men and 5.4 times in women, and the risk of sudden death by 6.9 times in men and 3.5 times in women.[6] Studies have shown that LVH can be reversed with HT treatment, underscoring the importance of diagnosing and treating LVH.[7] The aim of this study is to demonstrate the relationship between LVH, a crucial form of target organ damage in HT, and ED by using serum markers.

Materials and Methods

Our study was designed as a single-center, cross-sectional, and observational study. The Gülhane Medical Academy Ethics Committee approved the project on December 8, 2010, with the approval number 1491-1198/1539, confirming that it adhered to ethical principles in terms of purpose, method, and approach. Our study was conducted in accordance with the Helsinki Declaration.

Patients diagnosed with primary hypertension who presented to the internal medicine outpatient clinic were included in the patient group, while healthy controls were recruited from individuals visiting for routine check-ups. Some patients initially included in the patient group and followed up with a diagnosis of isolated HT were later found to meet the exclusion criteria after further investigations and were excluded from the study. Participants in the healthy group were selected from non-smokers who declared that they had no chronic diseases. Physicians participating in the study re-evaluated the participants' medical history, examination, and laboratory findings, leading to the exclusion of some patients. Additionally, since hsCRP, one of the parameters used in the study, can be influenced by acute infectious diseases, participants with such conditions were also excluded from the study.

Inclusion criteria:

1. Age between 18-65 years,
2. Having a diagnosis of essential hypertension,
3. Body mass index below 30 kg/m^2,
4. No additional chronic diseases other than hypertension (CRF, malignancy, DM, CAD, PAD, LVH, etc.),
5. To have signed the informed consent form.

Exclusion criteria:

1. Having secondary causes of hypertension,
2. Cardiovascular disease other than hypertension,
3. Diabetes, thyroid dysfunction, renal failure, malignancy and other systemic diseases detected during screening,
4. Unwillingness to continue the study,
5. Patients with any condition that may prevent them from signing the informed consent form.

Detailed clinical and family histories were obtained, and comprehensive physical examinations were performed on all patients included in the study. All routine laboratory investigations recommended by the ESC/ESH and JNC VII guidelines were conducted. In addition to these tests, signs of left ventricular hypertrophy were investigated for subclinical organ damage. Asymmetric dimethylarginine (ADMA), a widely used marker of endothelial dysfunction, and high-sensitivity C-reactive protein (hsCRP), a marker of vascular micro-inflammation, were also measured. The serum required for these tests was obtained from leftover blood samples collected during routine examinations and preserved at -80 °C under appropriate storage conditions.

Blood samples for biochemical analysis were collected after 12 hours of fasting. Serum glucose, total cholesterol, triglycerides, and HDL levels were measured using the enzymatic colorimetric method, while LDL cholesterol was automatically calculated using Friedewald's formula via the device software. Complete blood counts and other routine biochemical tests were performed using auto-analyzers.

Deproteinized serum samples were used for ADMA measurement. The HPLC system employed was an Agilent 1200 series HPLC device (Agilent Technologies, USA). hsCRP was measured using a Beckman AU 640 (CA, USA) autoanalyzer and the Beckman hsCRP kit (CA, USA).

All patients included in the study were evaluated via transthoracic echocardiography by the same cardiologist. All assessments were conducted using a General Electric

(GE) Vivid3 echocardiography device with a 3 MHz probe. Standard 2D, M-mode, and color Doppler techniques were used during the evaluation. The left ventricular mass index was calculated automatically using the Devereux formula. The upper limit for the presence of LVH was 131 g/m^2 in men and 100 g/m^2 in women. Patients with heart failure, moderate to severe valvular disease, cardiomyopathies, and systolic dysfunction were excluded.

The data were transferred to the SPSS (IBM, Statistical Package for Social Sciences, Chicago, IL, USA) 15.0 data program. The Kruskal-Wallis test was used for intergroup comparisons of parameters that did not show a normal distribution, while the Mann-Whitney U test was used to determine the group causing the difference and for evaluations involving two groups. The Chi-Square test and Fisher's Exact Chi-Square test were used to compare qualitative data.

No artificial intelligence-assisted technologies were used in writing this article.

Results

A total of 90 adults attending the internal medicine outpatient clinic were included in the study. Of the participants, 60 were hypertensive (group A) and 30 were healthy individuals with normal blood pressure and no comorbidities (group B, control group). The hypertensive patients were divided into 30 hypertensive patients with LVH (group A1) and 30 hypertensive patients without LVH (group A2).

The mean age of the hypertensive patients was 48.61±12.24 years, while the mean age of the healthy group was 42.73±12.08 years (p=0.035). Within the hypertensive group, the mean age of group A1 was 45.72±11.99 years, and the mean age of group A2 was 51.4±12.02 years (p=0.075). When the patient group was analyzed separately by gender, it was observed that female patients were significantly older than male patients (44.56±14.43 vs. 51.59±9.5, p=0.04).

In the patient group, 26 participants were male and 34 were female. In the control group, there were 9 male and 21 female participants (p=0.221). Within the patient subgroups, the male/female ratio was 8/22 in the group with LVH and 18/12 in the group without LVH (p=0.009).

The mean disease duration in the entire patient group (A1+A2) was 6.84 years. There was a statistically significant difference between the mean disease duration of 8.28 years in the group with LVH and 5.4 years in the group without LVH (p=0.019).

In terms of smoking history among hypertensive patients, 20 patients in the group with left ventricular hypertrophy (A1) and 19 patients in the group without hypertrophy (A2) had a history of smoking, with no significant difference between the groups. When the family history of cardiovascular disease was evaluated, 21 patients in the A1 group, 19 in the A2 group, and 9 in the control group had a family history of cardiovascular disease; the difference was not significant (p=0.069).

The mean blood pressures of the hypertensive patients were 141.56±12.5/86.57±10.03 in the A1 group and 137.73±15.85/84.23±12.06 in the A2 group, with no significant difference (p=0.229; p=0.419). The mean blood pressure of the control group was 112.6±13.75/69.43±9.95.

Fifteen of the 60 participants in the patient group and 2 of the participants in the control group had a history of alcohol use, which was statistically significant (p=0.036). When the patient group was evaluated internally, 5 people in the LVH group and 10 people in the non-LVH group had a history of alcohol use; this difference was not significant (p=0.136) (Table 1, 2).

Body mass index (BMI) was statistically significantly higher in the hypertensive group than in the control group (29.71±4.36 vs. 24.52±2.59, p<0.001). In the intergroup evaluation, both the A1 and A2 groups had significantly higher BMIs compared to the control group. However, when comparing the A1 and A2 patient groups, the mean BMI of A2 was higher, but this difference was not statistically significant (45.72±11.99 vs. 51.4±12.02, p=0.075) (Table 1, 2).

As expected, the left ventricular mass index (LVMI) was significantly lower in the control group compared to the entire HT group (110.21±32.36 vs. 72.1±37.29, p<0.001). Both patient groups (A1 and A2) had significantly higher LVMIs than the control group. When the A1 and A2 groups were compared with each other, the levels were higher in the group with LVH.

When analyzing all HT groups and the control group, ADMA levels were significantly lower in the control group (1.54±0.46 vs. 1.05±0.32, p<0.001). Both patient groups were found to have significantly higher ADMA levels compared to the control group. When comparing the two patient groups, the A2 group without LVH had higher ADMA levels than the A1 group, but this difference was not significant (1.47±0.41 vs. 1.6±0.49, p=0.281) (Table 2).

hsCRP levels were higher in all HT groups compared to the control group, but the difference was not significant (3.36±2.01 vs. 2.54±2.19, p=0.094). When both patient groups were compared separately with the control group, hsCRP levels were higher than those in the control group,

Table 1. HT and control group, demographic characteristics and laboratory

	Hypertensive (A1+A2, n=60)	Control (n=30)	
Gender (m/f)	26/34	9/21	0.221
Age (year)	48.61±12.24	42.73±12.08	0.035*
BMI (kg/m^2)	29.71±4.36	24.52±2.59	<0.001*
HT duration (year)	6.58±6.0	0	<0.001*
SBP (mmHg)	139.67±14.29	112.6±13.75	<0.001*
DBP (mmHg)	85.40±11.06	69.43±9.95	<0.001*
Alcohol, n (%)	15 (50)	2, 6.6%	0.036*
Smoking, n (%)	21 (70)	0	<0.001*
Glucose (fasting, mg/dl)	94.25±10.09	90.23±8.44	0.077
Urea (mg/dl)	30.28±9.8	24.41±5.85	0.002*
Creatinin (mg/dl)	0.9±0.15	0.85±0.13	0.215
Serum Na (mEq/l)	140.62±2.14	138.6±2.41	0.002*
Serum K (mEq/l)	4.32±0.31	4.42±0.31	0.207
ALT (u/l)	23.44±12.41	18±7.79	0.022*
AST (u/l)	22.08±6.01	23±15.32	0.788
Total cholesterol (mg/dl)	208.88±37.19	189.72±28.35	0.009
Triglyceride (mg/dl)	152.43±73.69	116.93±55.62	0.014
HDL (mg/dl))	48.34±12.28	50.32±12.43	0.491
LDL (mg/dl)	132.12±32.97	114.57±21.99	0.005
WBC (/mm^3)	7000±1675.83	6250±1496.9	0.06
Hgb (gr/dl)	14.49±1.5	13.93±1.35	0.117
Plt (x1000/mm^3)	257.26±50.72	254±48.46	0.792
MCV (/mm^3)	88.53±4.28	88.11±3.86	0.678
LVMI (gr/m^2)	110.21±32.36	72.1±37.29	<0.001*
LVM (gr)	208.12±47.95	121.45±67.14	<0.001*
hsCRP (mg/dl)	3.36±2.01	2.54±2.19	0.094
ADMA (µmol/L)	1.54±0.46	1.05±0.32	<0.001*

HT: Hypertension; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; HGB: Hemoglobin; Plt: Platelet; LVMI: Left ventricular mass index; LVM: Left ventricular mass; LVM: Left ventricular mass; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; hsCRP: High-sensitivity C-reactive protein; ADMA: Asymetric dimethyl-arginine.

but the differences were not significant, with p=0.093 for the A1 group and p=0.214 for the A2 group. When comparing the groups with and without LVH, hsCRP levels were higher in the A1 group with LVH, but again, the difference was not significant (3.55±2.37 vs. 3.17±1.61, p=0.47).

In the correlation analysis, there was no significant correlation between ADMA and LVMI (Table 3).

Discussion

In this study, we found that serum ADMA levels were significantly higher in hypertensive patients compared to the control group. However, the presence of LV hypertrophy did not significantly affect serum ADMA levels.

Table 2. Distribution of demographic and laboratory characteristics of the patient group according to gender

	Male	Female	p
n	26	34	0.302
Age (year)	44.56±14.43	51.59±9.5	0.04*
BMI (kg/m^2)	29.01±3.14	30.26±5.09	0.246
LVH (n)	8	22	0.009*
HT duration (year)	6.45±6.9	6.7±5.2	0.896
Smoking (n)	13	8	0.033*
Alcohol (n)	10	5	0.035*
Total cholesterol (mg/dl)	203.77±35.96	213.03±38.22	0.347
Triglyceride (mg/dl)	169.81±94.6	138.31±48.06	0.132
HDL (mg/dl))	43±10.68	52.69±11.92	0.002*
LDL (mg/dl)	131.03±31.56	133.01±34.54	0.821
SBP (mmHg)	137.73±13.55	141.15±14.87	0.358
DBP (mmHg)	87.15±12.7	84.06±9.61	0.306
LVMI (gr/m^2)	191.61±46.87	220.75±45.47	0.019*
LVM (gr)	96.41±28.24	120.77±31.67	0.003*
hsCRP (mg/dl)	2.95±1.42	3.66±2.35	0.152
ADMA (µmol/l)	1.63±0.48	1.47±0.43	0.184

HT: Hypertension; BMI: Body mass index; LVH: Left ventricular hypertrophy; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVMI: Left ventricular mass index; LVM: Left ventricular mass; hsCRP: High-sensitivity C-reactive protein; ADMA: Asymetric dimethyl-arginine; *: Values are given as mean±standard deviation.

Many factors are implicated in the etiology of LVH in hypertensive patients. Popular ones include endothelin, angiotensin, certain genetic mutations, and variations, but the mechanism has not been fully elucidated.[8–11] Endothelial dysfunction is a precursor and risk factor for many diseases because the affected tissue is the blood vessels, and the condition is widespread throughout the body.[12] HT, resulting from hemodynamic abnormalities, is one such condition, and endothelial dysfunction has been identified in HT patients at an early stage. In our study, we investigated the relationship between ED and LVH due to HT. Regarding the relationship between LVH and ED, we could not find a comprehensive study directly addressing this issue in the literature. Our study may contribute to the literature by directly exploring this relationship.

The mean age of hypertensive patients in our study was 48.61±12.24 years, and the mean age of the control group was 42.73±12.08 years, representing a younger population compared to other studies in the literature. The prevalence of HT in the 35–64 age group, considered "middle age," was 42.3% in the PatenT and HinT studies, which are among the HT prevalence studies conducted in our country.[1,9] The patient group in our study approximately falls within this age range.

Table 3. Correlation between LVH and parameters in group A1

	Total cholesterol	Triglyceride	HDL	LDL	DBP	LVM	ADMA
Total cholesterol							
r			0.407**	0.918**	-0.270*		-0.279*
p			0.002	0	0.041		0.034
Triglyceride							
r			-0.422**				0.279*
p			0.001				0.034
HDL							
r	0.407**	-0.422**			-0.305*	0.282*	-0.417**
p	0.002	0.001			0.02	0.032	0.001
LDL							
r	0.918**						
p	0						
SBP							
r					0.547**		
p					0		
DBP							
r	-0.270*		-0.305*				
p	0.041		0.02				
LVMI							
r			0.282*				
p			0.032				
hsCRP							
r							
p							
ADMA							
r	-0.279*	0.279*	-0.417**				
p	0.034	0.034	0.001				

HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LVM: Left ventricular mass; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LVMI: Left ventricular mass index; hsCRP: High-sensitivity C-reactive protein; ADMA: Asymetric dimethyl-arginine; r: Correlation coefficient; P: Statistical significance coefficient; * Sign indicate that the correlation is significant, as the number of * increases, the correlation strength increase.

Age is an independent factor for ADMA, a marker of endothelial dysfunction and increased left ventricular mass. In our study, evaluating a younger patient group while investigating the relationship of ED with HT and LVH may be considered an advantage in this regard.

As expected, there was a significant increase in ADMA levels between the patient group and the control group, favoring the patients. The mean blood pressure of the patients indicates that they were in the early stages of HT. Elevated ADMA levels in the patient group suggest that patients with HT have ED from early stages, regardless of the presence of LVH. However, there was no difference in ADMA levels between our HT patients with and without LVH. This lack of difference can be interpreted as a negative result regarding the relationship between LVH and ED. Additionally, in our correlation analysis, there was no significant correlation between ADMA and LVMI. However, when analyzing other variables for LVH, we found that LVMI was strongly correlated with DBD, SCB, and hsCRP, and weakly correlated with the duration of HT. The correlation that was not present with ADMA but was evident with other parameters, coupled with the lack of a difference in ADMA levels between the groups, suggests that the effect of ED on the development of LVH is limited. Furthermore, the process is associated with inflammation and inflammatory mediators, and the risk of developing LVH increases as HT progresses, particularly with systolic HT. Additionally, patients with LVH had a significantly longer disease duration than those without. This finding suggests that the duration of exposure to high blood pressure is an important factor in increasing left ventricular mass. The correlations of LVH with hsCRP, SDB, and disease duration are consistent with the literature.

When comparing the entire patient group and both patient subgroups with the control group in terms of body mass

index (BMI), BMI was significantly higher in the patient groups. This was considered expected due to the presence of overweight and obesity in the etiology of hypertension. In the comparison between the two patient groups (with and without LVH), BMI was higher in the hypertrophied group, but the difference was not statistically significant. The association between obesity and LVH has been demonstrated by extensive studies.[13] The results in our study were thought to be influenced by the small sample size and the relatively low mean BMI of 29.71 kg/m^2 in the patient group, which falls in the overweight-obese range. We believe the difference would be significant with a larger sample size.

All participants underwent echocardiographic examinations using the same machine and probe, conducted by the same physician. This consistency enhances the value of the study in determining the left ventricular mass index based on ECHO measurements, which is a crucial aspect of the study.

However, some limitations of this study should be emphasized. First, the number of patients in both the control and patient groups was not very high. Second, disease duration was not evaluated, which may also have affected serum ADMA levels.

Conclusion

Although hypertension is associated with elevated serum ADMA levels and endothelial dysfunction, no direct relationship between LVH and endothelial dysfunction was found. Additionally, inflammatory processes appear to play a more significant role in the development of LVH than endothelial dysfunction. The duration of exposure to high blood pressure and the stage of HT seem to influence this process.

Ethics Committee Approval: The Gülhane Medical Academy Ethics Committee granted approval for this study (date: 08.12.2010, number: 1491-1198/1539).

Authorship Contributions: Concept: KS; Design: KS, ÖK; Supervision: KS, MK; Fundings: ÖK; Materials: ÖK; Data Collection or Processing: MK, ÖK; Analysis or Interpretation: KS; Literature Search: ÖK; Writing: ÖK; Critical Review: KS.

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