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General Cardiology

Epicardial Adiposity is Associated with Microalbuminuria in Patients with Essential Hypertension

Mujgan Tek Ozturk,[1] Fatma Ayerden Ebinç,[2] Gülay Ulusal Okyay[3] and Aysun Akbal Kutlugün[2]

Background: Measurement of epicardial adipose tissue (EAT) is suggested as a novel cardiometabolic risk factor. Microalbuminuria is a marker of endothelial dysfunction and is associated with an increased risk for cardiovascular disease in patients with systemic hypertension. The aim of this study was to investigate the relationship of echocardiographic epicardial adipose tissue (EAT) thickness and microalbuminuria in hypertensive patients.

Methods: 75 essential hypertensive patients were included into the study. All subjects underwent transthoracic echocardiography to measure EAT thickness. Spot urine sample was collected for the assessment of microalbuminuria. Patients were divided into two groups according to their spot urine albumin to creatinine ratio (UACR); Group 1 included normoalbuminuria (0-30 μg/mg); and Group 2: included microalbuminuria (30-300 μg/mg).
Thereafter, we evaluated patient characteristics including smoking status, blood pressure, body mass index (BMI), antihypertensive treatment, statin therapy and serum levels of total cholesterol, low-density lipoprotein cholesterol, triglicerides, albumin, C-reactive protein (CRP), creatinine and hemoglobin.

Results: There was no difference in baseline characteristics between Group 1 and Group 2. Patients with microalbuminuria had significantly higher mean EAT thickness values compared to the normoalbuminuria group (7.1 ± 0.9 vs. 6.6 ± 0.9, $p = 0.01$). There were positive significant correlations between EAT and age ($r = 0.267$, $p = 0.020$), serum creatinine ($r = 0.292$, $p = 0.01$), UACR ($r = 0.251$, $p = 0.03$), left ventricular mass ($r = 0.257$, $p = 0.03$) and left ventricular mass index ($r = 0.242$, $p = 0.04$). UACR was independently associated with EAT ($p = 0.01$) after adjustments were made for age and BMI.

Conclusions: Epicardial Adipose Tissue (EAT) thickness could be associated with microalbuminuria in patients with essential hypertension. This association could support the recognition of EAT as a credible marker in cardiovascular risk stratification.

Key Words: Epicardial adipose tissue • Hypertension • Microalbuminuria

INTRODUCTION

Epicardial adipose tissue (EAT) is an extra-abdominal visceral fat deposit located around the heart particularly in cardiac grooves, over the left ventricular apex and right ventricular free wall. Epicardial adipose tissue is acknowledged to be a metabolically active endocrine organ that produces several proinflammatory and proatherogenic cytokines such as angiotensinogen and free fatty acids. Therefore, the epicardial adipose tissue has been proposed as a new cardiometabolic risk factor.[1,2] Epicardial adipose tissue may play a central role in the pathogenesis of cardiovascular disease. Its positive association with metabolic syndrome, insulin resistance,

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[1]Department of Cardiology; [2]Department of Nephrology, Kecioren Teaching and Research Hospital; [3]Department of Nephrology, Dışkapı Teaching and Research Hospital, Ankara, Turkey.
Corresponding author: Dr. Mujgan Tek Ozturk, Department of Cardiology, Kecioren Teaching and Research Hospital, Kecioren, Ankara, Turkey. Tel: +90-312-3569000; Fax: +90-312-3569002; E-mail: drmujgantek@hotmail.com

coronary artery disease, subclinical atherosclerosis and hypertension have been manifested.[3] EAT thickness can be measured by transthoracic echocardiography, cardiac computed tomography (CT), and cardiac magnetic resonance imaging (MRI) methods.

Microalbuminuria (urinary albumin excretion of 30-300 mg/24 h) represents a sign of renal and cardiovascular damage.[4] It is a well known predictor for several metabolic and non-metabolic clinical conditions in patients with essential hypertension.[5] Microalbuminuria is known to be related to obesity. Studies suggest that both subcutaneous and visceral adipose tissue are associated with microalbuminuria.[6] However, there is a lack of data regarding the association of epicardial fat with microalbuminuria in hypertensive individuals.

The aim of this cross-sectional study was to evaluate the possible relationship between echocardiographic epicardial adipose tissue thickness and microalbuminuria in patients with essential hypertension.

MATERIALS AND METHODS

The study protocol was approved by the Local Ethics Committee of Keçiören Education and Research Hospital, Ankara, Turkey and performed in accordance with the Declaration of Helsinki. All participants gave informed consent before enrollment.

Patients

We examined essential hypertensive patients who were admitted to the cardiology and nephrology outpatient clinics of Keçiören Education and Research Hospital, Ankara, from September 2014 to December 2014. The diagnosis of hypertension was considered when systolic blood pressure (SBP) $\geq$ 140 mmHg and diastolic blood pressure (DBP) $\geq$ 90 mmHg on at least three visits or when the antihypertensive therapy was present. Patients with chronic kidney disease, diabetes mellitus (or fasting blood glucose > 125 mg/dL), coronary heart disease, secondary causes of hypertension, previous stroke, valvular defects, heart failure, a neoplastic, inflammatory, hepatic or kidney disease (including a history of proteinuria, hematuria, serum creatinine greater than 1.3 mg/dl in men and 1.2 mg/dl in women and positive urine culture), febrile condition, anemia, disabling diseases such as dementia and inability to cooperate, and poor echocardiographic quality were excluded. There were 82 hypertensive patients included in the study. All subjects underwent transthoracic echocardiography after a complete medical history and laboratory examination including blood and spot urine samples. Patients' height, weight and blood pressure on the day of echocardiogram were recorded. Seven patients were excluded from the study after the results of blood examination due to high glucose or creatinine levels. Subsequently, 75 patients were analysed in the study.

Blood pressure measurement

The blood pressure (BP) of each patient was twice measured from the left arm by one of the clinicians of the research team following approximately 5 minutes of seated rest. Participants were advised to avoid alcohol, cigarettes, coffee/tea and exercise for at least 30 minutes before BP measurement. Standardized mercury sphygmomanometers were used, and one of two cuff sizes was chosen on the basis of the circumference of the participant's arm. The Korotkoff phase I (appearance) and phase V (disappearance) were recorded for the SBP and DBP, respectively.

Laboratory examinations

After a 12-hour fasting period, venous blood samples were collected from all patients and placed into tubes containing clot activator (to obtain serum).

Serum total cholesterol, triglycerides, creatinine, albumin, and CRP concentrations were measured enzymatically by the autoanalyzer (Konelab 60i, Thermo Scientific, Vantaa, Finland) using commercial kits (Konelab, Thermo Scientific). Low-density lipoprotein-cholesterol was calculated using the Friedewald formula. A Beckman Coulter Gen-S Hematology Analyzer was used for whole blood counts.

Study subject urine samples were collected a the first urine void in the morning for calculating UACR. Urinary albumin was estimated by use of the immunoturbidimetric method, and urinary creatinine was estimated by automated enzymatic assay. Urinary albumin excretion was calculated as the urinary albumin creatinine ratio (UACR). Microalbuminuria was defined when urine albumine/creatinine 30-300 μg/mg.

Transthoracic echocardiography and epicardial fat measurement

A single experienced cardiologist performed all the echocardiographic examinations by using Philips S5 cardiac ultrasound scanner and 2.5-3.5 MHz transducers. Patients were examined in the left lateral position by precordial M-mode, two-dimensional and Doppler echocardiography. Left ventricular internal dimensions, interventricular septum thickness and posterior wall thickness were measured at end-diastole. The left ventricular mass (LVM) was calculated according to the Devereux Formula.[7] The left ventricular mass was indexed to height$^{2.7}$.

We measured EAT thickness on the free wall of the right ventricle from the parasternal long-axis views. Epicardial fat was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography, and its thickness was measured perpendicularly on the free wall of the right ventricle at end-diastole for three cardiac cycles.[8] The intra-observer correlation coefficient was 0.956.

Statistical analysis

Data are presented as mean ± standard deviation (SD) for normally distributed continuous variables, median (minimum-maximum) for skew distributed continuous variables, and as frequencies for categorical variables. Pearson's chi-square test was performed for the comparison of categorical variables, and the means of normally distributed continuous variables were compared by Student's t-test. Correlation was tested with Spearman's analysis, where appropriate. Multivariate linear regression analysis was performed to assess the parameters associated with UACR, after adjustment for age and BMI. We used the Statistical Package for Social Sciences (SPSS) for Windows version 15.0 (SPSS Inc., Chicago, IL, USA) for the analysis and a two sided p value of < 0.05 was considered to be significant.

RESULTS

The demographic and clinical characteristics of the included patients are presented in Table 1.

Patients (n = 75) were assigned into two groups according to their urine albumin/creatinine ratios: 47 patients (12 men, 35 women, mean age of 62.04 ± 12.38) were in the normoalbuminuria group and 28 patients (7 men, 21 women, mean age of 62.28 ± 11.86) were in the microalbuminuria group.

Within our study population, 60 patients were previously treated for hypertension (normoalbuminuria/microalbuminuria: 39/21) and 15 patients were newly diagnosed hypertension (normoalbuminuria/microalbuminuria: 8/7). There were no significant differences in the rate of treated or untreated hypertensive patients between groups ($p > 0.05$). Also the groups were similar in regard to age, gender, BMI, smoking habits, medications, blood pressure measurements, serum creatinine, lipids, CRP, LVM and LVMI.

The mean thickness of EAT was found to be significantly higher in patients having microalbuminuria than those with normoalbuminuria (7.1 ± 0.88 vs. 6.6 ± 0.93, respectively, p = 0.01). Upon correlation analysis, EAT was found to be positively correlated with age (r = 0.267, p = 0.02), serum creatinine (r = 0.292, p = 0.01), UACR (r = 0.251, p = 0.03), LVM (r = 0.257, p = 0.03) and LVMI (r = 0.242, p = 0.04) (Table 2). Also, a positive correlation was found between UACR and LVM (r = 0.278, p = 0.02) and LVMI (r = 0.234, p = 0.04). There was no correlation of EAT with SBP, DBP, Pulse pressure, BMI, lipids and CRP. In linear regression analysis, UACR was independently associated with age (p = 0.009), and EAT (p = 0.01) (Table 3).

DISCUSSION

In the present study, we sought to evaluate a possible relationship between EAT and microalbuminuria in patients with essential hypertension. Our results indicated that the thickness of EAT measured by transthoracic echocardiography was independently associated with microalbuminuria in hypertensive patients. To the best of our knowledge, this is the first study describing this relationship.

Epicardial fat, a particular form of visceral fat deposited around the heart, is considered an important cardiovascular risk predictor.[1] The association of epicardial fat accumulation with hypertension has been demonstrated in recent studies.[9-11] Gastedalli et al. showed that both visceral and epicardial fat accumulations are independently associated with mean blood pressure val-

Table 1. Baseline characteristics of subjects

	Total group (n = 75)	Patients with normoalbuminuria (n = 47)	Patients with microalbuminuria (n = 28)	p
Age	62.13 ± 12.1	62.04 ± 12.3	62.2 ± 11.8	0.93
Gender (male, n, %)	19 (25.3%)	12(25.5%)	7 (25%)	0.96
Smoking (n, %)	11 (14.7%)	7 (14.8%)	4 (14.2%)	0.94
BMI (kg/m²)	30.1 ± 4.9	29.8 ± 14.6	30.4 ± 5.3	0.62
SBP (mmhg)	134.8 ± 20	133.5 ± 21	137 ± 20	0.47
DBP (mmhg)	77.7 ± 9.8	77.8 ± 10.4	77.5 ± 8.8	0.88
Pulse pressure(mmHg)	57.1 ± 16.1	55.6 ± 16.9	59.5 ± 16.4	0.33
Medications				
Statins (n, %)	10 (13.3%)	6 (12.7%)	4 (14.2%)	0.86
Beta-blockers (n, %)	19 (25.3%)	12 (25.5%)	7 (25%)	0.96
Ace-i (n, %)	15 (20%)	11 (23.4%)	4 (14.2%)	0.32
ARB (n, %)	37 (49.3%)	26 (55.3%)	11 (39.2%)	0.18
CCBs (n, %)	8 (10.6%)	3 (6.3%)	5 (17.8%)	0.17
Blood examinations				
Hemoglobin (g)	13.3 ± 1.5	13.2 ± 1.5	13.3 ± 1.5	0.72
Fasting glucose (mg/dl)	88.3 ± 12.7	90 ± 12.4	85.5 ± 12.8	0.46
Serum creatinine (mg/dl)	0.97 ± 0.2	0.95 ± 0.2	1.01 ± 0.2	0.19
Serum albumin (g/dl)	4.5 ± 2.7	4.7 ± 3.4	4 ± 0.3	0.17
CRP (mg/l)	1.2 ± 3.9	0.7 ± 0.9	1.9 ± 6.3	0.31
Total cholesterol (mg/dl)	214.5 ± 37	212.6 ± 36.2	217.5 ± 40.5	0.60
LDL cholesterol (mg/dl)	127.5 ± 34	125.7 ± 31.5	130.5 ± 40	0.59
Triglycerides (mg/dl)	189.3 ± 102	169.4 ± 73.7	222.8 ± 133.6	0.06
Urine examinations				
UACR (μg/mg)	49.02 ± 72.6	15.65 ± 7.8	105.03 ± 95.8	0.00
Echocardiographic evaluation				
Left ventricular mass (g)	160 ± 34	157.1 ± 36	166.7 ± 28	0.21
LVMI (g/m$^{2.7}$)	43.9 ± 9.7	42.9 ± 10.5	45.6 ± 8.3	0.23
EAT thickness (mm)	6.8 ± 0.9	6.6 ± 0.9	7.1 ± 0.8	0.01

ACE-İ, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCBs, calcium channel blockers; CRP, C-reactive protein; DBP, diastolic blood pressure; EAT, epicardial adipose tissue; LDL cholesterol, low-density lipoprotein cholesterol; LVMI, Left ventricular mass ındex; SBP, systolic blood pressure; UACR, urine albumin to creatinine ratio.

Table 2. Spearman's correlation analysis among epicardial adipose tissue thickness and other variables

	Epicardial adipose tissue thickness	
	r	p
Age (year)	0.267	0.02
BMI (kg/m²)	-0.032	0.78
SBP (mmHg)	-0.111	0.34
DBP (mmHg)	-0.063	0.59
Pulse pressure(mmHg)	-0.091	0.44
Total cholesterol (mg/dl)	0.087	0.46
LDL cholesterol (mg/dl)	-0.046	0.70
Triglycerides (mg/dl)	0.097	0.41
Serum creatinine (mg/dl)	0.292	0.01
UACR (μg/mg)	0.251	0.03
Serum albumine (g/dl)	0.076	0.52
CRP (mg/l)	0.226	0.06
LVM (g)	0.257	0.03
LVMI (g/m$^{2.7}$)	0.242	0.04

Table 3. Multivariate linear regression analysis to identify the independent determinants of UACR

Variables	B coefficient	SE	T-value	p-value
Gender (% male)	-0.25	19.2	-0.217	0.83
Age (year)	-0.340	0.758	-2.69	0.009
BMI (kg)	0.010	1.72	0.089	0.93
Serum creatinine (mg/dl)	0.057	41.8	0.444	0.66
Serum albumine(g/dl)	-0.066	3.069	-0.522	0.60
CRP (mg/l)	0.018	2.236	0.138	0.89
EAT (mm)	0.323	9.488	2.607	0.01
SBP (mmhg)	0.133	0.527	0.882	0.38
DBP (mmhg)	-0.117	1.110	-0.779	0.44
LVMI (g/m$^{2.7}$)	-0.001	0.931	-0.006	1.00
LVM (g)	0.081	0.266	0.634	0.53

SE, standard error.

ues.[9] Additionally, Lacecobellis et al. demonstrated a relationship between EAT and diastolic blood pressure values.[11] Although the exact pathophysiologic mechanisms behind these findings have not been definitely clarified, there have been some suggestions. Increased ventricular wall thickness secondary to increased blood pressure values might have stimulated EAT accumulation to provide an increased free fatty acid need of the myocardium. Elevated fatty acids might activate the autonomic nervous system via increased plasma catecholamines. By paracrine stimualtion, EAT could have increased smpathetic activity.[12]

Furthermore, some studies reported that EAT is related to subclinic target organ damage such as carotid intima-media thickness or carotid plaque.[13,14] Kim et al. have reported the relationship between EAT and brachial-ankle pulse wave velocity.[15] Natale et al. demonstrated that echocardiographic epicardial fat thickness is associated with carotid artery stiffness in hypertensive individuals.[16] Microalbuminuria is a sign of subclinic organ damage in hypertension and associated with several cardiovascular risk factors.

Abdominal obesity is another factor which is associated with microalbuminuria. The relation of abdominal obesity and albuminuria has been explored in previous studies.[17-19] Hanai et al. and Sibley et al. suggested that increased visceral adipose tissue (VAT), but not subcutaneous fat, is associated with microalbuminuria in patients with diabetes.[20] In the Framingham Heart Study both visceral adipose tissue and subcutaneous adipose tissue are found to be associated with microalbuminuria.[6] In addition to relationship between HT and EAT which was shown in previous studies, the relationship between microalbuminuria and obesity may suggest a possible association between microalbuminuria and EAT in hypertensive patients. As supporting this hypothesis, in our study we found significantly high EAT thickness in patients with microalbuminuria. Increased albuminuria at higher EAT levels may be explained with advanced endothelial dysfunction caused by proatherogenic, proinflammatory and bioactive molecules secreted from epicardial fat tissue. The association of EAT and microalbuminuria may also be related to the role of adiponectin in renal dysfunction.[21,22] The increased thickness of epicardial fat reduce the production of epicardial fat tissue derived adiponectins so lower adiponectin levels may promote glomerular damage.

LVH is a strong independent predictor of cardiovascular morbidity and mortality in hypertensive patients. High left ventricular mass detected in the echocardiography has been associated with increased EAT thickness.[23] Hypertension leads to hemodynamic overload, inducing LV hypertrophy which, in turn, increases myocardial energy requirement. EAT thickness could be increased in hypertension as an adaptation to incremental needs of the hypertrophied LV.[24] Although LVM was not significantly different in our study groups, we found positive correlation with EAT thickness and LVM.

Previous data have pointed out a close association between obesity and EAT accumulation;[25] EAT increases in parallel to body weight of the subjects. In our study, mean BMI values were similar in both groups and there was no significant correlation between EAT thickness and BMI. Also there were no significant correlations between EAT thickness and blood pressure and lipid profiles in our study. Our small number of study population could have affected our results. It was the major limitation of our study. Wang et al.demonstrated that EAT thickness in the left atrioventricular groove was most significantly associated with BMI and waist circumference.[26,27] We could not measure waist circumference and it was a significant limitation of our study.

Other limitations of our study; included an inability to measure adinopectin levels, insulin resistance and endothelial dysfunction markers that could be necessary to identify mechanisms of association between EAT and microalbuminuria. Although echocardiography is a simple and inexpensive imaging method, and recent studies have suggested echocardiographic measurements are correlated with MRI measurements,[8] the echocardiographic EAT is a linear measurement made from a single location and it may not be capable of assessing the total amount of epicardial adipose tissue. Wang et al. suggested that EAT should be measured by multi-detector computed tomography (MDCT) to clearly delineate the asymmetric distribution of EAT.[28] However, we could not confirm EAT thickness using MRI and MDCT methods.

CONCLUSIONS

We have shown an increase in EAT thickness in hy-

pertensive patients with microalbuminuria compared to that of patients with normoalbuminuria. Measure of EAT thickness might be helpful for detecting high risk group of hypertensive patients for cardiovascular risk and target organ damage. But larger prospective studies are needed to extend this observation to hypertensive patients and clarify the nature of the association. We consider that this association supports the characterization of EAT in cardiovascular risk stratification, since microalbuminuria is a well established marker of cardiovascular disorders.

CONFLICT OF INTEREST

None.

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