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Original Article CARDIOLOGY

Epicardial fat thickness is associated with retinopathy in patients with newly diagnosed hypertension

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ABSTRACT

OBJECTIVE: Hypertensive retinopathy develops based on endothelial dysfunction, inflammation, and atherosclerosis. Epicardial fat secretes various cytokines associated with endothelial dysfunction, oxidative stress, inflammation, and atherosclerosis. We aimed to evaluate whether epicardial adipose tissue (EAT) thickness is a marker for retinopathy in newly diagnosed hypertensive patients.

METHODS: A total of 73 newly diagnosed hypertension (HT) patients were included in the study. Transthoracic echocardiography (TTE) was used to measure EAT thickness. To evaluate the presence of retinopathy in HT patients, hypertensive retinopathy staging was performed by ophthalmologists, according to Scheie classification.

RESULTS: Retinopathy was detected in 27 (37.0%) of 73 patients. EAT thickness in HT patients with retinopathy was higher than the group without retinopathy (5.07±1.45 mm vs. 4.19±1.20 mm, p=0.007). Low-density lipoprotein cholesterol (LDL-C) levels in HT patients with retinopathy were higher than the group without retinopathy (162.4±41.2 mg/dl vs. 138.1±35.6 mg/dl, p=0.010). As a result of the regression analysis, LDL-C (OR=1.016, 95% CI 1.001–1.031, p=0.043) and EAT thickness (OR=1.674, 95% CI 1.069–2.626, p=0.043) were the independent predictors of retinopathy.

CONCLUSION: Increased EAT thickness is associated with the presence of retinopathy in hypertensive patients.

Keywords: Epicardial adipose tissue thickness; hypertension; retinopathy.

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Chronic complications of hypertension (HT) include retinopathy, nephropathy, and cardiovascular diseases. Due to their serious consequences, early detection of their risks can help prevent HT complications.

Hypertensive retinopathy is a condition characterized by retinal vascular symptoms in people with high blood pressure [1]. It is evaluated as the reflection of HT on endothelial dysfunction, inflammation, and atherosclerosis on the retina [2, 3]. The incidence of hypertensive retinopathy can cause vision loss and blindness, ranging from 6% to 10% [4–6]. Detection of hypertensive retinopathy by ophthalmoscopic examination is a part of the standard assessment of people with long-standing HT [7–9].

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Epicardial adipose tissue (EAT) thickness indicates the visceral adipose tissue between the pericardial and myocardial layers. It is metabolically active and functions as an endocrine organ. EAT may cause endothelial dysfunction, oxidative stress, inflammation, and atherosclerosis by its secreted cytokines [10, 11]. Hypertensive retinopathy is closely related to atherosclerosis, endothelial dysfunction, and inflammation, either. The thickness of EAT can be measured with different imaging techniques; these are echocardiography, magnetic resonance imaging (MRI), and multidetector computed tomography (CT) [12]. Echocardiography is a practical and inexpensive method, and echocardiographic measurements of EAT correlate well with MRI [13].

Studies have shown the relationship between EAT and the development of retinopathy in diabetic patients [14]. However, there is no study showing whether there is a relationship between EAT and the presence of retinopathy in hypertensive patients. In this study, we aimed to evaluate whether EAT measured in newly diagnosed hypertensive patients is a predictor in retinopathy development.

MATERIALS AND METHODS

Study Population

The research is a cross-sectional study conducted in the cardiology and ophthalmology departments between January 2019 and May 2019. HT was defined as elevated blood pressure levels, meeting the criteria specified in the 2018 European Society of Cardiology HT guideline, and newly diagnosed HT patients were evaluated [15]. Coronary revascularization, diabetes mellitus, chronic renal failure (eGFR <30 ml/min/1.73 m^2), and history of cerebrovascular disease, which are known to be associated with the development of retinopathy, were the exclusion criteria. After the excluded patients were removed, the study continued with 73 patients. EAT thickness was measured by transthoracic echocardiography (TTE). In addition, patients underwent a complete ophthalmological examination by ophthalmologists, including visual acuity, biomicroscopic examination, intraocular pressure measurement, and dilated fundus examination. After the fundus examination, patients were divided into two groups as those with and without hypertensive retinopathy. Our study was conducted under the principles stated in the Helsinki Declaration and was approved by the Recep Tayyip Erdogan Unıvercity Local Ethics Committee. Informed consent was obtained from all patients.

Highlight key points

- Routine eye examination should be recommended for patients with hypertension.
- Epicardial adipose tissue thickness should be considered during the routine echocardiography procedure performed in hypertensive patients.
- In patients with hypertension, increased epicardial adipose tissue thickness is associated with an increased risk of hypertensive retinopathy

Echocardiography

Two-dimensional TTE was performed to patients in the left lateral decubitus position using standard parasternal and apical images VIVID S5 (GE Vingmed Ultrasound AS, Horten, Norway). The images were examined by a single cardiologist blinded to patients' information to avoid inter-reader variability. In the parasternal long-axis window, the hypoechoic space in the free wall of the right ventricle was defined as EAT thickness, and it was measured from the parasternal long-axis view on the free wall of the right ventricle at the end of diastole during three cardiac cycles [16].

Ophthalmoscopy

After pupil dilation with Tropamid eye drops, the fundus examination was performed with 90 diopter Volk lenses and a slit lamp biomicroscope. The presence of hypertensive retinopathy was evaluated and staged according to Schei classification [17] (Stage 0: No change; Stage 1: Marked arteriolar narrowing; Stage 2: Apparent arteriolar narrowing accompanying focal irregularities; Stage 3: Stage 2 and retinal bleeding/exudates; and Stage 4: Stage 3 and optic disc edema). Patients with glaucoma, diabetic retinopathy, age-related macular degeneration, retinal artery/vein occlusion, and epiretinal membrane were excluded from the study. Retinal examination and classification of the patients were performed in our ophthalmology clinic by ophthalmologists aware of the patient's clinic.

Obtaining Demographic and Laboratory Data

The descriptive clinical feature, consisting of the patients' history and physical examination findings, was collected by the doctors in the cardiology clinic, and their demographic characteristics were evaluated. Patients who continued to use tobacco products or quit smoking in the past 1 year were considered smokers.

Statistical Analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Since continuous variables were normally distributed, the values were represented as mean + standard deviation. Other continuous variables were non-normally distributed and represented as median and minimum and maximum values. Categorical variables were defined as a percentage. The Student's t-test was used for the univariate analysis of the continuous variables for normally distributed variables. Mann–Whitney U-test was used to compare groups for non-normally distributed numerical variables. Chi-square test was used to determine differences between groups for the categorical variables. Continuous dependent variables Freidman test was used to compare the differences between three retinopathy groups. After Bonferroni correction, $p<0.017$ was considered statistically significant. After the significance determined, Wilcoxon test was used to compare binary groups. $P<0.05$ was considered statistically significant to this sub-analysis. ROC analysis was performed to determine the EAT thickness cutoff value. For multivariate analysis, possible parameters identified by univariate analyzes were evaluated by logistic regression analysis to determine independent retinopathy predictors. Hosmer-Lemeshow goodness-of-fit statistics was used to evaluate the model fit. The 5% type-I error level was used to reach statistical significance. The Statistical Program for the Social Sciences (for Windows 15; SPSS Inc., Chicago, Illinois) was used for all statistical calculations.

RESULTS

The study included 73 patients (36 men and 37 women) with newly diagnosed HT. Hypertensive retinopathy was detected in 27 (37.0%) of them. The mean age of patients with hypertensive retinopathy was 55.2±8.2, and the mean age of patients without retinopathy was 52.4±8.9 (p=0.185). There was no statistical difference between the genders in terms of hypertensive retinopathy (p=0.536). There was no difference between the two groups in terms of high-sensitive C-reactive protein (hs-CRP) levels (p=0.336) (Table 1).

In the group with retinopathy, the low-density lipoprotein cholesterol (LDL-C) level was higher than in the group without retinopathy (162.4±41.2 mg/dl vs. 138.1±35.6 mg/dl, p=0.010).

EAT was thicker in the patient with retinopathy than the patient without retinopathy (5.07±1.45 mm vs. 4.19±1.20 mm, p=0.007) (Fig. 1). According to the ROC analysis, the EAT thickness ≥4.5 mm is associated with hypertensive retinopathy with 58% sensitivity and 60% specificity.

As a result of the regression analysis, LDL-C (OR=1.016, 95% CI 1.001–1.031, p=0.043) and EAT thickness (OR=1.674, 95% CI 1.069–2.626, p=0.024) were determined as independent predictors for the development of retinopathy in hypertensive patients (Table 2).

TABLE 1. Demographic characteristics of the patients

	Retinopathy + (n:46)	Retinopathy – (n:27)	p
Age (years)	52.4±8.9	55.2±8.2	0.185
Gander (female), n (%)	23 (50%)	13 (48.1%)	0.536
Dyslipidemia, n (%)	2 (4.4%)	1 (3.7%)	0.879
Current smoker, n (%)	15 (33.3%)	7 (25.9%)	0.349
EF (%)	62.9±2.4	62.6±2.4	0.963
EAT (mm)	4.19±1.20	5.07±1.45	0.007
Diastolic dysfunction, n (%)	23 (85.2%)	33 (73.3%)	0.242
Fasting glucose (mg/dl)	98.3±21.4	104.0±15.2	0.237
Creatinine (mg/dl)	0.83±0.16	0.82±0.10	0.646
Total cholesterol (mg/dl)	223.9±50.4	239.5±46.8	0.201
Triglyceride (mg/dl)	165.6±92.7	146.0±62.8	0.336
LDL chol. (mg/dl)	138.1±35.6	162.4±41.2	0.010
HDL chol. (mg/dl)	49.8±11.7	47.7±13.1	0.490
CRP (mg/l)	0.29±0.40	0.40±0.52	0.336
Hemoglobin (mg/dl)	14.3±1.5	13.9±1.4	0.219

EF: Ejection fraction; EAT: Epicardial adipose thickness; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; Chol.: Cholesterol; CRP: C-reactive protein.

TABLE 2. Multivariate analysis for the estimation of factors independently determining the development of retinopathy

Variables	Odds ratio, 95 CI%	p
LDL	1.016 (1.001–1.031)	0.043
EAT	1.674 (1.069–2.626)	0.024

CI: Confidence interval; LDL: Low-density lipoprotein; EAT: Epicardial adipose thickness.

DISCUSSION

The present study showed that increased EAT thickness and LDL-C levels were associated with hypertensive retinopathy in newly diagnosed HT patients. We

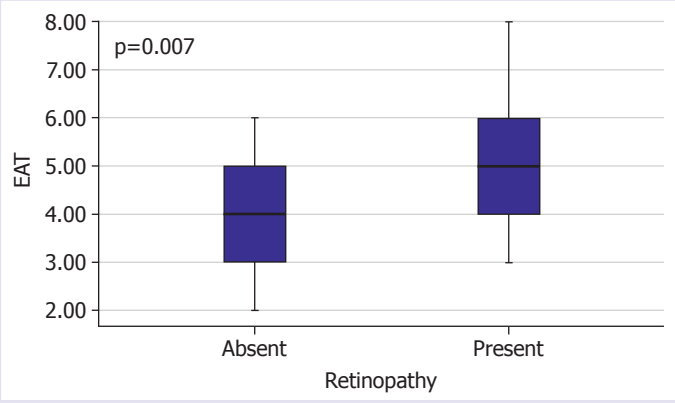

Figure 1. Relation of epicardial fat thickness with retinopathy.

found that the high LDL-C and EAT thickness levels were the independent predictors for the development of retinopathy in newly diagnosed HT patients. The current study is the first to evaluate the relationship between EAT thickness and retinopathy development in this patient group.

Due to high blood pressure, the retinal circulation undergoes some pathophysiological changes [2]. At first, autoregulatory mechanisms cause vasospasm, which reflects the clinic in the form of narrowing of the retinal arterioles. Permanent high blood pressure causes intimal thickening, hyperplasia of the media wall and degeneration of the hyaline in the subsequent sclerotic stage. The arteriolar narrowing can cause changes in the light reflex by holding the general or local areas. This phase is followed by an exudative phase in which the blood–retinal barrier is impaired, smooth muscles and endothelial cells are being in necrosis, blood and lipids are in exudation, and the retina is ischemic. These changes are manifested in the retina as microaneurysms, hemorrhages, hard exudates, and cotton wool stains. However, the specified stages may not be sequential in all patients [2, 3]. Studies have shown that there is a relationship between the development of retinopathy and HT [5, 18–20]. Two studies reported that retinal arteriolar narrowing was associated with high blood pressure [21, 22]. In another study, retinal arteriolar narrowing was associated with the risk of HT development in normotensive individuals [23]. As a result of the ophthalmoscopic examination, 37% of newly diagnosed HT patients were diagnosed with retinopathy in the current study. This rate was higher than the general incidence of hypertensive retinopathy. This finding suggests that the result is due to delayed diagnosis and treatment of patients, as shown in the previous studies. After HT treatment, particularly angiotensin-converting enzyme inhibitors treatment, regression in hypertensive retinopathy findings has been reported [24]. In the current study, retinopathy rates may be higher since the newly diagnosed HT patients had no antihypertensive treatment.

Studies demonstrated an increased risk of hypertensive retinopathy in patients with HT and hyperlipidemia [25]. The current study showed that the increase in the LDL-C level is an independent predictor for retinopathy development. This result shows that the treatment of hyperlipidemia may be necessary for preventing the development of hypertensive retinopathy.

hs-CRP is associated with inflammatory response, endothelial dysfunction, and development of atherosclerosis [26, 27]. Studies have been reported suggesting that the increase in the hs-CRP level in diabetic patients is valuable as a prognostic factor for vascular complications such as diabetic retinopathy [14, 28, 29]. In the present study, there was no relationship between the development of retinopathy and hs-CRP in newly diagnosed HT patients.

EAT is located between the myocardium and the pericardium and acts as an energy source for the myocardium. EAT can secrete various pro-atherogenic cytokines, which play a role in the pathogenesis of inflammation, endothelial dysfunction, and atherosclerosis [30]. The increase in EAT thickness is a marker of inflammation and subclinical atherosclerosis, and EAT is associated with major cardiovascular outcomes regardless of other risk factors [31].

EAT thickness is higher in hypertensive patients than normotensive subjects and associated with HT development [32–34]. The development of diabetic retinopathy is associated with EAT in diabetic patients [14]. In our study, EAT was higher in the group with retinopathy in newly diagnosed HT patients, and EAT thickness was an independent predictor of hypertensive retinopathy.

As far as we know, the present research is the first to evaluate the relationship between hypertensive retinopathy and EAT thickness. As a result, it is thought that the increase in EAT thickness and LDL-C levels can be used as an essential risk factor for the development of retinopathy. This result emphasizes the importance of the detection and treatment of hyperlipidemia in preventing hypertensive retinopathy due to HT. In addition, EAT thickness measurement can be performed quickly and cheaply by TTE, maybe an early stimulus in the presence of hypertensive retinopathy.

Limitation

The number of patients included in the study was relatively limited. The study was a cross-sectional study. EAT thickness evaluation was performed by two-dimensional echocardiography instead of CT or MR. More extensive studies should be planned to evaluate the effect of EAT on hypertensive retinopathy.

Conclusion

The increase in EAT thickness and LDL-C levels is independently associated with the presence of retinopathy. This result highlights the importance of the treatment of hyperlipidemia in the prevention of the development of hypertensive retinopathy. EAT, which can be easily evaluated during echocardiography, is associated with retinopathy in hypertensive patients. Thus, it can raise awareness about the development of retinopathy for the clinician and maybe a guide for retinopathy diagnosis before the symptom appears.

Ethics Committee Approval: The Recep Tayyip Erdogan University Clinical Research Ethics Committee granted approval for this study (date: 16.06.2020, number: 2020/118).

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