Neurological Sciences (2020) 41:49–56
https://doi.org/10.1007/s10072-019-04008-w

ORIGINAL ARTICLE

Increased epicardial fat thickness and carotid intima–media thickness in migraine patients

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Received: 21 March 2019 / Accepted: 9 July 2019 / Published online: 15 August 2019
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Abstract

Background Migraine is a common and debilitating neurological disorder characterized with episodic attacks. Epicardial fat is metabolically active and is an important predictor of metabolic and vascular diseases. We aimed to examine whether the echocardiographic measurement of epicardial fat thickness (EFT) and carotid intima–media thickness (CIMT) is increased in patients with episodic migraine (EM).

Methods We studied 96 volunteers, including 48 patients with EM (mean age 40.10 ± 10 years, 41 female patients) and 48 healthy subjects (mean age 42.69 ± 10 years, gender is the same). All necessary biochemical parameters were analyzed; subsequently, EFT and CIMT were measured in all subjects. The migraine characteristics of the patients were questioned in detail.

Results The patients with EM had a significantly higher EFT than the control group (5.34 ± 1.02 vs. 4.41 ± 0.68; $P < 0.001$) and CIMT was also found to be high (median 6.70 vs. 5.60; $P < 0.001$). Furthermore, there was a positive correlation between EFT and duration of disease and monthly frequency ($r = 0.730$; $P < 0.001$). EFT was significantly correlated with CIMT in the migraineurs ($P < 0.001$). As an optimal cut-off point, a high-risk EFT value of 5.54 mm was determined to predict EM, with 58.3% sensitivity and 96.8% specificity.

Conclusion We found that EFT and CIMT were significantly higher in EM patients than in healthy individuals. Increased EFT may be a new risk factor in migraine patients especially in patients with increased pain frequency.

Keywords Migraine · Subclinical atherosclerosis · Endothelial dysfunction · Epicardial fat thickness · Disease progression

Introduction

Migraine is a common neurovascular brain disease that is estimated to affect 13% of the general population [1]. Migraine is categorized as episodic migraine (EM) when there are < 15 headache days per month and chronic migraine (CM) when there are ≥ 15 headaches per month [2] About 0.5 to 5% of the population are estimated to fulfill the CM criteria [3, 4]. The new-onset CM development process arising from EM is called, "transformation," "chronification," or "progression" EM [5]. Previous studies have shown that there is a relationship between inflammation and the progression of migraine [6].

Adipose tissue is a multifunctional neuroendocrine organ that plays a role in energy homeostasis and inflammation [6]. Epicardial fat, the visceral fat depot of the heart, is located between the myocardium and visceral pericardium on the heart surface [7]. Epicardial fat consists mainly of adipocytes; however, it also includes stromovascular, immune cells along with ganglia and neurons [8]. Numerous cytokines playing an active role in migraine, such as IL-6 and TNF-α, are produced by adipocytes; in addition, adipocytes are responsible for the secretion of certain inflammatory agents [6]. Similarly, adipocytokine receptors are abundant in the central nervous system, cortex, brain stem, hypothalamus, and vascular endothelium [6].

Besides, epicardial fat has effects associated with endothelial function, coagulation, and inflammation and also exerts systemic effects [8]. Echocardiographically measured epicardial fat thickness (EFT) has strong association with obesity,

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impaired fasting glucose, insulin resistance, metabolic syndrome, hypertension, diabetes mellitus, and atherosclerosis [9]. Studies have also shown that EFT leads to an increase in carotid intima-media thickness and causes subclinical target organ damage [7]. Carotid intima-media thickness (CIMT) is a marker that can be easily measured ultrasonographically and subclinical vascular damage can be assessed [10]. The inflammatory process in migraine may disrupt the structure of the vascular wall as well as vascular endothelial function. Repeated sterile vascular inflammation results in impaired cerebral and systemic vascular reactivity as a result of endothelial damage of cranial vessels [1, 11]. Owing to these reasons, the prevalence of cerebral ischemic events and cardiovascular diseases increases during the chronic migraine period [12].

Currently, it is not clear why some migraine patients transformed into a chronic form. The absence of a suitable plasticity in the central nervous system (CNS) is thought to be important in the progression of pain [13]. In another analysis, it was shown that there is an increased risk of transition to CM when high-frequency EM (10–14 headache days/day per month) was compared with low-frequency EM (< 5 headache days/month) [14]. At this point, the significance of various modifiable and irrevocable risk factors comes up [14, 15]. Changeable risk factors are particularly valuable, as they can provide targets for future interventions designed to reduce risk of new-onset CM [5].

The aim of this study was to evaluate the EFT and CIMT values in patients with episodic migraine in the interictal period and healthy control group. In addition, it was also aimed to evaluate the relationship between the duration of migraine and the frequency of pain and the potential role in migraine pathophysiology and progression.

Methods

Study design and neurological follow-up

Forty-eight migraine (23 with high frequency, 25 with mild-moderate frequency) patients aged between 18 and 60 who have been diagnosed with episodic migraine and applied to a neurology clinic and 48 healthy controls have been included in this prospective and cross-sectional design study. Migraine diagnosis and classification were made according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) [2].

People who experienced head trauma, have infection, pregnant and lactating women, people using any drugs including for migraine prophylaxis and other conditions in the last 3 months except attack treatments, and have any neurological, psychiatric, and systemic disease other than migraine have been excluded from the study. Other exclusion criteria were cardiomyopathy, valvular heart disease, arrhythmia, and any signs indicating cardiac involvement and intense smoking (> 5–6 piece/day). Detailed history of migraine patients was taken. Systemic physical examinations and neurological examinations were performed. All patients were examined when they did not have an acute headache. The frequency of pain, severity of episode, and disease period were recorded. We examined headache in 3 categories to demonstrate the effect of EFT on transformation development, namely low-frequency headache (< 5 days per month), moderate-frequency headache (5–9 days per month), and high-frequency headache (10–14 days per month). We analyzed our statistical analysis between high-frequency migraine and low to moderate group.

Visual analog scale (VAS) was used to measure the severity of headache; 1–3, mild; 4–6, moderate; 7–8, severe; 9–10, extremely severe [16]. Migraine headache attack frequency was recorded monthly, and disease period was determined in years. Aura, photophobia, and phonophobia were investigated and to calculate body mass index (BMI), anthropometric measurements (i.e., weight and height) were also recorded [17].

Our study was approved by the Ethics Committee protocol (protocol number: 2017-KAEK189_2017.06.21_03) and all the participants provided written informed consent.

Measurements

The arterial blood pressure of all participants was measured after a resting period of 15 min using a standard manual sphygmomanometer; at least two measurements of the participants were < 140/90 mmHg blood pressure values. Moreover, we collected routine laboratory test data, including total cholesterol, high-density lipoproteins cholesterol (HDL), and triglycerides levels measured in a venous blood sample collected early in the morning after 12 h of fasting.

Measurement of epicardial fat thickness

All participants were referred to the cardiology outpatient clinic for echocardiographic evaluation. EFT was evaluated by transthoracic echocardiography using a Philips Logic Affiniti 50G machine (Philips, Amsterdam, Netherlands) and a broadband transducer by the same cardiologist who was unaware of the clinical data. EFT was measured from the parasternal long-axis view on the right ventricle's free wall at the end-diastole during three cardiac cycles. EFT was defined as the hypoechoic space between ventricular free wall and the visceral layer of pericardium.

Measurement of carotid intima–media thickness

Ultrasonography was performed on all patients using a Philips Logic Affiniti 50G machine (Philips, Amsterdam, Netherlands) with a 12–4 MHz linear array transducer.

CIMT was measured from the far wall of the right carotid artery within 1 cm proximal to bifurcation as the distance between the lumen–intima interface and the media–adventitia interface. Three measurements were obtained from contiguous sites and average of these three measurements was used for analyses.

Power analysis indicated that a sample size of 40 would be sufficient to detect a correlation of "Spearman's rho" = 0.35 at a power of 0.80 and $P < 0.05$ (two-tailed). Forty-eight healthy and 48 episodic migraine patients were found to be sufficient to detect a group difference at a moderate effect size of Cohen's $d = 0.6$ with a power of 0.08 and $P < 0.05$, using a two-tailed Student's T test. Power calculation was performed to other study data.

Statistical analyses

PASW statistics for windows (version 18.0; SPSS Inc., Chicago, IL) were used for the data analysis. The descriptive statistics of the continuous variables obtained in the study were given as mean ± SD. The descriptive statistics of the categorical variables were presented as numbers and percentages. The normality of the numerical variables was determined by Kolmogorov-Smirnov test. Comparisons between groups, with regard to the means of t numerical variables (independent t test), and comparison of the medians (Mann-Whitney U test) were conducted. The Pearson correlation test was used to evaluate the relationship between parametric continuous variables, whereas the Spearman correlation test was used for nonparametric continuous variables.

Subsequently, a logistic regression model was used to identify independent predictors of migraine. The model fit was assessed using appropriate residual and goodness-of-fit statistics. A 5% type-1 error level was used to infer statistical significance. R2 shows the percentage of variance in the dependent variable explained by independent variables in the model. The receiver operating characteristic curve analysis was performed to determine the cut-off high-risk EFT value. $P < 0.05$ was considered statistically significant.

Results

A total of 96 subjects, 48 with episodic migraine and 48 as healthy controls, were included in the study. Patients and controls were similar in age, body mass index, systolic and diastolic blood pressure, and biochemical parameters. The proportion of smokers was relatively higher in the study group (60%) than in the control (40%) group and five patients with aura symptom was low.

The baseline characteristics of the study and control groups are presented in Table 1. Left ventricular (LV) echocardiographic parameters did not differ significantly between the groups. EFT was significantly higher in the patient group (5.34 ± 1.02 vs. 4.41 ± 0.68 $P < 0.01$). EFT value and CIMT value are presented in Table 1.

Table 1 Demographic, biochemical parameters of the study population

	Patients($n = 48$)	Controls($n = 48$)	P
Age (years)	40.10 ± 10.27	42.69 ± 10.01	0.21
Sex (male/female)	7/41	7/41	–
Smoking (%)	8 (16.6%)	5 (10.41%)	–
BMI (kg/m^2)	26.11 ± 3.87	27.90 ± 5.52	0.70
Waist circumference(cm)	94.04 ± 7.71	97.08 ± 8.40	0.06
SBP (mmHg)	117 ± 13.87	120 ± 16.21	0.49
DBP (mmHg)	74.48 ± 9.41	74.46 ± 8.31	0.30
Glucose (mg/dL)	89.52 ± 6.86	92.16 ± 9.27	0.12
Total cholesterol (mg/dL)	200.14 ± 31.59	186.77 ± 38.38	0.06
HDL (mg/dL)	53.41 ± 11.39	55.70 ± 13.35	0.36
LDL (mg/dL)	121.82 ± 27.96	104.21 ± 33.08	*0.006*
Triglyceride (mg/dL)	125.08 ± 55.92	132.08 ± 61.88	0.56
Disease duration (years)	10.89 ± 8.07	–	–
Headache days per month	7.89 ± 4.23	–	–
VAS	7.66 ± 1.29	–	–
CIMT (mm)	6.70 (6.14–7.2)	5.60 (5.30–6.05)	*< 0.001*
EFT (mm)	5.34 ± 1.02	4.41 ± 0.60	*< 0.001*

Values are presented as mean ± SD, median (25th–75th)

BMI, body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *VAS*, visual analog scale; *CIMT*, carotid intima-media thickness; *EFT*, epicardial fat thickness

However, EFT and CIMT values were lower in the low and moderate frequency of migraine patients compared with the high frequency of migraine patients. Other clinical and laboratorial characteristics at baseline were not statistically different comparing high- and low-frequency migraineurs and are showed in Table 2.

Moreover, we found positive correlation between migraine characteristics and the EFT measurement. One of these was duration of disease, the other one was monthly frequency ($r = 0.404$, $P < 0.05$ vs. $r = 0.591$ $P < 0.01$) and also the CIMT measurement (duration of disease: $rho = 0.337$, $P = 0.019$; monthly frequency: $rho = 0.383$, $P = 0.007$) correlations were given Fig. 1. At the same time, EFT was significantly correlated with CIMT in migraineurs ($r = 0.730$, $P < 0.001$).

In the receiver operating characteristic curve analysis, the area under the curve (AUC) was found to be statistically significant (AUC = 0.771, 95% confidence interval, 0.676–0.865; $P < 0.001$). As an optimal cut-off point, a high-risk EFT value of 5.54 mm was determined to predict high frequency of migraine, with 39.6% sensitivity and 96.8% specificity. A cut-off CIMT value of 6.43 mm was determined to predict high frequency of migraine disease with 58.3%

Table 2 Echocardiographic measurements of controls and patients with migraine

	Low and moderate frequency of migraine patients ($n = 25$)	High frequency of migraine patients ($n = 23$)	P
Age (years)	36.60 ± 11.52	43.91 ± 7.17	*0.011*
BMI (kg/m^2)	27.05 (24.10–28.29)	26.17 (23.63–28.12)	0.529
Waist circumference(cm)	92.68 ± 7.29	95.52 ± 8.03	0.207
Glucose (mg/dL)	89.24 ± 7.29	89.82 ± 6.52	0.771
Total cholesterol (mg/dL)	197.36 ± 28.47	203.17 ± 35.06	0.534
HDL (mg/dL)	52.54 ± 11.33	54.35 ± 11.63	0.587
LDL (mg/dL)	118.52 ± 28.19	125.41 ± 27.89	0.399
Triglyceride (mg/dL)	120 (84–156.5)	113 (80–177)	0.836
Disease duration (years)	10 (3.5–13)	10 (5–20)	0.118
Headache days per month	4 (3–5.5)	12 (10–12)	*< 0.001*
VAS	7 (7–8)	7 (7–9)	0.627
Aura symptom	2 patients	3 patients	–
LVEF (%)	63.88 ± 1.94	63.26 ± 1.78	0.258
CIMT (mm)	6.30 (5.90–6.70)	6.90 (6.50–7.50)	*0.004*
EFT (mm)	4.70 ± 0.70	6.00 ± 0.80	*< 0.001*

Values are presented mean ± SD, median (25th–75th)

BMI, body mass index; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein; *VAS*, visual analog scale; *LVEF*, left ventricular ejection fraction; *CIMT*, carotid intima-media thickness; *EFT*, epicardial fat thickness

sensitivity and 96.8% specificity (ROC under area the curve 0.863; 95% Cl 0.781–0.945; $P < 0.001$) (Fig. 2).

A logistic regression analysis based on the comparison of the participants with migraine and non-migraineurs for the triggers of disease is shown in Table 3. We found that migraine increased the risk of epicardial fat and CIMT, while migraine was associated with a low risk of hyperlipidemia. An internal validation with the bootstrap technique showed $\beta = 11.073$ (95% CI −7.393–561058295.2) for the migraine and EFT model; $\beta = 10.020$ (95% CI −1.286–392650587.5, −0.45) for the migraine and CIMT model.

Discussion

In this study, we have shown that EFT and CIMT values were increased in patients with episodic migraine compared with the control group. Moreover, we found that both EFT and CIMT were increased in correlation with disease duration and number of monthly attacks. Our study provides evidence for the first time that the EFT is increased in migraine patients compared with the control group. We hypothesized that the echocardiographic EFT measurements could be higher, due to the increased risk of vascular disease in chronic migraine transformation. EFT was evaluated as an indicator of epicardial adiposity.

Visceral adipose tissue contains epicardial fat that secretes proatherogenic and proinflammatory cytokines with endocrine and paracrine functions [18]. These inflammatory mediators play a critical role in the initiation and progression of vascular diseases and subclinical atherosclerosis through systemic, metabolic, and inflammatory interactions [18, 19]. The role of epicardial fat in cerebral ischemic disease and systemic inflammatory disease has been shown as an independent risk factor [7, 20].

Epicardial fat differs significantly from subcutaneous fat, with most of the relatively enriched genes are associated with endothelial function, coagulation, insulin resistance, and inflammation [21, 22]. In addition, EFT has been shown to be associated with an increase in the CIMT, in symptomatic and asymptomatic adults, so this marker indicates high risk of atherosclerosis [23]. A well-established relationship has been shown for migraine with aura and cardiovascular diseases (CVD), less for migraine without aura [24]. As a result, endothelial inflammation and increased platelet aggregates may result in clot formation as evidence for endothelial dysfunction [1]. Strong evidence has been obtained in studies investigating endothelial dysfunction with migraine and it has been shown that nitric oxide-dependent vasodilatation is fundamentally impaired [25].

In this study, we have found a significant increase in CIMT value in migraine patients as well as EFT. Studies investigating the relationship between CIMT and migraine reported controversial results [10]. Intima-media thickening occurs as a result of the accumulation of neointimal cells in vascular smooth muscles and possibly the earliest structural features associated with oxidative stress in arteriosclerosis of medium-sized vessels [10, 26]. Therefore, the evaluation of

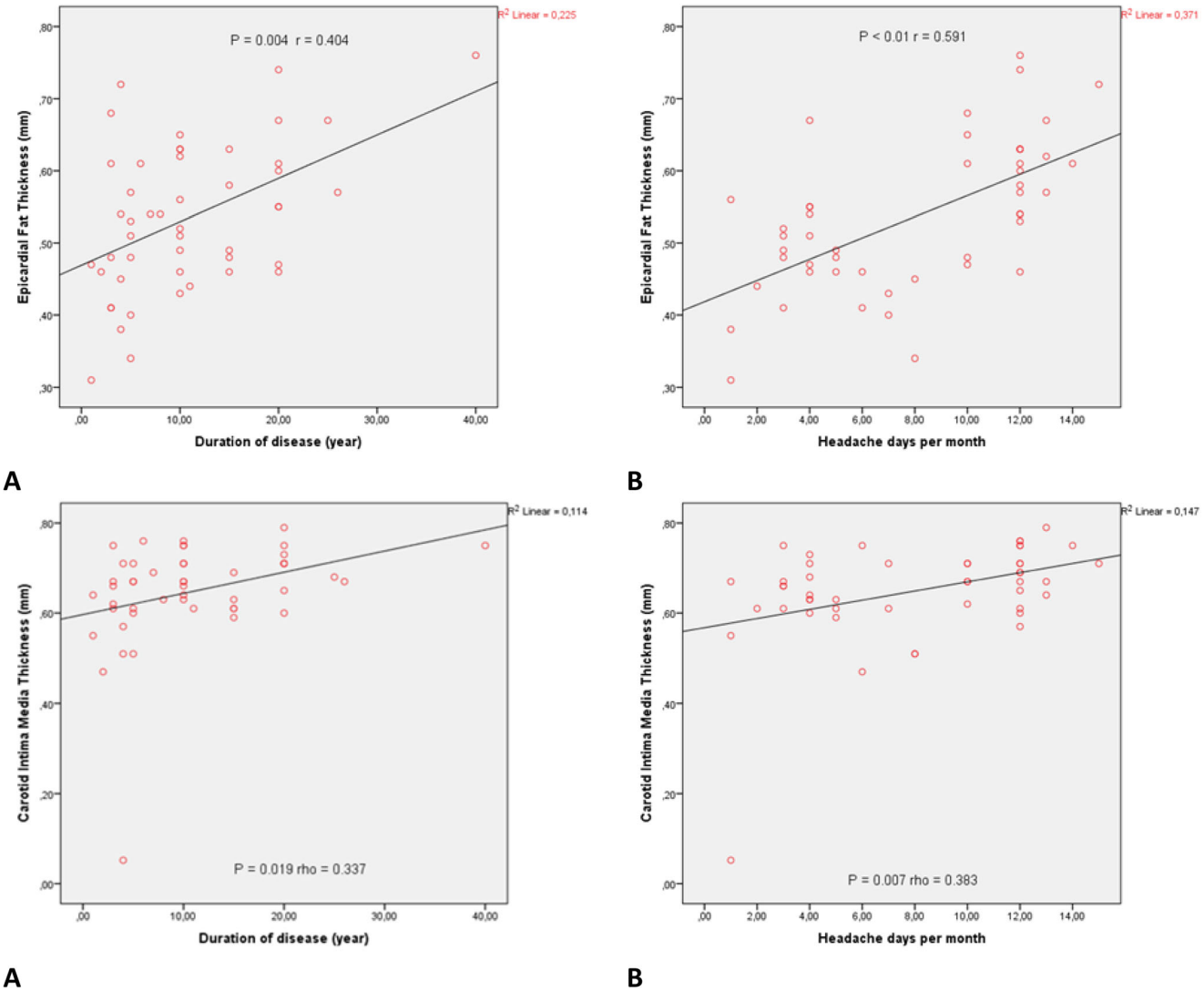

Fig. 1 Scatter plots show significant positive correlations between epicardial fat thickness/carotid intima-media thickness and A) duration of disease (year) and B) headache days per month

atherosclerosis and measurement of the mean intima-media thickness in the carotid arteries may play an important role in the early diagnosis of migraine patients with a risk of CVD [27]. Given the direct correlation between CIMT and CVD, carotid thickening should be considered a vascular disease [10]. In other studies, it has been shown that carotid plaques may increase with CIMT in the advanced stages of the migraine disease [10, 27]. Hence, it is reasonable to assume that increased CIMT in our patients might subsequently result in more subclinic atherosclerosis in relation to migraine.

When the risk factors for chronic migraine are evaluated, some of them are obesity, CVD, insulin resistance, dyslipidemia, and endothelial dysfunction [28]. In patients with migraine along with high LDL levels, cholesterol plaques spread to the inner layer of the arteries and become foam cells by subendothelial macrophages in the early stages of atheroma formation [18]. In our study, LDL was higher in the control group. Oxidative stress, possibly induced by exposure to vascular risk factors, endothelial dysfunction, and dyslipidemia, leads to two-way interaction in terms of both migraine transformation and vascular damage resulting in CVD [10, 26].

In this study, evidence suggests that increased CIMT and EFT may be a risk factor for the transformed migraine with the increase in the incidence of disease in patients who suffer from migraine without prophylactic treatment. Owing to the simplicity and treatability of imaging modalities, epicardial fat measurements have enabled the use of this method as an indicator for the efficacy of exercise and pharmaceutical treatments. After a low-calorie diet or moderate aerobic exercise program, the level of epicardial fat may decrease [8, 29].

Our data demonstrate that EFT, an indicator of visceral adiposity, is increased in episodic migraine patients compared with healthy individuals. Natale et al. noted that patients with an EFT > 7 mm had a significant increase in CIMT [30]. In our study, we determined an EFT ≥ 5.54 mm as the cut-off

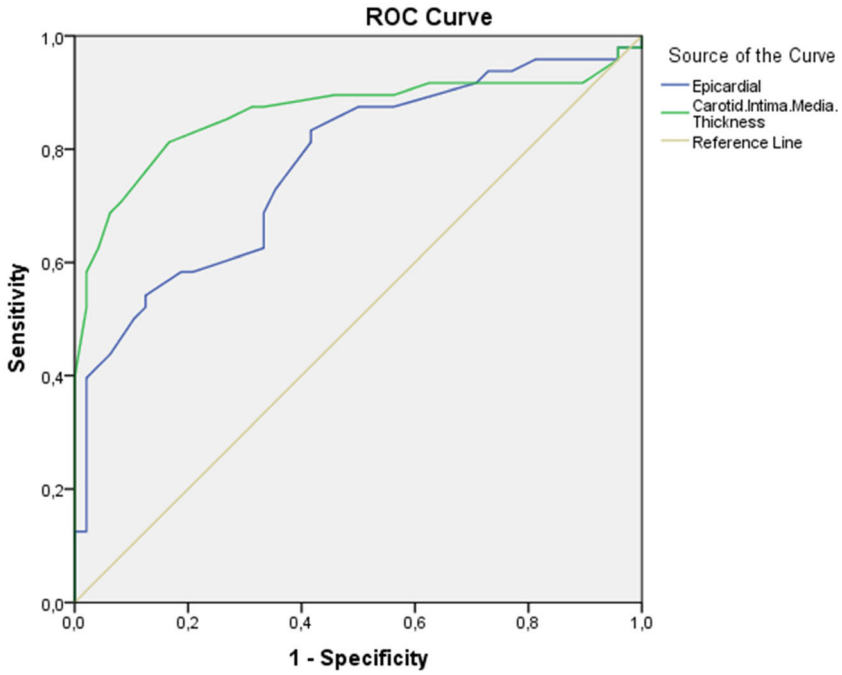

Fig. 2 ROC curve (showing sensitivity and specificity of the carotid intima-media thickness (Green line) and epicardial fat thickness (Blue line) to determine the high-risk cut-off value). ROC indicates receiver operating characteristic

value, above which the risk of progression significantly increases, with 58.3% sensitivity and 96.8% specificity. Studies conducted in various disease groups have reported different threshold values for EFT, but increased EFT seems to be related to the atherosclerotic process. In our study, we intended to emphasize the significance of CIMT and EFT measurement in the evaluation of subclinical vascular and endothelial effects in patients with episodic migraine. These findings suggest that echocardiographic EFT measurement can be considered as a new risk factor and maybe helpful in evaluating subclinical damage.

This study has some limitations. We aimed to keep the number of female participants high in order to increase the sample size and minimize selection bias. This study included patients and controls from every age group, and this in turn increased the reliability of the measurement of CIMT and EFT ratio in migraine progression. However, we could not assess the effects of sex steroids on EFT. In this respect, longitudinal studies with large patient series should be prioritized and included in male participants. We also believe that correlation studies on the biomarkers could provide guiding information to evaluate the pathophysiological effects.

Conclusion

We found in this study that migraine patients increased the risk of CIMT and EFT and also high frequency of pain attacks was

Table 3 Results of logistic regression analysis: the effect of the risk factors of pressure scores to migraine disease

Variables	*B*	Wald	*P*	Exp (B)	95.0% Cl for EXP (B)	
					Lower	Upper
BMI (kg/m^2)	0.002	0.000	0.984	1.002	0.849	1.182
Waist circumference	− 0.134	5.226	*0.022*	0.874	0.779	0.981
Glucose	− 0.036	0.899	0.343	0.965	0.895	1.039
Total cholesterol	− 0.009	0.210	0.647	0.991	0.953	1.030
TG	− 0.001	0.012	0.914	0.999	0.987	1.012
HDL	0.008	0.058	0.809	1.008	0.948	1.071
LDL	0.023	1.344	0.246	1.024	0.984	1.065
CIMT	10.020	4.042	*0.044*	22469.9	1.286	392650587.5
EFT	11.073	5.722	*0.017*	64406.2	7.393	561058295.2
Fix	3.375	0.264	0.607	29.230		

Nagelkerke *R* Square; 0.525

BMI, body mass index

associated with a high risk of these markers. Thus, evaluation of EFT and CIMT in migraine patients may be useful as an indicator or consequence of vascular damage. Given that carotid ultrasonography and echocardiography are simple and easily available, it should be considered for the assessment of vascular health in migraineurs in neurological practice. However, our results should be confirmed with a larger number of patients in future studies.

Clinical implications

• Chronification of disease is a very important aspect to assess in patients with migraine, together with measures of migraine frequency and severity.
• In the study, EFT and CIMT values were resulted in statistically significant and clinically meaningful in episodic migraine patients especially associated with high frequency of attacks.
• These data suggest that echocardiographic EFT measurement can be considered as a risk factor for transformation and confirming its role as a promising new therapy for the prevention of episodic migraine.

Compliance with ethical standards

Our study was approved by the Ethics Committee protocol (protocol number: 2017-KAEK189_2017.06.21_03) and all the participants provided written informed consent.

Conflict of interests The authors declare that they have no conflict of interest.

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