Original article

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Cardiovascular involvement in patients with pseudoexfoliation syndrome

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Aim **Pseudoexfoliation (PEX) syndrome, diagnosed by ocular examination, is a common disorder of the extracellular matrix. Previous studies have demonstrated accumulation of PEX material in the walls of blood vessels and myocardium. We aimed to investigate whether PEX is associated with cardiovascular involvement using carotid ultrasound measurements and myocardial tissue Doppler imaging (TDI).**

Methods **Thirty-six PEX patients and 34 age-matched and sex-matched healthy controls who had no PEX material were included. Fasting blood samples were taken and the following data were obtained from all cases: myocardial TDI measurements, the mean carotid intima-media thickness (IMT), total carotid plaque area and number.**

Results **There were no significant differences between the groups regarding clinical and biochemical data. The peak systolic TDI velocities at the septal (septal S) and lateral annuli (lateral S), and the isovolumic contraction velocity at the lateral annulus [lateral isovolumic contraction velocity (IVC)] were significantly lower in patients with PEX, than in controls ($P = 0.001$, <0.001 and 0.016, respectively) whereas IMT, total carotid plaque area and number were significantly higher ($P = 0.002$, 0.035 and 0.033, respectively). In a logistic regression analysis including age, septal S, lateral S, lateral IVC, IMT, total carotid plaque area and number, septal S, lateral S and IMT were significantly associated with PEX, ($P = 0.035$, 0.011 and 0.035, respectively).**

Conclusion **Peak systolic TDI velocities were significantly lower and IMT was significantly increased in patients with PEX. However, PEX was weakly associated with carotid plaque measurements.**

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Keywords: carotid plaque, intima-media thickness, pseudoexfoliation syndrome, tissue Doppler imaging

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Introduction

Pseudoexfoliation (PEX) syndrome is a common age-related disorder of unknown cause characterized by the widespread deposition of an abnormal extracellular fibrillar material on ocular and many extraocular tissues.[1,2] It is biomicroscopically diagnosed by recognizing abnormal fibrillar deposits on ocular structures.[1,2] The prevalence of PEX increases with age and may affect up to 30% of people older than 60.[1,3]

Although PEX syndrome was thought to be limited to the eye, recent studies have demonstrated that PEX material is widely distributed throughout the body, including heart, blood vessels and lungs.[1,2,4,5] Such deposits have been found in connective tissue portions of visceral organs adjacent to elastic fibers, collagen fibers, fibroblasts and to the walls of small blood vessels.[1,2,4] In myocardium, PEX aggregates were demonstrated to be closely related to myocytes.[2,4,5]

Some clinical studies showed an association between PEX syndrome and coronary artery disease (CAD), transient ischemic attacks, impaired systemic endothelial function, increased oxidative stress, asymptomatic impaired myocardial systolic and diastolic functions and elevated plasma homocysteine levels.[6–13] In contrast, others did not demonstrate any association between PEX and increased systemic vascular risk.[14,15]

Tissue Doppler imaging (TDI) is a well-tolerated and reproducible method for assessing systolic and diastolic myocardial functions.[16,17] Carotid intima-media thickness (IMT) and plaque area measurements are reliable and widely used screening methods to evaluate subclinical atherosclerosis, and are associated with future cardiovascular events.[18–21]

We aimed to investigate the association between PEX and increased cardiovascular risk, which still remains

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unclear, using tissue Doppler imaging, carotid IMT and carotid plaque measurements (total area of plaques, the number of plaques and the ratio of patients who had carotid plaque).

Methods

This study was designed as a prospective case–control study at Faculty of Medicine, Eskisehir Osmangazi University, Eskisehir, Turkey. Thirty-six PEX patients and 34 age-matched and sex-matched healthy controls were included. Each case underwent full ophthalmologic examination. The diagnosis of PEX was made by observing an abnormal extracellular fibrillar material on the anterior lens capsule and pupillary border by ophthalmologists.[1] Patients with unregulated hypertension prior to the study [systolic blood pressure (SBP) $\geq$160 and/or diastolic blood pressure (DBP) $\geq$90 mmHg], atrial fibrillation, suspected or known cardiovascular disease (CAD, carotid or peripheric artery disease), cardiomyopathy, moderate to severe valvular disease or severe systemic disease (renal dysfunction, malignancy) were excluded from the study. Coronary artery disease was defined as coronary artery stenosis on previous coronary angiography, a history of myocardial infarction or coronary revascularization, typical angina, ST-segment or T-wave changes specific for myocardial ischemia, pathological Q waves on electrocardiogram or regional wall motion abnormalities on echocardiography. Demographical and clinical characteristics including hypertension, diabetes mellitus, dyslipidemia, body mass index, tobacco use, family history of premature CAD and medications were recorded. Hypertension was considered as SBP more than 140 mmHg, DBP more than 90 mmHg or using an antihypertensive drug. Dyslipidemia was defined as total cholesterol level more than 200 mg/dl, low-density lipoprotein cholesterol (LDL-C) level more than 130 mg/dl or triglyceride level more than150 mg/dl. Laboratory values measured from fasting blood samples were as follows: glucose, creatinine, total cholesterol, HDL-C (high-density lipoprotein cholesterol), LDL-C, triglyceride, high sensitivity C-reactive protein (hs-CRP) and homocysteine. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki and the local ethical committee approved the study. Informed consent was obtained from the study participants.

Transthoracic echocardiography

Echocardiographic evaluation was performed by an echocardiography system (Acuson Sequoia C256, Mountain View, California, USA) equipped with a broadband transducer (3 V2c). Two-dimensional, M-mode and transthoracic Doppler echocardiographic examinations were performed on each participant. Early fast diastolic filling (E wave) and late diastolic filling (A wave) were obtained. Left ventricular hypertrophy was defined as left ventricular mass index at least 110 g/m^2 in women and at least 125 g/m^2 in men.[22] Mitral annular velocities from the septal and lateral annuli using pulse-wave TDI were recorded. Peak systolic velocity (S), early (Ea) and late (Aa) diastolic velocities, isovolumic contraction velocity (IVC) were obtained, and ratios of Ea/Aa and E/Ea were calculated for each annular side.

Carotid ultrasound measurements

Ultrasound measurements were performed by a high-resolution duplex ultrasound scanner (Siemens Acuson Y150 ultrasound system, Germany) equipped with an 8 MHz linear vascular probe by a single experienced neurosonologist blinded to clinical and demographic features of the patients. IMT was measured in areas without plaque in all carotid segments. IMT was calculated as a composite measure combining near and far walls of the common carotid artery IMT, bifurcation IMT and internal carotid artery IMT of both sides of the neck, and expressed as a mean of the maximum measurements of the 12 carotid sites.[18,23] Patients were considered to have plaque if they had a local intimal thickening of more than 1 mm.[19,24] The magnified longitudinal views of each plaque were measured in the common, internal and external carotid arteries on both sides. The plane, in which the measurement was made, was chosen by detecting the view showing the largest extent of plaque. The sum of cross-sectional areas of all plaques was calculated as total area of plaques.[19–21,24]

Statistical analysis

The analyses were performed using SPSS software (Statistical Package for the Social Sciences, Version 20.0, SPSS Inc., Chicago, Illinois, USA). Categorical variables were presented as frequencies, and differences between the groups were compared with the Chi-square test. The distribution of continuous variables for normality was tested with Shapiro–Wilk test and data were presented as mean $\pm$ SD for variables with a normal distribution, or median and interquartile ranges for variables with a not normal distribution. Variables with a normal distribution were compared using independent sample *t*-test. The groups for nonhomogeneously distributed variables were compared using Mann–Whitney *U* test. Spearman's ρ correlation analysis was used to test univariate relations in the PEX group. The independent predictors of PEX syndrome were assessed by univariate logistic regression analysis and model appropriateness was checked by Hosmer and Lemeshow test. All *P* values were two-sided, and a *P* value of 0.05 or less was considered significant.

Results

Of the 79 patients screened, three patients with PEX (1 had CAD, 1 had severe mitral regurgitation and 1 had cardiomyopathy) and six control patients (1 had CAD, 1 had carotid artery disease, 2 had severe mitral regurgitation, 1 had cardiomyopathy and 1 had malignancy) were

Table 1 Baseline clinical characteristics and laboratory findings of the groups

	PEX ($n=36$)	Controls ($n=34$)	P
Sex (male)	20 (55.6%)	14 (41.2%)	0.244
Age (years)	63.61 ± 7.42	60.76 ± 6.79	0.099
BMI	26.6 ± 4.6	28.6 ± 4.6	0.074
Heart rate (beats/min)	71.2 ± 9.6	72.5 ± 8.7	0.555
Hypertension (+/−)	12 (33.3%)	19 (55.9%)	0.091
Diabetes mellitus (+/−)	8 (22.2%)	4 (11.8%)	0.345
Dyslipidemia (+/−)	11 (30.6%)	14 (41.2%)	0.456
Family history for premature CAD (+/−)	3 (8.3%)	8 (23.5%)	0.106
Smoker (+/−)	8 (22.2%)	7 (20.6%)	1.000
Beta blockers (+/−)	4 (11.1%)	5 (14.7%)	0.731
ACEI (+/−)	0 (0%)	3 (8.8%)	0.109
ARB (+/−)	7 (19.4%)	8 (23,5%)	0.774
Calcium antagonists (+/−)	1 (2.8%)	4 (11.8%)	0.192
Statins (+/−)	4 (11.1%)	6 (17.6%)	0.508
Fasting glucose (mg/dl)	94.00 (81.75–112.50)	97.00 (89.50–105.25)	0.344
Creatinine	0.90 (0.72–0.98)	0.80 (0.70–0.90)	0.070
Total cholesterol (mg/dl)	205.39 ± 38.59	209.12 ± 28.46	0.649
HDL (mg/dl)	53.00 (39.75–62.00)	47.00 (41.00–58.25)	0.417
LDL (mg/dl)	131. 92 ± 36.18	134.94 ± 26.26	0.692
Triglyceride (mg/dl)	115.00 (91.00–188.75)	146.50 (110.75–200.50)	0.318
High-sensitive CRP (mg/l)	2.00 (0.80–4.40)	2.20 (1.10–3.45)	0.883
Homocysteine (μmol/l)	14.16 (10.77–17.25)	11.60 (7.99–15.62)	0.063

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PEX, pseudoexfoliation syndrome.

excluded from the study. Thus, 70 patients (36 PEX patients and 34 controls) were enrolled.

Clinical characteristics, medications and laboratory values of the groups

Baseline clinical characteristics, medications and laboratory values of the patients are presented in Table 1. No racial-based difference was present (all patients were white). Age was higher, body mass index and the frequency of hypertension were lower in patients with PEX, but they were not significant ($P=0.099$, 0.074 and 0.091, respectively). In addition, serum creatinine and homocysteine levels were higher in patients with PEX, but not significantly ($P=0.070$ and 0.063, respectively). The other clinical characteristics, medications and laboratory parameters of the groups were similar.

Analyses of echocardiographic and carotid ultrasound measurements

Two-dimensional and Doppler echocardiographic findings are summarized in Table 2. There were no significant differences in ejection fraction, E wave, A wave, E/A ratio, the frequency of left ventricular hypertrophy, and left ventricular mass index between the groups. The S-wave velocities at the septal and lateral annuli, and the IVC-wave velocity at the lateral annulus were significantly lower in patients with PEX syndrome than controls ($P=0.001$, <0.001 and 0.016, respectively). The ratio of

Table 2 Transthoracic echocardiographic findings of the groups

	PEX ($n=36$)	Controls ($n=34$)	P
EF (%)	61.17 ± 7.18	63.06 ± 7.21	0.276
LVH (+/−)	7 (19.4%)	3 (8.8%)	0.308
LV mass index (g/m^2)	102.84 ± 25.14	100.22 ± 19.59	0.630
E (cm/s)	69.50 (59.25–78.00)	67.50 (59.00–75.25)	0.609
A (cm/s)	76.75 ± 12.24	73.29 ± 11.32	0.962
E/A	0.92 (0.71–1.10)	0.88 (0.81–1.04)	0.110
Septal S (cm/s)	11.52 ± 2.26	13.52 ± 2.32	0.001
Septal IVC (cm/s)	10.50 ± 2.76	11.59 ± 2.30	0.076
Septal Ea (cm/s)	12.85 (11.00–14.00)	13.00 (12.00–15.00)	0.110
Septal Aa (cm/s)	14.00 (12.85–16.75)	15.00 (13.00–18.00)	0.257
Septal E/Ea	5.40 (5.07–6.29)	5.03 (4.22–5.90)	0.067
Septal Ea/Aa	0.85 (0.75–1.07)	0.85 (0.78–0.95)	0.773
Lateral S (cm/s)	11.81 ± 2.24	13.76 ± 2.01	<0.001
Lateral IVC (cm/s)	10.00 (9.00–12.00)	11.70 (10.00–14.00)	0.016
Lateral Ea (cm/s)	15.00 (12.00–16.00)	14.00 (11.75–15.17)	0.373
Lateral Aa (cm/s)	14.00 (12.00–16.00)	14.00 (13.00–17.00)	0.324
Lateral E/Ea	4.76 (4.31–5.44)	4.91 (4.12–5.46)	0.888
Lateral Ea/Aa	1.00 (0.82–1.17)	0.90 (0.82–1.07)	0.279

A, late diastolic filling wave; Aa, peak late diastolic velocity; E, early fast diastolic filling wave; Ea, peak early diastolic velocity; EF, ejection fraction; IVC, isovolumic contraction velocity; LV, left ventricle; LVH, left ventricular hypertrophy; S, peak systolic velocity; PEX, pseudoexfoliation syndrome.

E/Ea was higher in patients with PEX, but it was not significant (0.067). The other TDI parameters were similar between the groups. The IMT, total carotid plaque area and total plaque number were significantly higher in patients with PEX syndrome than in controls ($P=0.002$, 0.035 and 0.033, respectively). The ratio of patients who had carotid plaque were similar ($P=0.147$) (Table 3).

Univariate associations of age with various outcome measures in pseudoexfoliation syndrome patients

In the PEX goup, when age was taken as the dependent variable, and septal S, lateral S, IMT, total plaque area and number as independent, we found that IMT ($r=0.623$, $P<0.0001$), total plaque area ($r=0.535$, $P=0.001$) and total plaque number ($r=0.526$, $P=0.001$) were independently correlated with age. Figure 1 shows that age is positively and significantly correlated with IMT.

Logistic regression analysis results

Seven variables including age, septal S, lateral S, lateral IVC, IMT, total plaque area and number were assessed by univariate logistic regression analysis. The model found to be appropriate by Hosmer and Lemeshow test ($P=0.977$). Table 4 presents univariate logistic regression analysis results. Septal S, lateral S and IMT were significantly associated with PEX ($P=0.035$, 0.011 and 0.035, respectively) whereas the others were not.

Discussion

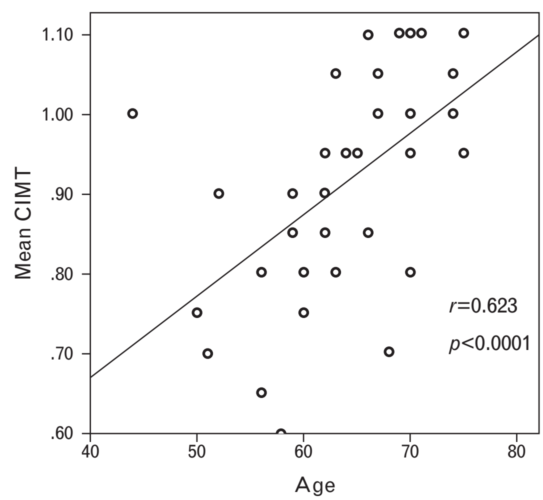
This study demonstrated that myocardial peak systolic TDI velocities were lower and IMT was increased in patients with PEX syndrome when compared with age-matched and sex-matched controls. On the contrary, PEX and carotid plaque measurements were weakly associated. In addition, age was independent, correlated with IMT, total plaque area and number in patients with PEX.

The prevalence of PEX syndrome markedly increases with age and differs between countries. High rates have been reported in older age groups (>70 years) in northern Finland (25.3%), Iceland (31.5%) and Saudi Arabia (26.5%).[25] In the other European countries and the United States, the prevalence has been reported as about 4–6% in older ages.[26]

Many clinical studies have stated a possible link between PEX syndrome and systemic vascular diseases previously. These include transient ischemic attacks, higher prevalence of CAD, myocardial systolic dysfunction detected by TDI, myocardial diastolic dysfunction detected by pulse Doppler echocardiography and aneurysms of the abdominal aorta.[6,7,11,12,27] Elevated plasma homocysteine was found to be more common in patients with PEX and it has been suggested hyperhomocysteinemia, which may cause endothelial dysfunction, might also participate in the pathogenesis of PEX syndrome.[13] Another study has demonstrated impaired brachial artery flow-mediated and nitroglycerine-mediated dilatations in PEX patients, revealing systemic endothelial dysfunction.[8] In addition, some studies showed significantly high levels of hydrogen peroxide and xanthine oxidase, in contrast with a lower level of catalase and paraoxonase activities, suggesting an increased oxidative stress and decreased total antioxidant capacity in such patients.[9,10] On the contrary, other studies did not demonstrate any association between PEX and increased cardiovascular risk.[14,15]

Immunohistochemical studies have shown PEX material is a complex glycoprotein/proteoglycan structure bearing epitopes of the basement membrane and elastic fiber

Fig. 1



Relationship between age and mean carotid intima-media thickness (CIMT).

Table 3 Carotid ultrasound findings of the groups

	PEX ($n=36$)	Controls ($n=34$)	P
Mean carotid IMT (mm)	0.90 ± 0.14	0.80 ± 0.14	0.002
Total plaque area (cm^2)	0.00 (0.00–0.38)	0.00 (0.00–0.03)	0.035
Total plaque number	0 (0–2)	0 (0–1)	0.033
Carotid plaque (+/−)	17 (47.20%)	10 (29.40%)	0.147

IMT, intima-media thickness; PEX, pseudoexfoliation syndrome.

Table 4 Univariate logistic regression analysis results

	OR	95% CI	P
Age	0.997	0.906–1.098	0.958
Septal S (cm/s)	0.710	0.517–0.976	0.035
Lateral S (cm/s)	0.637	0.449–0.903	0.011
Lateral IVC (cm/s)	1.088	0.858–1.379	0.487
Mean carotid IMT (mm)	630.317	1.574–252359.368	0.035
Total plaque area (cm^2)	4.285	0.115–160.331	0.431
Total plaque number	0.945	0.338–2.642	0.915

CI, confidence interval; IMT, intima-media thickness; IVC, isovolumic contraction velocity; OR, odds ratio; PEX, pseudoexfoliation syndrome; S, peak systolic velocity.

system, and the characteristic fibrils are composed of microfibrillar subunits.[1,2] Elastin is a major part of the extracellular matrix of arterioles and previous studies have demonstrated accumulation of PEX material in the adventitial and subendothelial connective tissues of blood vessels, and elastosis of tunica media.[27,28] In addition, the PEX fibers have been shown to closely appose to myocardial cells and their interrupted basement membranes.[1,2,4] These deposits may lead to impaired endothelial function. Endothelial dysfunction is an independent predictor of future cardiovascular events. A proteolytic imbalance between matrix metalloproteinases and tissue inhibitor of metalloproteinases, low-grade inflammatory process, increased cellular and oxidative stress have been put forward as possible mechanisms of accumulation of PEX material.[1]

For these reasons, there may be an association between PEX and an increased cardiovascular risk. We aimed to investigate this matter using TDI, IMT and carotid plaque measurements.

Tissue Doppler examination findings

We found that the lower septal and lateral S velocities were significantly associated with PEX, suggesting the accumulation of PEX deposits in myocardium. These findings were compatible with a previous study demonstrating myocardial systolic velocities detected by TDI significantly lower in patients with PEX, suggesting subclinical myocardial ischemia.[11] The accumulation of PEX fibers in myocardium, systemic endothelial dysfunction and increased oxidative stress may explain impaired myocardial systolic functions in patients with PEX.

On the contrary, we did not find any myocardial diastolic abnormality using TDI in our study. In myocardial ischemia, the first myocardial abnormality is generally diastolic dysfunction, but we found myocardial systolic functions were impaired whereas diastolic functions were not. The accumulation of fibrillar material in the myocardium could be responsible for the impairment of systolic functions before diastolic functions in our study.

Carotid ultrasound measurements

Carotid IMT, the total plaque area and the number of plaques have all been reported to be predictors of cardiovascular events, and combination of IMT and carotid plaque measurements have been demonstrated to improve the prediction of ischemic cardiovascular events.[19–21] The IMT is strongly associated with age and hypertension and increased IMT may not always reflect the atherosclerotic process.[20,24,29] However, carotid plaque measurements are more reliable for the atherosclerotic burden than IMT.[20,30]

We showed an independent association between PEX and IMT. Accumulation of PEX fibers in arterial walls, systemic endothelial dysfunction and oxidative stress may explain the significant increase of IMT in PEX. In contrast, we did not find a significant link between PEX and carotid plaque measurements. Our findings suggest that accumulated material in PEX patients may not represent atherosclerotic burden. For this reason, PEX deposits could not have any significant impact on atherosclerotic parameters.

Our results show the accumulation of PEX material in myocardium and carotid artery wall in PEX patients. Impaired endothelial function and increased oxidative stress are strong predictors for cardiovascular disease, and they have been demonstrated in PEX patients, as mentioned above. Such accumulations may indicate impaired endothelial function and increased oxidative stress in PEX patients and may be related to an increased cardiovascular risk. For this reason, in the future, PEX patients may be screened for cardiovascular involvement. In addition, histopathological examinations of the atherosclerotic plaques of PEX patients obtained postmortem or from endarterectomy specimens can further clarify an association between PEX and atherosclerosis.

Other parameters

The fasting blood measurements did not differ between the groups in our study. This finding may be related to the small population size of our study. In addition, we could not find any difference in E wave, A wave and E/A ratio between the groups, in contrast to a previous study that demonstrated a possible relationship.[12]

Limitations

The main limitation of our study is its noninvasive nature. By obtaining tissue biopsies from carotid arteries and myocardium in such patients, one can precisely conclude whether there is an association between PEX deposits and cardiovascular involvement. The number of patients was relatively small in our study; however, we were able to reach several significant findings. As shown by other studies, our methods have some weaknesses. For example, TDI parameters may be affected by age and preload, and IMT is affected by age and hypertension.[21,31,32] In addition, left ventricular hypertrophy and left ventricular mass index measurements using two-dimensional echocardiography make important geometric assumptions about the left ventricle which leads to inaccuracies.

In conclusion, myocardial peak systolic TDI velocities at the septal and lateral annuli are significantly lower and IMT is significantly increased in patients with PEX. However, PEX syndrome is weakly associated with carotid plaque measurements. Further studies investigating the existence of the deposits in atherosclerotic plaques or intimal layer in such patients may clarify this matter. The accumulated material in arterial walls and myocardium in PEX patients may be the result of endothelial dysfunction and increased oxidative stress, and may indicate increased cardiovascular risk. Screening for cardiovascular involvement and more aggressive cardiovascular prevention in PEX patients may be needed.

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