Endothelial Function and Novel Vascular Risk Factors in Pseudoexfoliation Syndrome

Psödoeksfoliasyon Sendromunda Endotel Fonksiyonları ve Yeni Vasküler Risk Faktörleri

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ABSTRACT Objective: Pseudoexfoliation syndrome (PES) is characterized by ocular and extraocular manifestations. Recent trials suggested a possible relation between PES and an increased risk of cardiovascular disease. We tried to delineate this association by determining various cardiovascular risk markers ranging from plasma lipids to intimal medial thickness of common carotid artery intima-media thickness (carotid IMT) in patients with PES. **Material and Methods:** Twenty-six patients with ocular PES (study group) and 24 healthy subjects (control group) were enrolled in the study. Plasma lipids, lipoprotein (a), apolipoprotein A and B, homocysteine, urinary protein and albumin were measured. Endothelial dependent and independent brachial artery dilation and carotid IMT were also determined by ultrasonography. **Results:** The study group had significantly higher levels of lipoprotein (a) (1.03 vs 0.13 mg/dL; p= 0.001), apolipoprotein A (2.04 vs 1.1 mg/dL; p< 0.001), homocysteine (22.85 vs 11.6 mmol/L; p< 0.001), urinary protein excretion (59.95 vs 4.3 mg/L; p< 0.001), urinary albumine excretion (11.38 vs 6 mg/L; p= 0.023), mean carotid IMT (0.12 vs 0.07; p< 0.001) and brachial artery diameter (0.4 ± 0.05 vs 0.37 ± 0.02 cm; p= 0.016) than those of the control group. However, flow mediated dilation and trinitroglycerin mediated dilation (8.61% vs. 11.6%; p= 0.001 and 13.23 ± 3.54% vs. 16.38 ± 2.08%; p= 0.005, respectively) were significantly lower in the study group. The only risk factors of PES were trinitroglycerin mediated dilation and homocysteine. **Conclusion:** Patients with PES had high novel coronary risk factors such as lipoprotein (a), apolipoprotein A and homocysteine as well as impaired brachial artery dilation and increased carotid IMT. Our findings imply that the patients with PES have many cardiovascular risk factors and therefore may have an increased risk of future cardiovascular events.

Key Words: Exfoliation syndrome; carotid artery diseases

ÖZETAmaç: Psödoeksfoliyasyon sendromu (PES) oküler ve ekstraoküler tutulumla karakterizedir. Yapılan çalışmalar, PES ile kardiyovasküler risk faktörlerinin artışı arasında muhtemel bir ilişki olduğunu düşündürmektedir. Çalışmamızda bu ilişkiyi, PES'li olgularda, plazma lipidlerinden karotis kommunis arterinin intimal mediyal kalınlığı (karotis İMK)'na kadar birçok kardiyovasküler risk faktörünü belirleyerek ortaya koymayı amaçladık. **Gereç ve Yöntemler:** Oküler PES'li 26 olgu (çalışma grubu) ve 24 sağlıklı birey (kontrol grubu) çalışmaya alındı. Plazma lipidleri, lipoprotein (a), apolipoprotein A ve B, homosistein, idrar protein ve albümin düzeyleri çalışıldı. Brakiyal arterin endotele bağımlı ve bağımsız dilatasyonu ile karotis İMK ultrasonografiyle belirlendi. **Bulgular:** Çalışma grubunda kontrol grubuna göre lipoprotein (a) (1.03'e karşın 0.13 mg/dL; p= 0.001), apolipoprotein A (2.04'e karşın 1.1 mg/dl; p< 0.001), homosistein (22.85'e karşın 11.6 mmol/L; p< 0.001) idrar protein seviyeleri (59.95'e karşın 4.3 mg/L; p< 0.001), idrar albümin seviyesi (11.38'e karşın 6 mg/L; p= 0.023), karotis İMK (0.12'ye karşın 0.07; p< 0.001) ve brakiyal arter çapı (0.4 ± 0.05'e karşın 0.37 ± 0.02 cm; p= 0.016) belirgin şekilde yüksekti. Ancak akım aracılı dilatasyon ve trinitrogliserin aracılı dilatasyon (sırasıyla %8.61'e karşın %11.6; p< 0.001 ve %13.23 ± 3.54'e karşın %16.38 ± 2.08; p= 0.005) çalışma grubunda daha azdı. PES'nin risk faktörleri yalnızca trinitrogliserin aracılı dilatasyon ve homosistein idi. **Sonuç:** PES olgularında lipoprotein (a), apolipoprotein A ve homosistein gibi yeni risk faktörlerinin daha yüksek olduğu bulundu. Aynı zamanda brakiyal arter dilatasyonu bozulmuş ve karotis IMK artmıştı. Çalışmamızın sonuçları, PES'li olgularda pek çok kardiyovasküler risk faktörünün olduğunu ve bu nedenle gelecekteki kardiyovasküler olay riskinin artmış olduğunu ifade etmektedir.

Anahtar Kelimeler: Eksfoliyasyon sendromu, karotis arter hastalığı

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Pseudoexfoliation syndrome (PES) is an age-related disease characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues and is frequently associated with severe chronic secondary open angle glaucoma and cataract.[1] PES may affect up to 30% of people older than 60.[1] In PES, the abnormally produced material appears as periodic acid-Schiff positive, eosinophilic, bush-like, nodular or feathery aggregates in light microscopy[2] and aggregates ocular and extraocular sites such as the vascular wall.[3] Schumacher et al[4] reported exfoliation material in the adventitial tissue and the subendothelium of abdominal aorta. Therefore, patients with PES may have an increased risk of cardiovascular events because of vascular damage.

Indeed, the findings of recent studies have implied that there is a possible relation between PES and cardiovascular events such as angina, myocardial infarction or stroke.[5] However, these findings were not confirmed in other studies.[6,7] Nevertheless, the association between PES and aneurysms of the abdominal aorta or transient ischemic attacks has been reported.[8,9]

In this cross-sectional case-control study, we aimed to determine the presence of various cardiovascular risk factors in PES patients.

MATERIAL AND METHODS

The study was conducted between 2007-2008 in the First Ophthalmology Clinic of Ankara Numune Training and Research Hospital. The study group comprised 26 consecutive newly diagnosed PES patients (mean age 66 ± 8 years, 16 male and 10 female) with a diurnal intraocular pressure below 20 mmHg, normal visual field with normal optic disc and without any medication. None of the patients had hypertension, diabetes, dyslipidemia and smoking history. The presence of hypertension, diabetes and hyperlipidemia were defined as blood pressure over 140/90 mmHg, fasting glucose level over 126 mg/dL and total cholesterol levels over 240 mg/dL or low-density lipoprotein (LDL)-cholesterol levels over 160 mg/dL, respectively. Smoking was defined as any amount of current cigarette use. The control group consisted of 24 healthy subjects (mean age 64 ± 3 years, 15 male and 9 female). All participants underwent detailed physical examination, complete blood count, routine blood chemistry, electrocardiography, and echocardiography to rule out systemic diseases. This study was reviewed and approved by the local ethics committee and signed written informed consents were obtained from all participants.

DIAGNOSIS OF PSEUDOEXFOLIATION SYNDROME

PES was diagnosed by visualization of the typical dandruff-like material at the papillary margin or the anterior lens surface with slit-lamp biomicroscope before and after midriasis. Glaucoma group medications were not allowed before the study tests were completed and were initiated after patients provided blood and urine samples and underwent ultrasonographic examination.

EVALUATION OF ENDOTHELIAL FUNCTION

Endothelial function was assessed with endothelial-dependent flow-mediated vasodilatation (FMD) of the brachial artery by an experienced operator. All subjects were prepared according to the principles of the International Brachial Artery Reactivity Task Force report.[10] The assessment was done following 8-12 hours fasting in a quiet and temperature controlled room. After placing the cuff of the sphygmomanometer above the antecubital fossa the baseline rest images of brachial artery were acquired with 10 MHz multiple linear-array transducer (Vivid 7, Vingmed Ultrasound, General Electric, USA). Thereafter, arterial occlusion was created by cuff inflation to 250 mmHg for 4.5 minutes. After cuff deflation, the same images of brachial artery were recorded within 45-60 seconds. Both in resting and reactive hyperemia state pulsed wave Doppler flow velocities, which were derived from a mid-artery sample volume, were recorded. The vessel diameter change was expressed as follows: (reactive diameter-resting diameter/resting diameter) x 100. After this procedure, in order to assess endothelium-independent vasodilatation, patients were allowed to rest 10 to 15 minutes and following sublingual nitroglycerin spray administration brachial artery images were recorded again within 3 to 4 minutes.

INTIMAL MEDIAL THICKNESS OF COMMON CAROTID ARTERY

Carotid ultrasound studies were performed with 10 MHz phased-array scanner (Vivid seven, Vingmed Ultrasound, General Electric, USA) as previously described.[11] A minimum of 4 measurements of the common carotid far wall were taken 10 mm proximal to the bifurcation to derive the mean intimal medial thickness of the common carotid artery (carotid IMT).

STATISTICAL ANALYSIS

Statistical analyses were performed by SPSS for windows version 15.0 (SPSS Inc., Chicago, IL, USA). Normality test was done using the Shapiro-Wilk test and graphically for continuous variables. Normally distributed variables (age, cholesterol level, etc.) were expressed as mean ± standard deviation, abnormally distributed variables [triglyceride and C-reactive protein (CRP) levels, etc.] were expressed as median [Inter Quartile Range (IQR)] and categorical variables as frequency. In comparison of the variables, independent samples t-test and the Mann-Whitney U test were used according to the normality test results. The distribution of gender in groups was compared by Pearson's chi-square test. In order to delineate predictive factors for the PES presence, stepwise logistic regression analysis was made and the unadjusted odds ratio (OR) as an estimate of relative risk and the 95% confidence intervals (95% CI) were calculated. Only parameters with a p value below 0.1 for the comparison of groups were chosen for logistic regression analysis. Finally, discriminatory power of independent parameters was quantified in terms of area under Receiver Operating Characteristics (ROC) curve. Pairwise comparison of ROC curves was done by MedCalc software version 9.2.0.1 (Medcalc Software, Mariakerke, Belgium). A p value ≤ 0.05 was set as statistically significant.

RESULTS

The difference between PES and controls for age, gender, body mass index (BMI), serum lipid profile, glucose and CRP was not significant (Table 1). While the comparison of apolipoprotein B did not show a significant difference between the PES group and the controls, the difference was significant for lipoprotein (a), apolipoprotein A and homocysteine between the groups (Table 1). In patients with PES, the carotid IMT was significantly thicker than controls ($p< 0.001$) (Table 1). Brachial artery diameter at resting state was not different between PES and control groups (Table 1). However, both the flow mediated dilatation (endothelium dependent), and nitroglycerin mediated dilatation (endothelium-independent) of brachial artery were significantly attenuated in PES patients than in controls (Table 1). Urine protein content was higher in patients than in controls (Table 1).

According to stepwise logistic regression analysis, homocystein (OR= 2.07; 95% CI= 1.19-3.58, p= 0.009) and nitroglycerine-induced dilatation of brachial artery (OR= 0.63; 95% CI= 0.41-0.95, p= 0.029) were risk factors for PES. The cut-off values for predicting PES by homocystein is 14.6 mmol/L with a sensitivity and specificity of 76.9% and 100%, respectively, and by nitoglycerine induced dilatation is 14.89% with a sensitivity and specificity of 69.2% and 84.6%, respectively. Areas under curves (AUCs) for predicting PES was 0.936 and 0.8 for homocystein and nitroglycerine induced dilatation of brachial artery, respectively (Figure 1, 2). Pairwise comparison of receiver operating characteristic (ROC) curves revealed that, the difference between AUCs, standard error, 95% CI and p value were 0.136, 0.086, -0.032 to 0.304 and 0.112, respectively.

DISCUSSION

The main result of our study is significantly high levels of novel cardiovascular risk factors and impaired endothelium-dependent and-independent vasodilatation response in patients with PES in whom carotid IMT was increased. Of these, nitroglycerin mediated dilatation (endothelium-independent) and homocysteine were risk factors for PES. The discriminatory power of nitroglycerine mediated dilatation and homocysteine was similar (p= 0.112). Our study also implied that ocular exfoliation material might be an early sign of vascular disease.

TABLE 1: Characteristics and their comparison of groups.

	Control group (n= 24)	Patient group (n= 26)	Test statistics	p
Gender	Male 15, Female 9	Male 16, Female 10	χ^2= 0.005	0.944
Age (year)	63.85 ± 2.94	65.50 ± 7.92	t= 0.725	0.473
BMI (kg/m^2)	27.38 (3.49)	27.46 (6.13)	Z= 0.030	0.988
Total cholesterol (mg/dL)	208.77 ± 23.80	207.50 ± 43.47	t= 0.098	0.923
HDL (mg/dL)	49.15 ± 7.72	45.73 ± 5.91	t= 1.536	0.133
LDL (mg/dL)	137.95 ± 12.94	135.88 ± 26.84	t= 0.262	0.795
VLDL (mg/dL)	28.65 ± 10.89	34.69 ± 13.17	t= 1.427	0.162
Triglyceride (mg/dL)	139.00 (93.50)	126.00 (76.50)	Z= 0.939	0.353
Fasting glucose (mg/dL)	96.08 ± 7.32	94.50 ± 8.42	t= 0.760	0.259
CRP (IU)	4.00 (5.20)	3.17 (2.83)	Z= 1.163	0.255
Lipoprotein (a) (mg/dL)	0.13 (0.24)	1.03 (2.21)	Z= 3.278	0.001
Apolipoprotein A (mg/dL)	1.10 (0.42)	2.04 (2.01)	Z= 4.098	< 0.001
Apolipoprotein B (mg/dL)	1.09 (0.26)	1.87 (2.16)	Z= 1.818	0.071
Homocysteine (mmol/L)	11.60 (2.95)	22.85 (19.54)	Z= 4.395	< 0.001
Urine protein (mg/L)	4.30 (2.45)	59.95 (35.67)	Z= 5.037	< 0.001
Urine albumine (mg/L)	6.00 (2.56)	11.38 (19.95)	Z= 2.265	0.023
Carotid IMT	0.07 (0.03)	0.12 (0.03)	Z= 4.663	< 0.001
Brachial artery diameter at basal state (cm)	0.37 ± 0.02	0.40 ± 0.05	t= 2.526	0.016
FMD %	11.60 (2.39)	8.61 (4.18)	Z= 3.308	0.001
TNGMD %	16.38 ± 2.08	13.23 ± 3.54	t= 2.954	0.005

t= Independent samples t-test result, Z= Mann-Whitney u-test results, χ^2: Pearson's chi-square test results.

BMI: Body mass index; HDL: High density lipoprotein; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; CRP: C-reactive protein; carotid IMT: Intimal medial thickness of common carotid artery; FMD: Flow mediated dilation; TNGMD: Trinitroglycerine mediated dilation.

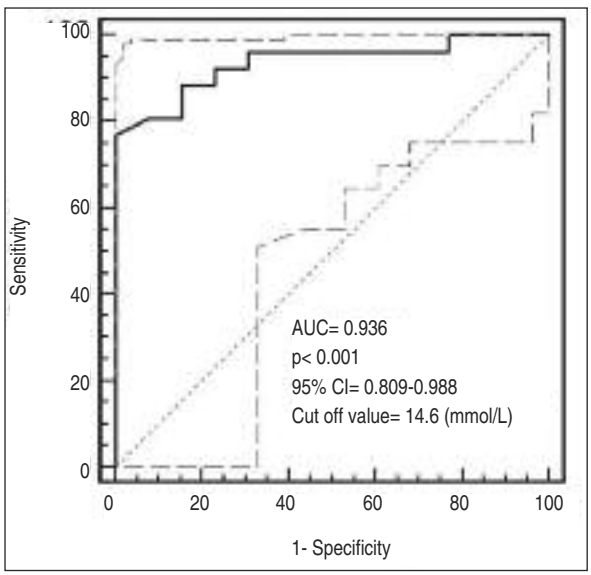

FIGURE 1: Receiver operating characteristics (ROC) curve for predicting pseudoexfoliation by homocysteine.

AUC: Area under curve; CI: Confidence interval. Dashed lines represent the upper and lower bounds of 95% confidence interval.

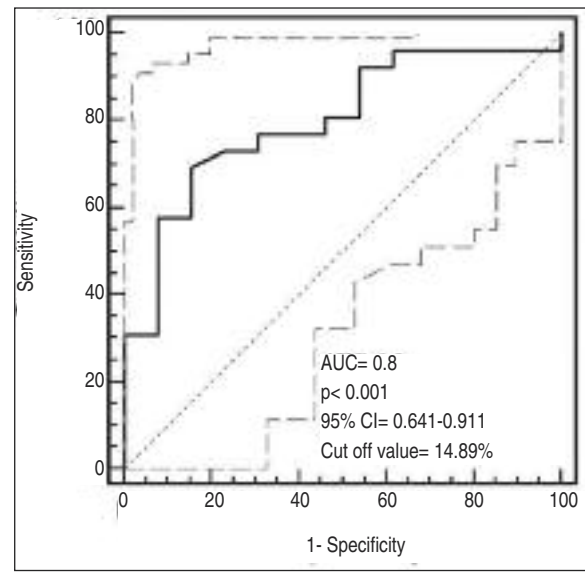

FIGURE 2: ROC curve for predicting pseudoexfoliation by nitroglycerine-induced dilatation of brachial artery.

AUC: Area under curve; CI: Confidence interval. Dashed lines represent the upper and lower bounds of 95% confidence interval.

There is evidence for vasculopathy of ocular tissues and blood-aqueous barrier dysfunction in PES patients.[7,12-14] In extraocular locations, exfoliation material was primarily found in connective tissue portions of visceral organs, often in the periphery of blood vessels, and it seemed to originate from connective tissue fibroblasts, smooth and striated muscle cells and heart muscle cells.[3] Many studies showed the association of PES with transient ischemic attack,[9] hypertension, myocardial infarction or stroke,[5] abdominal aortic aneurysm,[4] asymptomatic myocardial dysfunction,[15] and acute cerebrovascular events.[16] These findings in conjunction with our results suggest that the accumulation of exfoliation material on arterial wall impairs arterial structure and function.

Elevated levels of homocysteine have been found both in plasma and aqueous humor in PES patients irrespective of glaucoma presence.[17,18] Homocysteine has many adverse effects leading to enhanced proinflammatory response and oxidative stress such as smooth muscle proliferation, endothelial dysfunction, LDL cholesterol oxidation, increased expression of monocyte chemoattractant protein, and interleukin-8.[19-22] In the Framingham Study, the authors found a link between plasma homocysteine levels and an increased risk for congestive heart failure among adults without prior myocardial infarction.[23] The patients within highest homocysteine level quintile had an odds ratio of 6.8 for peripheral artery disease.[24] Therefore, depressed endothelial function in our study is not an unexpected finding. However, it is still not clear whether PES causes hyperhomocysteinemia or the opposite.

Analysis of the aqueous humor revealed an increased amount of the vasoactive peptide endothelin 1, growth factors and decreased levels of nitric oxide in patients with PES.[25-27] All these factors may lead to endothelial dysfunction, platelet aggregation, reduction of nitric oxide bioavailability, and abnormal perivascular metabolism. If these findings are true for systemic involvement, it also may explain the increased resistance in blood vessels, such as in our study.

In a study conducted by Yılmaz et al[28], increased serum concentrations of malondialdehyde and decreased serum concentration of vitamin C was shown in PES patients, reflecting free radical damage to lipid peroxides. In addition, it is well known that PES is associated with ocular ischemia.[29, 30] All of these findings suggest that, vascular involvement might be a consequence of PES.

Several studies in patients with[31,32] and without[33] cardiovascular disease could not find any correlation between carotid IMT and FMD. This discrepancy may be related to carotid IMT and brachial artery FMD providing distinct information identifying different stages in atherogenesis. Carotid IMT was shown to correctly identify histological abnormalities and to correlate with traditional and emerging cardiovascular risk factors[34,35] and more importantly, it was a potent independent predictor of incident myocardial infarction and of stroke.[36,37] Although our subjects were selected among those without classical atherosclerotic risk factors, the carotid IMT was higher in the patient group, a finding that may be related to the increased novel risk factors such as homocysteine, lipoprotein (a), and apolipoprotein A in the patient group.

Several evidences suggest that brachial artery FMD is a valid measure of vascular integrity, which was shown to be nitric oxide dependent.[10,38] Impaired FMD was shown in autoimmune diseases.[39,40] Results of our study revealed that brachial artery FMD and trinitroglycerin-induced dilatation, which were risk factors for PES, were impaired in patients with PES our findings were in line with previous studies.[41] In healthy subjects, no relationship between FMD and lipid parameters was found.[42] Our results also support the previous findings such that while there was no difference between controls and PES patients in serum lipid profiles, both brachial artery endothelial functions and carotid artery structure were impaired in patients with PES. All these findings imply an increased risk of coronary artery disease in patients with PES. A very recent study declared the link between coronary artery disease and PES.[43]

The results of our study also showed an increase in the 24 hours urine protein and albumin.

This finding may be related to the multiorgan involvement of PES, particularly affecting the arteriolar basement membrane, which was suggested by Shimizu et al.[44] To the best of our knowledge, this is the first study showing renal functional impairment in PES. Although our subjects had no main confounding factors that affect the microalbuminuria such as hypertension, smoking, obesity and diabetes mellitus, the only logical explanation for this finding is progressive decrease of glomerular filtration rate due to the histological change of glomerular basement by exfoliation material. Microalbuminuria is also a sign of endothelial dysfunction, not necessarily confined to the kidney, reflecting a cardiovascular disease related to risk factors such as aging, high blood pressure, Type 2 diabetes, smoking, obesity, elevated serum cholesterol, reduced HDL, increased intermediate and small, dense LDL. Although the level of microalbuminuria and proteinuria were subclinical, progression to renal failure in the natural course of the disease is likely, which is suggestive of renal involvement in PES. Only Han et al reported that PES eyes had higher perfusion time with unwashed areas with dye.[13] Urinary excretion of microalbumin and protein are not only signs of endothelial dysfunction, but also are risk factors for cardiovascular disease and cerebrovascular events.[6] The only factor in this ominous course may not be aging and PES may contribute to the process.

In conclusion, we found that patients with PES had impaired endothelial function, structural vessel wall abnormality, increased levels of serologic atherosclerotic risk factors, such as homocysteine, lipoprotein (a), and apolipoprotein A, and minimal renal involvement probably due to microvascular structural abnormalities. Besides, homocysteine levels and endothelium-independent vasodilatation were risk factors for PES. Our study revealed impaired endothelial functions in patients with PES and this might be due to elevated cardiovascular risk factors in pathophysiologic mechanisms of PES. As a result, cardiovascular risk factors should be investigated in patients with PES and if possible should be managed effectively.

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