High-Sensitivity C-Reactive Protein Levels in Patients with Pseudoexfoliation

Psödoeksfoliasyonlu Hastalarda Yüksek Duyarlıklı C-Reaktif Protein Düzeyleri

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ABSTRACT

Purpose: To evaluate the systemic high sensitivity C-reactive protein (hs-CRP) levels in pseudoexfoliation syndrome (PES).

Materials and Methods: Thirteen cases with PES, 9 cases with pseudoexfoliation glaucoma (PEG) and 24 control subjects were included to our prospective controlled study. All of the cases were between 40 and 80 year-old and none of them had histories of any systemic medicine, systemic hypertension, diabetes mellitus, cardiovascular disease, chronic liver or kidney disease, any type of malignancy, any type of infection and inflammatory diseases.

Results: No statistically significant difference was observed in terms of age, gender and body mass index between groups ($p>0.05$). The median value of the hs-CRP in the study group was 3.00 mg/dl (0.3-160.9 mg/dl), while it was 3.70 mg/dl (0.4-97.4 mg/dl) in the control group. There was no statistically significant difference between the groups in terms of hs-CRP values ($p>0.05$).

Conclusion: There were no significant changes in hs-CRP levels between the cases with PES compared with healthy subjects.

Key Words: High sensitivity C-reactive protein, pseudoexfoliation syndrome, vascular endothelial dysfunction, atherosclerosis.

ÖZ

Amaç: Psödoeksfoliasyon sendromunda (PES) yüksek duyarlıklı C-reaktif proteinin (yd-CRP) sistemik düzeylerini değerlendirmek.

Gereç ve Yöntemler: Prospektif kontrollü çalışmamıza, PES'lu 13 olgu, psödoeksfoliasyon glokomlu (PEG) 9 olgu ve kontrol grubu olarak 24 sağlıklı birey dahil edildi. Hastalar 40-80 arasında olup, hiçbirinde sistemik ilaç kullanımı, sistemik hipertansiyon, diabetes mellitus, kardiyovasküler hastalıklar, kronik karaciğer veya böbrek hastalığı, malignensi, infeksiyöz ve inflamatuvar hastalık öyküsü mevcut değildi. Çalışma ve kontrol grubunda yer alan katılımcıların periferik kan örneklerinde yd-CRP düzeyleri ölçüldü. Ayrıca, iki taraflı psödoeksfoliatif materyal birikimi, kilo, boy, vücut kitle indeksi, cinsiyet ve yaş parametreleri değerlendirildi. İstatistiksel analiz için Chi-square, Student-t test ve Mann-Whitney U testleri kullanıldı.

Bulgular: Gruplar arasında yaş, cinsiyet ve vücut kitle indeksi dağılımı açısından anlamlı farklılık yoktu ($p>0.05$). Çalışma grubundaki ortanca yd-CRP düzeyi 3.00 mg/dl (0.3-160.9 mg/dl) iken, kontrol grubundaki 3.70 mg/dl (0.4-97.4 mg/dl) idi. İki grup arasında yd-CRP düzeyleri yönünden anlamlı farklılık yoktu ($p>0.05$).

Sonuç: PES'lu ve sağlıklı bireyler arasında serum yd-CRP seviyeleri arasında anlamlı farka rastlanmadı.

Anahtar Kelimeler: Yüksek duyarlıklı C-reaktif protein, psödoeksfoliasyon sendromu, vasküler endotelyal disfonksiyon, ateroskleroz.

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INTRODUCTION

Pseudoexfoliation syndrome (PES) is characterized by accumulation of an extracellular matrix material called "Pseudoexfoliation Material" (PEM) which is especially seen in the anterior segment of the eye. Its prevalence rises in the fifth and sixth decade.[1] Today we know that, PES is a disease that has a chronic process with systemic features. PEM is not only seen in the anterior segment of the eye, but also in vessel walls of the visceral organs and can cause endothelial dysfunction. The association between inflammation markers and endothelial dysfunction supports the inflammation based hypothesis in the etiopathogenesis of the vascular diseases seen in PES.[2,3]

C-Reactive Protein (CRP) is one of the markers and regulatory proteins of many inflammatory processes. CRP also plays an important role in the pathogenesis of atherosclerosis and endothelial dysfunction. Inflammation plays a fundamental role at the initiation, progression and thrombotic complications of atherosclerosis. Thus, significant relationship between cardiovascular disease risk and raised CRP levels was revealed before.[4,5] Researchers showed the significant relationships between normal tension glaucoma, nonarteritic ischemic anterior optic neuropathy and high CRP levels as well as cardiovascular disease risk.[6,7]

As we look at the literature, we can see studies about the relationship between PES and cardiovascular diseases.[8] In this study, we aimed to evaluate the relationship between PES and CRP, which plays an important role at the initiation, progression and risk scoring of the cardiovascular diseases and peripheral endothelial dysfunction.

MATERIALS AND METHODS

The study was initiated after receiving approval from the Clinical Research Ethics Committee of the Mersin University Faculty of Medicine (2010/41) and was designed as prospective controlled study. Patients who were referred to our clinic between January 2011 and April 2012, and had been recently diagnosed as ~~having~~ PES and pseudoexfoliation glaucoma (PEG) in their routine ophthalmological examinations were involved in the study. The participants were between 40 and 80 years of age with no systemic diseases and medicine. The exclusion criteria were systemic hypertension, diabetes mellitus, cardiovascular disease, chronic liver or kidney disease, any types of malignancy, any types of infection and inflammatory diseases. The study group involved 22 patients with PES or PEG and the control group involved 24 subjects. None of the cases and the control group had any ocular diseases such as uveitis, other types of glaucoma, cataract, age related macular disease and other retinal pathologies. One investigator (AY) performed the complete ophthalmologic examination of the all participants. Bilaterality of the PEM, weight, height, body mass index, gender and age of the participants were noted carefully. Written informed consent was obtained from all the patients before blood samples were collected. The study adhered to the tenets of the Declaration of Helsinki. Two ml peripheral blood samples of the participants were collected in the EDTA tubes at the morning to evaluate the hs-CRP levels. The blood samples were centrifuged 10 minutes at 4000 rpm. Afterwards the serum samples were saved at -20°C for the study. Serum levels of the hs-CRP were measured by the Hitachi Cobas 501 (Roche Diagnostics, Manheim, Germany) tool.

Study results were noted by mean, standard, median and frequency value. Gender distributions were analyzed with chi-square test. Before assessing the variations between the groups in terms of constant varieties, accommodation control was made for normal variation. Student-t test was used for the variations between the groups which have shown normal variations. Mann-Whitney U test was used for the analysis of the other variations. p value of less than 0.05 is considered as significant.

RESULTS

The study group involved 22 people (9 males, 13 females), while the control group involved 24 people (9 males, 15 females). The mean age of the study group was 57.36 ± 9.26 years while it was 57.36 ± 9.26 years in the control group. No statistically significant difference was observed in terms of age and gender between groups (p=0.058, p=0.81, respectively) (Table 1). The mean body mass index in the study group was 26.17 ± 2.66 kg/m^2. It was 28.65 ± 5.39 kg/m^2 in the control group. No statistically significant difference was observed in terms of body mass index between groups (p=0.72) (Table 1).

Table 1. *Comparison of PES and PEG group in terms of BMI, age, gender, and hs-CRP levels. (PES: pseudoexfoliation syndrome, PEG: pseudoexfoliation glaucoma, hs-CRP: high-sensitivity C-reactive protein, BMI: body mass index)*

	Patient Group	Control Group	p value
Body Mass Index (kg/m^2) (mean ± sd)	26.17 ± 2.66	28.65 ± 5.39	0,72
hs CRP (mg/dl) (med)	3.00	3.70	0.64
Age (mean ± sd)	57.36 ± 9.26	52.96 ± 5.18	0.058
Gender	9 male, 13 female	9 male, 15 female	0.81

The median value of the hs-CRP in the study group was 3.00 mg/dl (0.3-160.9 mg/dl), while it was 3.70 mg/dl (0.4-97.4 mg/dl) in the control group. There was no statistically significant difference between the groups in terms of hs-CRP values (p=0.64) (Table 1). Twenty-two cases in the study group were divided into two subgroups as having no glaucoma or having glaucoma. Thirteen (59.1%) of the 22 patients were in the PES group and 9 (40.9%) of them were in the PEG group. Serum hs-CRP levels of the both groups were analyzed individually and compared with the control group. The serum hs-CRP level was 3,6 mg/dl (0,3-160,9 mg/dl) in the PES group, 1.9 mg/dl (0,5-6,3 mg/dl) in the PEG group and 3.70 mg/dl (0.4-97.4 mg/dl) in the control group. No statistically significant difference was observed in the three groups in terms of serum hs-CRP levels (p>0.05). Twenty two patients who have PES or PEG were divided into the subgroups in terms of having PEM unilaterally or bilaterally. There was no statistically significant difference between the groups in terms of serum hs-CRP levels (p=0.35) (Table 2).

DISCUSSION

Pseudoexfoliation syndrome is accepted as not only an ocular disease, but also a part of a systemic disorder. Presence of PES has been revealed as a disorder that increases the risk of endothelial dysfunction and cardiovascular disease by many researchers.[1,9,10] On the other hand, raised serum, plasma and aqueous humor levels of homocysteine were observed in PES. Homocysteine, which is a non-protein α-amino acid, stimulates inflammatory cytokines (~~e.g~~ TNF-alpha) and markers (~~e.g~~ CRP).[7,11,12] It is also a risk factor for vascular diseases.[1,2,4,5] By making vascular endothelial dysfunction and blood flow disorders, PES can be seen with the cardiovascular diseases such as atherosclerosis.[13] Atherosclerosis is a chronic inflammatory process. CRP is an important marker of chronic inflammatory processes such as atherosclerosis and atherosclerosis is a risk factor for coronary artery diseases.[14,15] That's why many researchers have studied the relationship between PES and CRP.[16-18]

Yuksel et al[16] have compared the serum levels of hs-CRP in the groups of PES, PEG and healthy participants. No statistically significant difference was observed between the groups. Researchers suggested that CRP is not a safe marker in determining the blood flow disorder in PES if there is no cardiovascular disease. Serum triglyceride, creatinine, alanine transaminase, high density lipoprotein levels, systolic and diastolic blood pressure values, heart rates and body mass index values were analyzed in the same study and no statistically significant difference was observed between the groups. Mocan et al[17] have also compared the levels of hs-CRP in the groups of PES, PEG and healthy participants. No statistically significant difference was observed between the groups. Researchers told that they had similar results with the study of Yuksel et al and they suggested that PES associated inflammation was not enough to stimulate the synthesis of CRP in liver. They also suggested that CRP could be a part of the limited local and subclinical inflammation in the affected tissues. This study differs from the others by including patients with hypertension and coronary artery disease.[17]

Sorkhabi et al[19] compared the levels of TNF-alpha and hs-CRP in the PES and healthy groups. They revealed that the levels of TNF-alpha and hs-CRP in the PES group were significantly higher than the control group. They suggested that CRP and TNF-alpha, two very important proinflammatory cytokines have played a role in the pathogenesis of PES. Sekeroglu et al[20] studied the trombophilic factors seen in PES and PEG. They found that some factors such as methylenetetrahydrofolate reductase (MTHFR) gene C677T mutation, prothrombin G20210A mutation, factor-V Leiden mutation, activated protein-C resistance, protein-S, protein-C have increased in the study group, but they revealed that there was no statistically significant difference between the control and the study groups. In our study, there was no statistically significant difference between the control and the study groups in terms of serum hs-CRP levels. These results were similar with the studies of Yuksel et al and Mocan et al but it differs from the study of Sorkhabi et al. Having glaucoma or not did not make any difference in our study, although the hs-CRP levels of the PEG group were a little bit lower than the other groups. This may be due to the low participant numbers in the PEG group. We observed that the serum hs-CRP levels in the bilateral PEM group were higher than the unilateral group, but this was not statistically significant either.

In conclusion; it is possible that there might be a local limited inflammation in the affected tissues in PES. That's why, in most of the studies, serum hs-CRP levels could not be determined as a striking marker for blood flow disorders seen in PES. We think that, more studies in expanded groups are needed to further investigate the role of inflammatory cytokines and systemic inflammation in the pathogenesis of PES.

Table 2. *Comparison of unilateral and bilateral PEM groups in term of hs-CRP levels. (PEM: pseudoexfoliation material, hs-CRP: high-sensitivity C-reactive protein)*

	Unilateral PEM	Bilateral PEM	Control	P value
hs CRP (mg/dl) (med)	1.9	5	3.7	0.35

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