·Clinical Research·

Total oxidative stress, paraoxonase and arylesterase levels at patients with pseudoexfoliation syndrome and pseudoexfoliative glaucoma

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Abstract

• AIM: To investigate the oxidative stress status of the aqueous humor and serum of patients with pseudoexfoliation (PEX) syndrome and pseudoexfoliative glaucoma (PEG) and to measure paraoxonase (PON) and arylesterase (ARE) levels.

• METHODS: A total of 78 patients were enrolled in the study, with 26 patients in each separate group. The patients were divided into three groups: the first group entailed PEX syndrome patients, while the second group consisted of patients with PEG and the third group involved patients with no additional systemic diseases, other than the diagnosis of cataract as control. Total oxidative stress (TOS), total antioxidant capacity (TAC), PON, and ARE levels in aqueous humor and serum were measured.

• RESULTS: TAC, PON and arylesterase levels in aqueous humor and serum of the PEX syndrome and PEG patients were significantly decreased compared with control group (P<0.05). TOS values were higher in patients with PEX syndrome and PEG than controls (P< 0.05). TAC, PON and ARE levels of aqueous humor did not differ significantly between the PEX syndrome and PEG groups

• CONCLUSION: These findings are potentially of significance and add to the growing body of evidence for oxidative stress in PEX syndrome and PEG. Decreased antioxidant defense and increased oxidative stress system may play an important role in the pathogenesis of PEX syndrome and PEG.

• KEYWORDS: pseudoexfoliation syndrome; oxidative stress; paraoxonase; arylesterase

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INTRODUCTION

Pseudoexfoliation (PEX) syndrome is characterized with extracellular fibrillar or granular PEX material deposit in the anterior segment of the eye[1]. PEX material may develop on the iris, lens surface, ciliary body, and zonula and trabecular meshwork in PEX syndrome that can be unilateral or bilateral [2,3]. PEX also affects organs such as skin, lung, heart, gall bladder, and meninx with eye[4]. Pseudoexfoliative glaucoma (PEG) is the most common form of secondary open-angle glaucoma worldwide [5]. When patients having PEG are compared with primary open-angle glaucoma patients, their intraocular pressure is often higher, they have larger cupping and visual field defects, and progression of the disease is often faster[6].

The increase of concentration reactive oxygen species (ROS) which play important roles in the physiological and pathological processes levels in the cell induces oxidative damage of mitochondrial DNA (mtDNA), proteins, and lipids [7]. Various enzymatic systems in the body fluids and cell regulates the reactive oxygen species. Antioxidants prevent the oxidative chain reactions that may cause tissue damage by removing free radicals intermediate, and inhibit other oxidation reactions [8]. Superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase can be named among the most important antioxidant enzymes [9]. The oxidative stress mechanisms have been demonstrated to play a major role in ocular diseases including glaucoma, cataract, diabetic retinopathy, uveitis and macular degeneration [10,11]. Studies have claimed that tissue damage caused by increased oxidative stress and changes in extracellular matrix play a role in the pathophysiology of PEX syndrome and PEG [12,13]. For this purpose, intensive studies have been carried out to determine free radicals and oxidative stress biomarkers.

Paraoxonase (PON) is one of the antioxidant enzymes in the body. PON1, a 43-45 kDa glycoprotein, is synthesized mainly in the liver, which hydrolyzes organophosphates[14,15]. PON and arylestase (ARE) were grouped in the same category initially, but started to be studied under different categories after 1989 [16,17]. The PON gene family has three members: PON1, PON2 and PON3. All of these enzymes have antioxidant features. A decrease in PON activity has been shown to be associated with increased oxidative stress in serum [18]. Aqueous humor (AH) levels of PON and ARE enzymes were first studied in diabetic patients, but no difference was observed among the patients with or without retinopathy and control group[19].

To our knowledge this is the first study investigating PON1 and ARE levels of AH in patients with PEX syndrome and PEG. In the present study, it aimed to determine the serum and AH levels of total oxidative stress (TOS), total antioxidant capacity (TAC), PON and ARE in cataract patients having PEX and PEG, in addition to compare the results with those of the control group composed of cataract patients having no PEX.

SUBJECTS AND METHODS

Subjects The current study was performed at the Department of Ophthalmology at Cumhuriyet University Medical Faculty Glaucoma Clinic between September 2010 and October 2011. The eyes of 78 patients who were enrolled with hazy vision, diagnosed with cataract and suggested to receive surgical treatment were included in the study. All procedures were conducted in accordance with the principles of Declaration of Helsinki and informed consent was obtained from all patients. The Cumhuriyet University Medical Faculty ethics committee approved the study.

All patients underwent a complete ophthalmic examination including best corrected visual acuity, slit-lamp examination, Goldmann applanation tonometry, and fundus examination with a dilated pupil. We have excluded patients on a severe systemic disease; known thyroid, kidney, or liver function disorder; acute myocardial infarction; psychological disorder; acute infection; and hormone replacement therapy in their history and those receiving antihyperlipidemic medicines, and nicotinic acid during the preceding 8wk. Patients experiencing significant weight loss and consuming cigarettes and alcohol at least during the preceding one year were also excluded from the study. Moreover, a history of intraocular surgery and ocular disease, such as diabetic retinopathy, dry eye, uveitis, and primary open-angle glaucoma were treated as exclusion criteria, as well.

METHODS

Patient groups Presence of exfoliation material on the anterior lens capsule or edge of pupil by biomicroscopic evaluation and/or in the angle on gonioscopy after mydriasis, having an intraocular pressure less than 21 mm Hg, and having no glaucomatous optic nerve damage and change in visual field were the conditions for diagnosing PEX syndrome. PEG diagnosis was made in the presence of exfoliation material on the anterior lens capsule or edge of pupil and/or in the angle on gonioscopy, an intraocular pressure more than 21 mm Hg, glaucomatous optic nerve damage, and change in visual field. Gonioscopy has been performed for all patients. All patients had an open angle (grade 3 or 4 of the Shaffer classification). Patients were divided into three groups: group 1 was composed of 26 PEX syndrome with cataracts, group 2 was composed of 26 PEG with cataracts and group 3 (control) was composed of 26 cataract patients having no PEX syndrome.

Serum collection Venous blood samples (5 mL) were collected (after 12h fasting) from patients before surgery. The blood samples were centrifuged for 15min at 4℃. The samples were immediately stored -80℃ until analysis.

Aqueous humour sampling AH samples (0.1-0.2 mL) were obtained at the beginning of cataract surgery; through a paracentesis, using a 27-gauge needle attached to a tuberculin micro syringe under an operating microscope. Samples were frozen and stored at -80℃ until biochemical analysis.

Biochemical Determinations

Total antioxidant capacity TAC levels were measured using commercially available kits (Relassay, Turkey). This novel automated method is developed by Erel[20] and based on the bleaching of characteristic color of a more stable ABTS [2, 2′ -Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)] radical cation by antioxidants. The assay has excellent precision values, which are lower than 3%. The results were expressed as mmol Trolox equivalent/L.

Total oxidative stress TOS levels were measured using commercially available kits (Relassay, Turkey). In this method, oxidants present in the sample oxidized the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction was enhanced by glycerol molecules abundantly present in the reaction medium. The ferric ion produced a colored complex with xylenol orange in an acidic medium. The color intensity, which could be measured spectrophotometrically, was related to the total amount of oxidant molecules present in the sample. The assay was calibrated with hydrogen peroxide, and the results were expressed in terms of micro molar hydrogen peroxide equivalent per liter (μmol H_2O_2 equivalent/L)[21].

Paraoxonase and Arylestase PON and ARE activity was measured by methods used by Kirbas *et al*[22]. PON activity was measured in absence and presence of NaCl [17]. The rate of paraoxon hydrolysis was measured by the increase of

Table 1 Demographic characteristics

Characteristics	PEX	PEG	Control
M	14 (53.8%)	15 (57.7%)	12 (46.2%)
F	12 (46.2%)	11 (42.3%)	14 (53.8%)
Age	66.19±6.88 (56-83)	67.34±6.93 (55-79)	67.03±6.34 (57-81)

PEX: Pseudoexfoliation; PEG: Pseudoexfoliative glaucoma.

Table 2 Serum TAC, TOS, PON1, ARE levels

Groups	TAC (mmol Trolox equivalent/L)	TOS (μmol H_2O_2 equivalent/L)	PON1 (U/L)	ARE (U/L)
PEX	1.30±0.27	8.57±0.95	77.96±9.44	10292.26±2050.92
PEG	[2]1.05±0.34	8.90±1.05	[2]69.35±12.10	[2]8471.19±1155.84
Control	[1]1.52±0.37	[1]0.73±0.52	[1]86.38±12.68	[1]12088.34±2192.15
P	0.001	0.001	0.001	0.001

PEX: Pseudoexfoliation; PEG: Pseudoexfoliative glaucoma; TAC: Total antioxidant capacity; TOS: Total oxidative stress; PON: Paraoxonase; ARE: Arylesterase. [1]P<0.05 comparison of control with PEX and PEG. [2]P<0.05 comparison of PEX and PEG.

Table 3 Aqueous humour TAC, TOS, PON1, ARE levels

Groups	TAC (mmol Trolox equivalent/L)	TOS (μmol H_2O_2 equivalent/L)	PON1 (U/L)	ARE (U/L)
PEX	1.01±0.94	2.53±1.19	0.94±0.47	2219.93±147.27
PEG	0.80±0.70	2.79±0.67	0.92±0.35	2123.63±137.81
Control	[1]1.55±0.62	[1]1.10±0.81	[1]1.37±0.31	[1]10539.41±929.28
P	0.002	0.001	0.001	0.001

PEX: Pseudoexfoliation; PEG: Pseudoexfoliative glaucoma; TAC: Total antioxidant capacity; TOS: Total oxidative stress; PON: Paraoxonase; ARE: Arylesterase. [1]P<0.05 comparison of control with PEX and PEG.

absorbance at 412 nm at 25℃. The amount of generated p-nitrophenol was calculated from the molar absorptivity coefficient at pH 8 and it was measured as 17.100 mol/L•cm^{-1}. PON activity was measured and expressed as U/L serum. Phenylacetate was used as a substrate to measure arylesterase activity in which the reaction was initiated by addition of serum and the increase in absorbance was read at 270 nm. On the other hand, blanks were included to correct spontaneous hydrolysis of phenylacetate. Enzymatic activity was calculated from the molar absorptivity coefficient of the produced phenol and it was 1310 mol/L•cm^{-1}. One unit of arylesterase activity was defined as 1 mmol phenol generated/ minute under the above conditions and expressed as U/L serum. Phenotype distribution of PON was determined in presence of 1 mol/L NaCl. The ratio of salt-stimulated PON activity to arylesterase activity was used to assign individuals to one of the three possible phenotypes[23].

Statitical Analysis SPSS Version 14.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. Data were expressed as mean±standard deviation. Along with descriptive statistical methods, variance analysis, the Tukey test, and the Chi-square test were used to compare the quantitative data. The results were evaluated with 95% confidence intervals. P<0.05 was considered to be statistically significant.

RESULTS

The eyes of 78 patients were included in the study. The demographic data of the subjects are shown in Table 1. There were no significant differences between the groups for age and gender (P>0.05).

The mean serum TAC, PON1, ARE and TOS levels results are summarized in Table 2. Serum TAC, PON1, ARE values were higher in patients with control group than PEX syndrome and PEG (P<0.05). Furthermore, the values obtained in the PEX syndrome group were statistically significantly higher compared to PEG group (P<0.05). Serum TOS values were lower in patients with control than PEX syndrome and PEG (P<0.05). Although the mean TOS value in PEG group was higher than the PEX syndrome group, the difference was not statistically significant (P>0.05).

The mean AH TAC, PON1, ARE and TOS levels results are summarized in Table 3. AH TAC, PON1 and ARE values were higher in patients with control group than PEX syndrome and PEG (P<0.05). Although the mean TAC, PON1 and ARE values in PEX syndrome group was higher than the PEG, the difference was not statistically significant (P>0.05). AH TOS values were higher in patients with PEX syndrome and PEG groups than control (P<0.05). Although the mean AH TOS value in PEG group was higher than the PEX syndrome group, the difference was not statistically significant (P>0.05).

DISCUSSION

PEX syndrome is a systemic disease characterized by the deposition of an extracellular fibrillar material in ocular tissues and many other tissues in the body. It is associated

with various ocular problems, such as increased intraocular pressure and glaucomatous optic atrophy, corneal endotheliopathy, central retinal vein occlusion, cataract, zonular instability, decreased dilatation, and increased cataract surgery complication risk[2].

Although the etiology and pathogenesis of PEX are not fully known yet, various factors have been blamed. Yagci *et al*[24] measured superoxide dismutase (SOD) enzyme activity and levels of malondialdehide (MDA) and nitric oxide (NO) in serum in order to study oxidant-antioxidant balance in serum in cases having PEX syndrome. They found that SOD levels were significantly low in the PEX group. Moreover, MDA and protein carbonyl levels associated with free radical damage in the organism were found to be higher in the PEX group when compared to the control. In a study conducted to research antioxidant balance in AH in cases of patients having PEX, Uzun *et al* [25] found that the average TAC values of PEX cases were significantly lower compared to the values of the control group and that the average glutathione peroxidase and catalase activity of PEX cases were higher when compared to the average values obtained in the control group. Although the enzymes studied are different, the results of the study of Uzun *et al* [25] and the present study are parallel, as both showed that antioxidant enzymes are lower and that TOS is higher in PEX patients compared to the control group. These results suggest that the oxidant-antioxidant balance in AH is impaired in favor of the oxidant system in the pathogenesis of PEX.

It is known that there are various agents, such as hydrogen peroxide and superoxide anion, that are associated with oxidative damage in AH [26]. Chronic oxidative stress damage caused by these agents may lead to the impairment in trabecular meshwork function [27]. De la Paz and Epstein [28] stated that the possible role of oxidative damage in the pathogenesis of primary open-angle glaucoma was associated with chronic exposure to the harmful effects of super oxide radicals in AH. Ferreira *et al* [29] measured TAC, ascorbic acid, catalase activity, glutathione peroxide, and SOD enzyme activity to study the antioxidant balance in AH in patients having PEG. As a result of their study, TAC was found to be significantly lower in primary open-angle glaucoma and PEG groups when compared to the controls. Also, TAC was found to be significantly lower in PEG when compared to the primary open-angle glaucoma group. Ascorbic acid and glutathione peroxidase levels of both groups were lower compared to the controls, while the said levels were significantly lower in the PEG group when compared to the primary open-angle glaucoma group. SOD enzyme activity was found to be 67% higher in both glaucoma groups when compared to the controls, while there was no significant difference between glaucoma groups. The results of this study showed that the oxidant-antioxidant balance in AH was impaired in favor of the oxidant system in PEG patients when compared to the primary open-angle glaucoma group and the control group. In another study performed in serums of PEG and primary open-angle glaucoma patients, TAC, SOD, TOS, NO, protein carbonyl, and MDA levels were measured. TAC levels were found to be lower in the said groups when compared to the control group and there was no significant difference between glaucoma groups. SOD enzyme activity was found to be lower in glaucoma groups when compared to the control group. Serum levels of TOS, NO, protein carbonyl, and MDA, which are the indicators of the oxidant system, were higher in glaucoma groups when compared to the control group; however, there was no significant difference, except MDA levels, between glaucoma groups. Serum MDA level was found to be significantly higher in the PEG group when compared to the primary open-angle glaucoma group [30]. In the present study, parallel to the results obtained in the above-mentioned study, AH TAC, PON, and arylesterase enzyme activities were lower and TOS levels were higher in the PEG group when compared to the control group. TAC, PON, and ARE levels in AH were lower and TOS level was higher in cases of patients with PEG when compared to cases of patients with PEX, but the difference was not statistically significant. Although, Koliakos *et al* [12] showed that prooxidant-antioxidant balance was significantly increased in PEG patients compared with PEX patients, we found that there was only a significant difference in serum levels whereas the difference in the AH was not statistically significant. These results may be related with difference of study areas and biochemical techniques and markers.

PON is an A-esterase group serum esterase synthesized from the liver and having the ability to hydrolysis of paraoxon, which is an active metabolite of parathione, an organic phosphorus insecticide [31]. PON1 and ARE enzymes are considered to be the antioxidant defense systems, as they prevent the oxidation of lipid peroxides. The PON1 enzyme prevents oxidation of LDL and HDL particles and prevents or slows down the atherosclerotic process in other mechanisms. It has been reported in previous studies that decreased PON 1 activity could be a consequence of another specific decreased activity, glycosylation, a circulating inhibitor, or a decrease in serum concentration [32]. Some of the studies have blamed decrease in serum PON activity for oxidative stress developing, which is associated with free oxygen radicals in diseases such as Behcet disease, rheumatoid arthritis and ulcerative colitis[16,33,34]. Yagci *et al* [35] studied serum levels of PON, xanthine oxidase and adenosine deaminase enzymes in

cases of patients with PEX and found that PON activity was significantly lower in PEX patients when compared to the control group. Levels of xanthine oxidase and adenosine deaminase were found to be significantly higher compared with control group. It has been reported that decreased PON activity could be associated with increased oxidative stress due to an increased free oxygen radical level in cases having PEX. In the present study, both in serum and AH, the PON1 enzyme level, which has not been studied before in AH, was found to be lower in PEX cases compared to the control group. Similarly, the increase in TOS level and decrease in TAC levels support the notion that decreased PON activity is associated with increased oxidative stress damage.

As a result, PEX, which is characterized by the progressive production and deposit of fibrillar material in ocular tissue, is an age-related and generalized disorder of the extracellular matrix. The fact that it is resistant to treatment and has a rapid progression when it causes glaucoma, along with the previously reported ocular diseases, makes PEX a hot-button issue and cause studies on its pathogenesis and treatment to be continued. In conclusion, it can be predicted that a deficiency in the antioxidant protection system, along with the effects of free radicals, could be playing a role in the pathogenesis of PEX and its complications. To prevent and treat the clinical picture, eliminating the reasons causing oxidative stress may be one of the targets of future treatments. Treatment plans to prevent these factors will be possible only after further studies and their outcomes.

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