

ORIGINAL ARTICLE

What is the Effect of Pseudoexfoliation Syndrome on Renal Function in Patients without Glaucoma?

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ABSTRACT

Purpose: To evaluate renal function in patients with pseudoexfoliation syndrome.

Materials and Methods: This prospective, cross-sectional, case-control study involved 49 patients with pseudoexfoliation syndrome (PEX) and 42 control subjects. Renal function was examined by biochemical parameters and Doppler ultrasonography. Serum creatinine, blood urea nitrogen, urea levels, urine microalbumin level and creatinine clearance were measured. Renal volume, resistive index and pulsatility index were calculated using Doppler ultrasonography.

Results: The mean laboratory values for both groups were as follows: Creatinine, PEX: 0.81 ± 0.28 mg/dL – Control: 0.79 ± 0.22 mg/dL; urea, PEX: 31.6 ± 9.7 mg/dL – Control: 32.2 ± 8.4 mg/dL; blood urea nitrogen, PEX: 14.8 ± 4.6 mg/dL – Control: 15.1 ± 4.0 mg/dL; creatinine clearance, PEX: 89.1 ± 35.6 mL/min – Control: 99.0 ± 47.2 mL/min; microalbumin, PEX: 5.8 ± 22.7 mg/dL – Control: 2.7 ± 6.0 mg/dL. The differences between groups were not significant ($p > 0.300$). Renal volume, resistive index and pulsatility index values were similar in both groups ($p > 0.200$).

Conclusions: This study showed that pseudoexfoliation syndrome does not affect biochemical and ultrasonographic parameters associated with renal function.

Keywords: Biochemical parameters, blood-aqueous barrier, Doppler ultrasonography, glomerular filtration barrier, pseudoexfoliation syndrome, renal function

INTRODUCTION

Pseudoexfoliation syndrome (PEX) is a disorder characterized by accumulation of abnormal, extracellular, fibrillar material in the anterior segment of the eye. Besides eyes, same material is found in many tissues and organs, such as the heart, lung, liver, gall bladder, kidney and cerebral meninges.^{1,2} Previous studies showed a significant association especially between PEX and systemic vascular diseases.^{3,4}

There are important barrier systems in the human body. Glomerular filtration barrier is one of them.⁵ The glomerulus works as a macromolecular sieve, retarding the passage of plasma proteins and certain exogenous tracers, while allowing relatively free flow of water and small solutes.⁵ The fenestrated

glomerular endothelium may play a direct role in determining protein sieving.^{6,7} The pseudoexfoliation material, basically a glycoprotein–proteoglycan complex, is histologically similar to the basement membrane. It has been suggested that the overproduction and abnormal metabolism of the glycosaminoglycans, together with abnormally increased synthesis and the deposition of the elastotic fibrillar material in the tissues, have an important role in the pathophysiology of PEX.^{8–11} Recently, it has been reported that there may be a significant relation between PEX and endothelial dysfunction and systemic atherosclerosis.¹² Because of the systemic nature of PEX, in theoretically, exfoliation material may cause damage to glomerular filtration barrier and renal vascular structures.

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TABLE 1 The demographic and laboratory data of the subjects.

Parameters	PEX group (<i>n</i> = 49)	Control group (<i>n</i> = 42)	<i>p</i> Value
Age, year			0.443
Mean ± SD (range)	71.1 ± 10.3 (51–90)	69.5 ± 9.0 (50–87)	
Distribution, <i>n</i> (%)			
50–59	6 (12)	5 (12)	
60–69	15 (31)	13 (31)	
70–79	20 (41)	17 (41)	
80+	8 (16)	7 (16)	
Sex, M/F	27/22	20/22	0.413
Hypertension, <i>n</i> (%)	17/49 (34.7)	16/42 (38.1)	0.671

PEX, pseudoexfoliation; M, male; F, female; *n*, patients.

Doppler ultrasound (US) provides noninvasive information about renal parenchymal vascular bed resistance.¹³ Exfoliation material may accumulate in the renal parenchyma and affect renal perfusion. Resistive index (RI) and pulsatility index (PI) data, obtained by Doppler US from intrarenal arteries, are nonspecific parameters used in the assessment of renal perfusion.¹⁴ In renal parenchymal diseases (especially tubulointerstitial and vascular diseases), a significant correlation was reported between histological findings and RI values.^{15–17}

In this study, it was aimed to evaluate renal functions of patients with PEX by using biochemical parameters and Doppler US and to show a possible relationship between PEX and renal disorder.

MATERIALS AND METHODS

This prospective, cross-sectional, case-control study included 91 subjects with and without PEX. All subjects were at least 50 years old and they had an intraocular pressure lower than 21 mmHg, normal optic nerve appearance and visual field. Exclusion criteria were diabetes mellitus, chronic renal failure (defined as a glomerular filtration rate of <29 mL/minute/1.73 m² of body surface area), cardiovascular disease (except well controlled hypertension), history of smoking and/or alcohol consumption. The study protocol was approved by the Local Ethics Committee of University of Namik Kemal and performed according to the Helsinki declaration. Written informed consents were obtained from all subjects.

Both groups included subjects who had admitted for routine eye examination with refraction-related symptoms. All participants underwent ophthalmologic examination, including visual acuity (Snellen chart), intraocular pressure measurement by applanation tonometer, slit-lamp biomicroscopy, fundoscopy and visual field testing (Humphrey visual field testing). After pupillary dilation with tropicamide 1%, detection of typical exfoliative material in the anterior lens capsule and pupillary margin was defined as PEX. Initially, 49 consecutive patients who have PEX in one

or both eyes and who meet the criteria constituted PEX group. Then, 42 age-matched patients without PEX constituted control group (Table 1).

For evaluation of renal functions of patients, blood samples were obtained to analyze urea, blood urea nitrogen (BUN) and creatinine levels in the morning after fasting for at least 8 h. A 24-hour urine collection was performed for measurement of microalbumin levels and creatinine clearance. All blood and urine samples were assessed within four hours after sampling. Normal laboratory values were as follows: creatinine, 0.7 to 1.2 mg/dL; urea, 17 to 43 mg/dL; BUN, 7 to 18 mg/dL; creatinine clearance, 80 to 125 mL/min; microalbumin, 3 to 200 mg/dL.

After ophthalmologic examination, all subjects underwent a renal Doppler US assessment in the Department of Radiology. An experienced Radiology Specialist (KAG) performed US examination and she was unaware of presence or absence of PEX in the patients. All subjects were advised to keep away from foods that would increase intestinal gas formation for three days. Following 6–12 hours fasting, Doppler US was carried out via Acuson X 300 ultrasound imaging system (Siemens, Mountain View, CA). A 3.5 MHz transabdominal convex probe was used. The subjects were instructed to breathe deeply and hold their breaths during examination. Subjects who were unable to cooperate, thus leading to non-conforming results, were excluded from the study. The kidneys were evaluated in supine and lateral decubitus position, both in gray scale and Doppler US. The superior and inferior poles were clearly identified and marked in the longitudinal scan of the kidney; the renal length (L) was taken as the longest distance between the poles using an electronic caliper. The anteroposterior diameter (AP) (thickness) was also measured on longitudinal scan, and the maximum distance between anterior and posterior walls at the mid-third of the kidney was taken as AP diameter. The renal width (W) was measured on transverse scan, and the maximum transverse diameter at the hilum was taken as the renal width. The unit of measurement was centimeter (cm).

TABLE 2 The laboratory and ultrasonographic data of the subjects.

Parameters Mean \pm SD (range)	PEX group (<i>n</i> = 49)	Control group (<i>n</i> = 42)	<i>p</i> Value
<i>Biochemical</i>			
<i>Serum</i>			
Urea (mg/dL)	31.6 \pm 9.7 (14.7–59.4)	32.2 \pm 8.4 (19.4–59)	0.728
BUN (mg/dL)	14.8 \pm 4.6 (7–28)	15.1 \pm 4.0 (9–28)	0.712
Creatinine (mg/dL)	0.81 \pm 0.28 (0.43–2.09)	0.79 \pm 0.22 (0.39–1.23)	0.690
<i>Urine</i>			
Microalbumin (mg/dL)	5.8 \pm 22.7 (0.1–131)	2.7 \pm 6.0 (0.1–35.2)	0.441
Creatinine clearance (mL/min)	89.1 \pm 35.6 (24.3–160)	99.0 \pm 47.2 (23.2–224)	0.301
<i>Ultrasonographic</i>			
Renal volume (mm ³)	134.1 \pm 46.3 (57.1–268.8)	128.6 \pm 43.3 (44–280.4)	0.554
RI	0.69 \pm 0.07 (0.54–0.88)	0.68 \pm 0.07 (0.50–0.89)	0.377
PI	1.30 \pm 0.26 (0.15–2.19)	1.27 \pm 0.24 (0.64–1.93)	0.201

PEX, pseudoexfoliation; BUN, blood urea nitrogen; RI, resistive index; pulsatility index; *n*, patients.

Kidney volume was calculated by using the formulae: $L \times W \times AP \times 0.523$.¹⁸

Spectral Doppler analysis was used to obtain Doppler waveforms in the segmental arteries. At least three measurements were performed in segmental arteries of the upper, middle and lower third of each kidney. For assessment of renal vascular resistance, the RI and PI values were automatically calculated by Acuson software (Siemens, Mountain View, CA) from Doppler waveform images. The mean value for each index was calculated. Normal values for RI and PI are 0.50 to 0.70 and less than 1.50, respectively.

Statistical analysis was performed with SPSS for Windows, Version 16.0 (Statistical Product and Service Solutions, Inc., Chicago, IL) package program. In descriptive analysis, the measurement variables were given as average and standard deviation. The differences between groups were assessed by using Chi-square, Fisher's exact test, and independent sample *t* tests. The relationship between RI and creatinine and creatinine clearance in each group was evaluated by using Pearson correlation analysis. *p* Values less than 0.05 were considered as statistically significant.

RESULTS

For both groups, demographic data were summarized in Table 1. No difference was observed between two groups regarding age, gender and hypertension ($p > 0.05$). There were no significant differences between PEX and control groups regarding serum urea, BUN, creatinine, urinary microalbumin and creatinine clearance levels (Table 2) ($p > 0.05$). Creatinine, urea and BUN levels were found to be higher than upper limit of normal values in 3 (6.1%), 5 (10.2%) and 10 (20.4%) of 49 patients with PEX and in 1 (2.4%), 3 (7.1%) and 7 (16.7%) of 42 control subjects, respectively ($p = 0.621$, $p = 0.721$ and $p = 0.648$, respectively). Fourteen (28.6%) of 49 PEX patients and 11 (26.2%) of 42 control subjects had lower than

TABLE 3 Doppler ultrasound parameters of the subjects.

Groups	RI		PI	
	0.5–0.7	0.7 <	<1.5	1.5 \leq
<i>PEX</i>				
Total ^a , <i>n</i> = 98	59/98	39/98	78/98	20/98
HT (+) ^b , <i>n</i> = 34	16/34	18/34	26/34	8/34
HT (–) ^c , <i>n</i> = 64	43/64	21/64	52/64	12/34
<i>Control</i>				
Total ^d , <i>n</i> = 84	50/84	34/84	70/84	14/84
HT (+) ^e , <i>n</i> = 32	18/32	14/32	26/32	6/32
HT (–) ^f , <i>n</i> = 52	32/52	20/52	44/52	8/52

PEX, pseudoexfoliation; HT, hypertension; RI, resistive index; PI, pulsatility index; *n*, kidney.

Chi square test, RI (%), a versus d, $p = 0.926$; b versus c, $p = 0.053$; e versus f, $p = 0.632$; b versus e, $p = 0.455$; c versus f, $p = 0.527$.

PI (%), a versus d, $p = 0.519$; b versus c, $p = 0.576$; e versus f, $p = 0.688$; b versus e, $p = 0.635$; c versus f, $p = 0.633$.

normal values of creatinine clearance ($p = 0.800$). Microalbuminuria was not observed in both groups.

Renal volume, RI and PI values were comparable in both groups (Table 2) ($p > 0.05$). When the patients with and without hypertension were evaluated separately, no significant differences were found within the groups or between two groups in terms of RI and PI values ($p > 0.05$) (Table 3). The correlation between RI values and creatinine and creatinine clearance levels in each groups were presented in Table 4.

DISCUSSION

As known, exfoliation material is produced by many intraocular cell types including pre-equatorial lens epithelium, non-pigmented ciliary epithelium, trabecular endothelium, corneal endothelium, vascular endothelial cells and all cell types of the iris.¹⁹ This material is mainly deposited on the surface that is in contact with the aqueous humour in the anterior segment.²⁰ Glaucoma, phacodonesis, lens subluxation and increased risk of complications during cataract

TABLE 4 Correlation between RI and creatinine and creatinine clearance in each groups.

Parameters	RI	
	PEX group (n = 49)	Control group (n = 42)
Creatinine		
r value	0.022	0.088
p value	0.888	0.604
Creatinine clearance		
r value	0.071	-0.524
p value	0.670	0.002

PEX, pseudoexfoliation; RI, resistive index.

surgery are important ophthalmologic problems caused by PEX. Presence of PEX material in many organs in autopsy studies formed the basis for investigation of relationship between PEX and systemic diseases.^{1,2} PEX is known to be associated with cardiovascular and cerebrovascular system diseases.^{3,12,21}

Electron microscopy studies and fluorescein angiography revealed that PEX cause damage to vascular structures of the iris.^{8,22-24} PEX material accumulated around the iris vessels leads to chronic degenerative alterations in the blood vessels. This causes iris hypoperfusion and reduced partial pressure of oxygen in the anterior chamber.²⁵ Another important problem caused by iris vasculopathy is the deterioration of blood-aqueous barrier. Regarding this, protein concentration of aqueous humour is increased.²⁶ However, there are also studies suggesting the opposite.^{27,28}

Because PEX is a systemic disorder, it can be guessed that PEX may cause damage to other barrier systems of the body. Glomerular capillary wall is a barrier system, which is composed of basement membrane, fenestrated endothelium and podocytes. In diseases affecting the renal parenchyma, this barrier is damaged.⁵ The final diagnosis of diseases affecting renal parenchyma and glomerular filtration barrier can be made by histological examination. Serum urea, BUN, creatinine levels and 24-hour urine microalbumin and creatinine clearance data are biochemical parameters that assist in minimally invasive assessment of renal function.²⁹ In a study by Yuksel et al., serum creatinine levels of patients with PEX and control groups were reported to be similar.³⁰ In our study, no statistically significant difference was observed between biochemical data obtained from patients with PEX and the control group.

US, an inexpensive and noninvasive imaging method used to evaluate the kidneys, provides information on anatomy. Renal volume measurement with US provides more accurate data than length and width measurements. Kidney length decreases with age and its thickness and width increases,

whereas the volume changes are very small.³¹ The renal volume may be affected in hypertensive subjects with renal parenchymal disease.^{32,33} In this study, renal volume values were similar in PEX and control groups.

Doppler US allows functional evaluation of the kidneys by analyzing vascular structures of the kidneys.³⁴ Under normal conditions, blood flow in the renal arterial system shows a continuum with non-stop antegrade flow in diastole. Therefore, difference between systolic and diastolic velocities in flow waveforms of renal arteries is less.¹⁴ RI and PI are Doppler parameters obtained from blood flow velocities during systole and diastole. They are used to measure renal vascular resistance to blood flow and have predictive properties in noninvasive estimation of renal function.^{14,34}

Advancing through periphery of the renal arterial system, arterial flow velocity, resistance and Doppler indices (RI, PI) are reduced. Therefore, if comparison of data obtained from multiple intrarenal vascular structures or calculation of average is intended, sampling should be done from all same levels (intrarenal segmental or interlobar artery).³⁵ RI of intrarenal segmental and interlobar arteries does not exceed 0.7,³⁴⁻³⁷ the PI value is between 0.7-1.40.³⁸ RI and PI increase is due to the increase in microvascular resistance, and is also associated with the severity of renal parenchymal disease.^{14,39} In the study by Peterson and colleagues, RI values greater than 0.75 and PI values greater than 1.55 are associated with a rapid decrease in renal function.¹⁴ In our study, when Doppler index parameters were evaluated, no significant difference was observed between two groups. These data suggest that PEX does not affect renal perfusion in a cross-sectional examination.

Ninety percent of renal parenchyma consists of vascular and interstitial components. RI and PI values usually increase in medical renal pathology affecting vascular compartment.¹⁵ As renal perfusion will be reduced due to high renal vascular resistance in patients with hypertension even if there is no nephropathy, Doppler index values are expected to rise.⁴⁰ When patients with and without hypertension were evaluated separately in our study, RI and PI values were similar in both groups.

Some studies have shown a correlation between the values of RI and biopsy findings of various renal parenchymal diseases. RI was generally high in tubulointerstitial renal diseases or diseases of vascular compartments¹⁵ and normal in glomerular pathology (other than crescentic and proliferative glomerulonephritis).¹³ In addition, a correlation was found between serum creatinine values and RI in patients with medical renal disease.^{15,36} In our study, there was no significant correlation between serum creatinine levels and RI value in both groups. Although there

was a significant negative linear correlation between creatinine clearance and RI value in the control group, no correlation was observed in PEX group. Praveen *et al.*'s study demonstrated that there is a significant association between PEX and systemic atherosclerosis.¹² Intrarenal resistive index values may increase in the presence of systemic atherosclerosis.⁴¹ These factors may be the cause of loss of negative correlation between resistive index and creatinine clearance in patients with PEX.

This study has some limitations. First, we only investigated non-glaucomatous patients with pseudoexfoliation syndrome. In addition, the duration of PEX in patients was not known. The long-term effects of PEX on the renal function were not evaluated in this study. Second, the use of angiotensin-converting enzyme (ACE) inhibiting drugs could be a confounder on the PI and RI values.^{42,43} In our study, the subjects taking antihypertensive drugs were not evaluated separately according to each antihypertensive drug class. These factors may have affected RI values. On the other hand, the number of well-controlled hypertensive patients was similar in both groups. We think that the effect of this confounding factor on the RI value is limited. Third, the vascular compliance can vary from individual to individual and it may affect RI.⁴⁴ But, some factors that may affect the vascular compliance such as diabetes mellitus, smoking, alcohol consumption were excluded from the study, and the groups were age-matched. Consequently, although individual differences in the vascular compliance are important, its effect on the RI values is limited in this study.

In summary, this cross-sectional study showed that PEX does not affect biochemical and ultrasonographic parameters that are used to evaluate renal functions. The differences in structure and function of the glomerulus and the localization of pseudoexfoliation material in renal parenchyma may explain why glomerular filtration appears unaffected by pseudoexfoliation syndrome. However, studies examining the laboratory and radiological data obtained from long-term follow-up of glaucomatous or nonglaucomatous patients with pseudoexfoliation syndrome are needed.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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