

## Original Research Article

# Epidemiology of pseudoexfoliation syndrome: a hospital based comparative study

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### ABSTRACT

**Background:** Pseudoexfoliation syndrome (PEX), is an age-related condition with generalized disorder of the extracellular matrix (ECM) characterized by a pathological accumulation of polymorphic fibrillar extracellular material in ocular tissue and various visceral organs. The search for the etiology of pseudoexfoliation syndrome has been directed towards both genetic and environmental factors. It is associated with many ocular and systemic complications.

**Methods:** The study was a hospital based comparative clinical study with 100 consecutive patients with pseudoexfoliation and age and sex matched 100 patients as control without pseudoexfoliation. The patients were registered on a Pre-structured Proforma which included patients' demographic detail, history and examination. Examination protocol including visual acuity with snellen's chart for literate patients and E-Chart for illiterate patients, intraocular pressure (by Goldmann applanation tonometry), slit lamp examination and fundus examination.

**Results:** The mean age of cases was  $65.93 \pm 7.82$  years ranging from 49 to 85 years. The mean age of controls was  $63.98 \pm 7.06$  years ranging from 50 to 80 years ( $p=0.139$ ). 72% of cases were more than 60 years old. Male female ratio was 1.63:1. Most of the cases were from Budgam, Bandipora and Ganderbal areas. Spring water was proportionately more frequently used as water source in cases ( $\chi^2=18.5$ ,  $p=0.000$ ), and tube well water in controls. The mean duration of smoking was  $26.63 \pm 24.74$  pack years for cases and  $14.88 \pm 17.10$  pack years for controls ( $p=0.000$ ). Average duration of daytime exposure for cases was  $6.68 \pm 2.13$  hours and for controls it was  $4.52 \pm 2.53$  hours. Among cases 12 patients (12%) were on treatment for glaucoma whereas among controls, 1 patient (1%) was on treatment for glaucoma. With respect to dietary habits, there was no difference between cases and controls. Farmers comprised of 49% of cases, followed by House wives and government employees.

**Conclusions:** The study concludes that PEX is very common in our region, increasing with age and more in men. Smoking, occupations involved with sunlight exposure, spring water as water source are possible risk factors for PEX. Glaucoma and cataract are common ocular complications of the syndrome.

**Keywords:** Age, Glaucoma, Pseudoexfoliation, Sunlight exposure

### INTRODUCTION

Pseudoexfoliation syndrome (PEX), is an age-related condition with generalized disorder of the extracellular matrix (ECM) characterized by a pathological accumulation of polymorphic fibrillar extracellular

material in ocular tissue and various visceral organs. It was first described in 1917 by Lindberg in a Finnish population.<sup>1</sup> This syndrome affects about 0.2-30% of people older than 60 years worldwide.<sup>2</sup> Judging from early reports, it was considered that PEX syndrome and PEX glaucoma dominate in Scandinavian countries.<sup>3</sup> The prevalence of pseudoexfoliation based on hospital reports

from India varies between 1.87% and 13.5%.<sup>4</sup> Population-based studies from south India have recently reported the prevalence of pseudoexfoliation to be between 3.8% and 6.0% among persons aged 40 years.<sup>5,6</sup>

The clinical diagnosis is made by the presence of typical pseudoexfoliation material (PXM) on the anterior capsule surface. In addition to PXM, other features include endothelial pigmentation, loss of pupillary ruff, iris transillumination, Sampaolesi line, and pigment deposition in the trabecular meshwork.<sup>7</sup> PEX syndrome is one of the systemic elastosis that primarily affects elastic microfibers.<sup>8</sup>

The search for the etiology of pseudoexfoliation syndrome has been directed towards both genetic and environmental factors. In a study by Altintas an elevated plasma homocysteine level was found in persons with both pseudoexfoliation syndrome and pseudoexfoliation glaucoma, but not in patients with open-angle glaucoma (OAG) or control subjects.<sup>9</sup> The authors linked these results with reports of increased vascular disease risk among PEX patients, pointing to hyper homocysteinemia as a common culprit. Similar disturbances in the plasma levels of homocysteine, folic acid and vitamins B6 and B12 are evident with Alzheimer's disease and certain cardiovascular diseases. Thorleifsson was the first to identify two risk variants in the lysyl oxidase-like 1 (LOXL 1) gene to be strongly associated with exfoliative glaucoma.<sup>10</sup> The LOXL 1 is one of the enzymes essential for the formation and maintenance of elastin fibres.<sup>11</sup> Some studies have experimentally showed the increased concentration of endothelin-1, a potent vasoconstrictor, in the plasma and aqueous humour in PEX patients.<sup>12</sup>

In all reports, the prevalence of pseudoexfoliation syndrome (PEX) has been shown to increase with age. Major gene for PEX/PXG has been identified in *LOXLI*. Rodent studies suggest that *LOXLI* expression decreases considerably with age and therefore even small changes in *LOXLI* expression may become more significant with increased age. There can be other genes involved with this complex and late-onset disorder.<sup>13</sup> Furthermore, the cumulative exposure to environmental risk factors, like UV exposure, increases with age.

The influence of sex has been shown to vary much more. Some studies have shown PEX to be significantly more prevalent in women than in men, while other studies show no gender difference and some find the condition to be more prevalent in men.<sup>3,5,14-18</sup>

Considerable emphasis has been placed on the effect of geography in PEX research over several decades, specifically whether race or certain environmental factors might play a role in the pathogenesis of the disease. The prevalence of PEX is higher in specific geographical areas, varying substantially even within the same country.<sup>19</sup>

There is the striking trend of the disease being more common with greater distance from the equator, which has been observed throughout Europe, the Middle East, Asia and North America.<sup>19-21</sup> In addition, Stein et al, confirmed that in the United States, current residence in the southern tier was associated with the lowest risk of pseudoexfoliation syndrome; in this study, several climatic factors were explored to elucidate the latitude gradient-of these, colder temperatures in the summer and winter months as well as greater number of sunny days per year were identified as independent predictors of increased risk of pseudoexfoliation syndrome.<sup>21</sup> One study from Andhra Pradesh, India, found that working in occupations involving outdoor activities was associated with PEX<sup>20</sup>. Taylor found a high prevalence of pseudoexfoliation among aborigines in Australia.<sup>17</sup> His results pointed to a possible correlation with exposure to ultraviolet (UV) light.

A study by Koliakos et al, suggests that in persons with PEX, the oxidative stress (perhaps originated through radiation, environmental chemicals or atmospheric oxygen) is counterbalanced in the aqueous humour by antioxidants, but that this equilibrium is disrupted with the further development of PEX glaucoma whereby oxidants levels increase.<sup>22</sup>

More frequent consumption of dietary fibre-rich vegetables is associated with a lowered risk of having definite PXF at baseline, and the same applies to eating green or yellow vegetables. These results may be suggestive of dietary antioxidative effect being protective for PEX. Moderate users of alcohol (once weekly) are less likely to have definite PEX at baseline, again pointing to the possible influence of antioxidants.<sup>23</sup> Coffee consumption has been shown to increase plasma homocysteine (Hcy) levels in several randomized clinical trials. Elevated homocysteine may enhance pseudoexfoliation material formation by contributing to vascular damage, oxidative stress, and extracellular matrix alterations. Non caffeine components in coffee may be responsible for increased homocysteine levels, although the exact mechanisms involved are unclear.<sup>24</sup>

The smoking status was analyzed in some studies, but none of them found significant associations with PEX.<sup>16,23,25,26</sup> but Špečkauskas et al, identified that longer smoking duration increases the risk of PEX.<sup>27</sup>

#### **Association with systemic diseases**

Pseudoexfoliation material has been identified in various tissues in patients with ocular Pseudoexfoliation syndrome. PEXs have been found in the skin, lungs, liver, heart, kidney, gall bladder and meninges, mainly in areas containing connective tissue.<sup>10</sup> They are also in blood vessels in the body. Systemic associations reported include angina, hypertension, myocardial infarction, stroke, and abdominal aortic aneurysm.<sup>25</sup> Cardiac

arrhythmia is the most common finding in patients with this syndrome.<sup>28</sup>

Pseudoexfoliation syndrome is often associated with Alzheimer's disease.<sup>29</sup> Due to similarities in the pathogenesis, some authors call pseudoexfoliation glaucoma "eye Alzheimer's disease". However, the syndrome does not result in an increased rate of mortality from cerebrovascular disease.<sup>28</sup>

### **Complications**

Pseudoexfoliation syndrome is associated with various ocular complications. Elevated intraocular pressure and glaucomatous nerve damage had been demonstrated in patients with Pseudoexfoliation.<sup>30,31</sup> PEX glaucoma is classified as secondary open-angle glaucoma and is characterized with rapid progression, more resistance to medical treatment and worse prognosis than primary open-angle glaucoma.<sup>32</sup> Elevated intraocular pressure (IOP), with or without glaucomatous changes, has been reported in about a quarter of eyes with PEX, which is 6-10 times more frequent than in normal eyes. The intraocular pressure elevation seen in PEX is more likely caused by PEX material detaching from the cells that produce it and then floating in the anterior segment until it attaches itself in the trabecular meshwork, thereby creating an increased resistance to outflow of aqueous humour.<sup>11,32</sup> Cataracts were reported to be more common in patients with pseudoexfoliation. It is a mixed, corticonuclear type, with large, pigmented nucleus (brunescens).<sup>33</sup>

Lens capsule is thin and easily and unexpectedly torn during capsulorhexis of cataract surgery. Lens suspensory zonules (Zinnzonules) are weakened, leading to a tendency towards dislocation of the lens during minor trauma, and during the operational lens extraction. Split of the lens capsule and intraocular artificial lens dislocation, vitreous loss and inflammation are common complications of cataract surgery in subjects with the syndrome.<sup>34</sup>

## **METHODS**

The present study was conducted in the department of Ophthalmology SKIMS Medical College Hospital, Srinagar, which is a tertiary care hospital located in the summer capital of Jammu and Kashmir.

### **Source of data**

#### **Study population**

Patients who attended the outpatient department of Ophthalmology, SKIMS Medical College Bemina Srinagar during the study period. The study was a hospital based comparative clinical study with 100 consecutive patients with pseudoexfoliation and age and sex matched 100 patients as control without

pseudoexfoliation.

All the patients with Pseudoexfoliation attending the Ophthalmology OPD during the study period were included in the study according to the inclusion criteria. The patients were registered on a Pre-structured Proforma which included patients' demographic details (including age, sex, and ethnic origin. Ethnic origin was ascertained based on the patients' registration information sheet). history and examination. Detailed medical history of the patients was taken and ocular examination of the patients will be performed.

*Study design:* Hospital based comparative study.

*Study period:* 15<sup>th</sup> Dec 2015 to 15<sup>th</sup> Dec 2016

### **Methodology**

All patients went through a standard examination protocol including:

- Visual acuity with snellen's chart for literate patients and E-Chart for illiterate patients.
- Intraocular pressure (IOP) -by Goldmann applanation tonometry.
- Slit lamp (Haaag Streit Koeniz) examination -for presence of:
  - Pseudoexfoliation deposits.
  - Cataract grading.
- Fundus examination-By direct and indirect ophthalmoscope.

Subjects with open angles had their pupils dilated with 5-10% phenylephrine and 1% tropicamide eye drops. If phenylephrine was contraindicated, 1% homatropine eye drops were used instead. The anterior lens capsule was examined for PEX deposits under dilatation.

The anterior lens surface and pupillary ruff were inspected under high magnification. PXF was diagnosed if typical pseudoexfoliative material was present on the anterior lens capsule and/or pupillary margin in either one or both eyes. Cataracts were assessed and classified morphologically as follows: nuclear sclerosis (NS), cortical (C), and posterior subcapsular (PSC).

Furthermore, all patients were required to answer a comprehensive questionnaire regarding lifestyle, food consumption, health, diseases, previous surgery and medication.

### **Inclusion criteria**

- All patients diagnosed as pseudoexfoliation syndrome.
- Patients who give informed consent of being included in the study.

**Exclusion criteria**

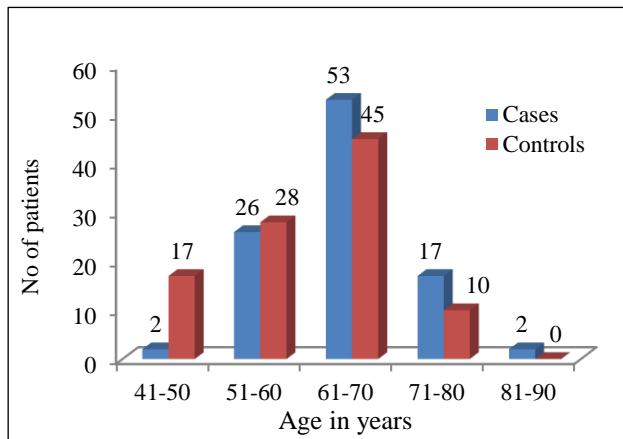
- Patients with occupational disorders, e.g. History of exposure to infrared rays (glass blowers)
- Patients with complicated cataract.
- Patients with history of trauma.

**RESULTS**

A total of 100 patients with unilateral or bilateral pseudoexfoliation were registered as cases along with 100 sex and age matched patients without pseudoexfoliation as controls.

The mean age of cases was 65.93±7.82 years ranging from 49 to 85 years. Thus, minimum age of patient with pseudoexfoliation was 49 years. The mean age of controls was 63.98±7.06 years ranging from 50 to 80 years. The difference in age between cases and controls was not statistically significant (p=0.066).

Among cases, there were 62 males (62%) and 38 females (38%) corresponding to a male to female ratio of 1.63:1. Among controls, there were 63 males and 37 females. This difference in gender was not statistically significant (p=0.884). With respect to marital status, all the 100 cases as well as 100 controls were married.



**Figure 1: Age distribution of cases and controls.**

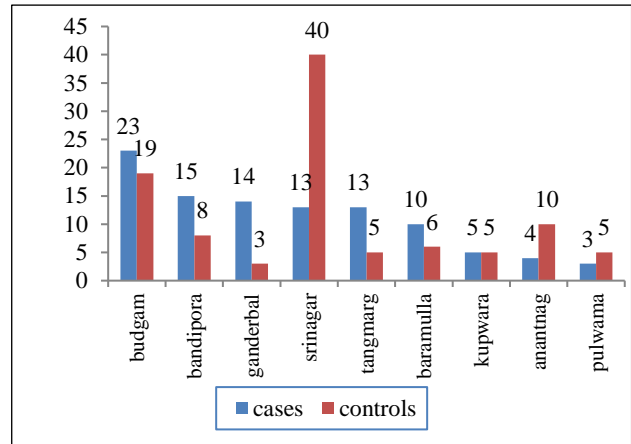
Majority of the cases (76%) were from rural areas as were the controls (63%) (Table 1).

**Table 1: Demographic characteristics.**

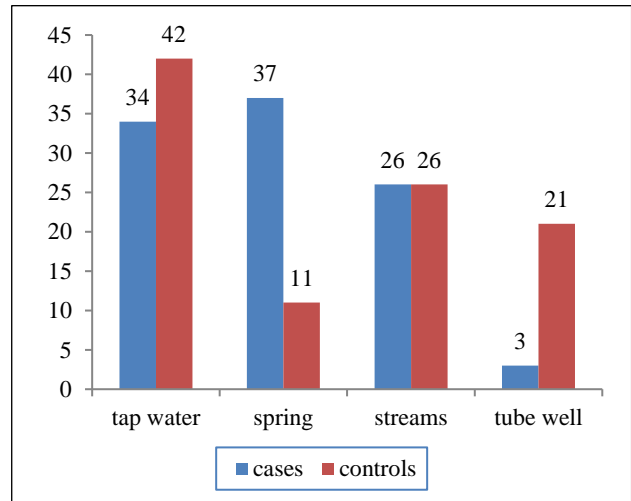
	Cases	Controls
Rural	76	63
Urban	24	37

The average height from MSL for cases was 1649.1±175.4 meters and for controls it was 1618.9±289.8 meters (p-value= 0.37).

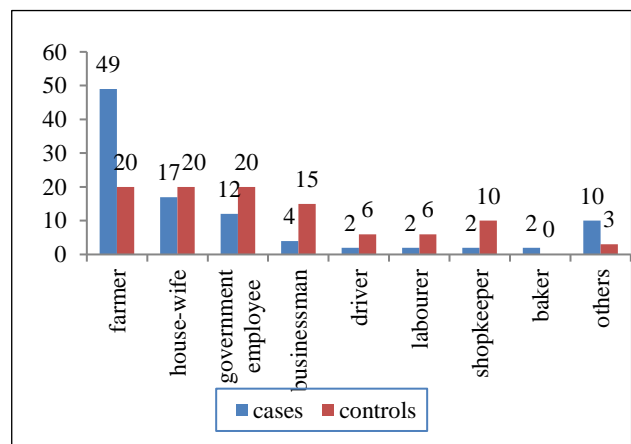
Most of the cases were from Budgam, Bandipora and Ganderbal areas. Srinagar and Anantnag had proportionately more controls (Figure 2).



**Figure 2: District wise distribution of cases and controls.**



**Figure 3: Water source of cases and controls.**



**Figure 4: Occupation of cases and controls.**

Spring water was proportionately more frequently used as water source in cases ( $\chi^2 = 18.5, p=0.000$ ), and tube well water in controls (Figure 3).

Farmers comprised of 49% of cases, followed by House wives and government employees (Figure 4). Among cases 40 patients were known hypertensives whereas

among controls 34 patients had a history of hypertension. Among cases 12 patients had a history of diabetes whereas among controls 25 patients were diabetics. None among cases or controls had a history of coronary heart disease, chronic bronchitis, osteoporosis, gout or atopy. 4 patients among cases had a history of asthma whereas none among controls was asthmatic (Table 2).

**Table 2: Systemic diseases in cases and controls.**

Systemic disease	No. of cases with disease	No. of controls with disease	Odds ratio	p-value
Hypertension	40	34	1.29	0.380, not significant
Diabetes	12	25	0.41	0.018, significant
Asthma	4	0	not defined	0.043, significant

**Table 3: Smoking as a risk factor for pseudoexfoliation.**

	Smokers (current or former)	Non-smokers
Cases	70	30
Controls	57	43

**Table 4: Day time exposure among cases and controls.**

Average daytime exposure (Cases)	Average daytime exposure (Controls)	t-value	p-value
6.68±2.13 hours	4.52±2.53 hours	6.53	0.000

**Table 5: Ocular diseases in cases and controls.**

Ocular disease	No. of cases with disease	No. of controls with disease	Odds Ratio	p-value
Myopia	13	20	0.60	0.182, not significant
Hypermetropia	12	15	0.77	0.535, not significant
Cataract	96	67	11.82	0.000, highly significant
Glaucoma	12	1	13.5	0.002, significant

Among cases 70 patients were current or former smokers whereas among controls 57 patients were current or former smokers (Table 3).

Odds ratio =  $70 \times 43 / 57 \times 30 = 1.76$

$\chi^2 = 3.646, df=1, p=0.056$ .

The mean duration of smoking was 26.63±24.74 pack years for cases and 14.88±17.10 pack years for controls.

t-value= 3.91, df=198, p=0.000

None among cases or controls was a former or current alcoholic. Average duration of daytime exposure for cases was 6.68±2.13 hours and for controls it was 4.52±2.53 hours (Table 4).

A 13 patients among cases were myopic as compared to 20 among controls. 12 cases were hypermetropic as compared to 15 among controls. Cataract of varying grades was present in 96 cases and 67 controls (Table 5).

Among cases 12 patients (12%) were on treatment for glaucoma whereas among controls, 1 patient (1%) was on treatment for glaucoma. With respect to dietary habits, there was no difference between cases and controls. Mean IOP in the right eye of cases was 16.96 mmHg±3.95 and of controls it was 16.5 mmHg ±2.84. In the left eye, the mean IOP in cases was 17.27mmHg±4.49 and in controls it was 16.22 mmHg±2.67 (Table 6).

Among cases 41 patients (41%) had bilateral pseudoexfoliation, 19 patients had pseudoexfoliation only in the right eye, and 40 had pseudoexfoliation only in the left eye (Figure 5).

**DISCUSSION**

Arnarsson et al found greater rates of prevalence with increasing age: 2.5% of people aged 50-59 years had PEX; whereas 40.6% of those aged 80 years or more were affected.<sup>38</sup> A 72% of our cases were older than 60 years. Many studies (Åström, 2007; McCarty and Taylor, 2000; Arvind, 2003; Miyazaki, 2005; Damji, 1999; Anastasopoulos, 2011; Alia R Sufi, if not in all, found that the prevalence of PEX significantly increases with age.<sup>3,5,15,16,35,36,37</sup>

Studies have revealed varying gender difference in prevalence of PEX. 62% of cases were males in this study. Male preponderance was also seen in number of studies (McCarty and Taylor 2000), but some also reported female preponderance by Hiller et al<sup>14,16</sup> Alia R

Sufi, reported a male preponderance in a study of PEX in eye camps in Kashmir.<sup>37</sup> Males comprised 64.62% of the patients with PEX ranging in age from 49 years to 89 years.

The average duration of day time exposure for cases (6.68±2.13 hours) was significantly higher as compared to controls (4.52±2.53 hours),  $p=0.000$ . The cases also belonged to places of higher altitude, though difference was not statistically significant ( $p=0.37$ ), probably because of small sample size. These findings suggest the possibility of the role of high UV exposure in pathogenesis of PEX. This is in line with studies of McCarty and Taylor.<sup>16</sup> Taylor identified exposure to ultraviolet light as a risk factor for PEX in Australian aborigines, and Thomas et al, confirmed this finding in an Indian population.<sup>17,20</sup> In a study by Alia R Sufi, on prevalence of PEX in Kashmir, prevalence was found to be higher in patients involved with outdoor activities ( $P$  value < 0.001).<sup>37</sup>

Our study found prevalence of PEX to be higher in farmers than other occupation likely to be associated with outdoor exposure. One study from Andhra Pradesh, India, found that working in occupations involving outdoor activities was associated with PXS.<sup>20,34</sup> However, only one study has evaluated current time spent outdoors in a general population and did not identify it as risk factor for Pseudoexfoliation syndrome.<sup>23</sup> In this study, pseudoexfoliation was more commonly seen in north Kashmir districts of Budgam, Bandipora and Ganderbal ( $p=0.000$ ) as compared to other districts. Similar geographical variation was reported by Alia R Sufi in her study.<sup>39</sup> Thus, the data is limited, and time spent outdoors at different life stages has been little explored.

More frequent consumption of dietary fibre-rich vegetables is associated with a lowered risk of having definite PEX at baseline, and the same applies to eating green or yellow vegetables more frequently in their 20s and 30s. Moderate users of alcohol (once weekly) are less likely to have definite PEX at baseline, again pointing to the possible influence of antioxidants.<sup>23</sup> A study by Koliakos et al, suggests that in persons with PEX, the oxidative stress (perhaps originated through radiation, environmental chemicals or atmospheric oxygen) is counterbalanced in the aqueous humour by antioxidants, but that this equilibrium is disrupted with the further development of PEX glaucoma whereby oxidants levels increase.<sup>22</sup> No association with any diet was found in this study.

The smoking status was analyzed in some studies, but none of them found significant associations with PEX (Mitchell et al, 1997; McCarty and Taylor; Arnarsson; Arnarsson et al.<sup>16,23,25,27</sup> But Špečkauskas et al, identified, that longer smoking duration increases the risk of PEX. In this study the mean duration of smoking in cases (26.63±24.74 pack years) was significantly higher than in controls (14.88±17.10 pack years) ( $t=3.91$ ,  $p=0.000$ ).

Distribution of PEX for bilateral vs. unilateral cases is highly variable in reported cases (Nouri-Mahdavi, 1999; Kozartand Yanoff, 1982.<sup>18,38</sup> The percentage of bilateral involvement varies from 25% -75%. In this study, 41% patients had bilateral PEX. Most studies indicate that PEX is basically a bilateral syndrome although the clinical presentation is often unilateral in the study by Arnarsson et al. A 71% of clinically unilateral cases had converted to bilateral in 12 years.<sup>26</sup>

Pseudoexfoliation syndrome has been known to be associated with a greater prevalence of cataract, though the exact etiology of this association is not known (Hiller, 1982; Arvind, 2003; Schlötzer-Schrehard and Naumann, 2006).<sup>5,14,32</sup> In this study, are in strong agreement with the above-mentioned studies. Cataract was detected in 96% of cases in the PEX group compared to 67 % in the non-PEX group ( $p = 0.000$ ). However, there are studies where connections between PEX and cataract formation have not been found. Arnarsson, and McCarthy in their population-based studies with large group of subjects did not find a significant effect on the risk of cataract from PEX.<sup>16,23</sup>

One reason for the elevated IOP in PEX is the increased outflow resistance in the trabecular meshwork. There is evidence that decreased outflow is a result from a blockage of the outflow channels by EXM together with trabecular cell dysfunction, which may have causative relationship for glaucoma development and progression (Schlötzer-Schrehardt U and Naumann 1995)<sup>39</sup>. 12 cases of PEX had glaucoma, compared to 1 in control group. In the Thessaloniki eye study subjects with PEX compared to those with no PEX had higher percentage of IOP > 22mmHg. This finding was mainly explained by the higher proportion with glaucoma among PEX participants.<sup>36</sup> However, there is a large population-based study from Australia (N = 5147), in which no significant relationship was found between IOP and PEX<sup>16</sup>. Similar conclusions were made by investigators in the Arvind comprehensive eye survey study<sup>4</sup>.

In a study conducted by McCarty and colleagues strong relationship between PEX and glaucoma was found after checking for age; although not highly sensitive, PEX was found to be a specific predictor of glaucoma status.<sup>16</sup> In earlier studies, the prevalence of glaucoma in eyes with PEX has been found to vary considerably, from 7% in the USA to 22.7% in Norway, 13.0% in the India.<sup>5,6,38</sup>

In this study 12 PEX patients had diabetes compared to 25 patients in control group ( $P=0.018$ , significant). In a case control study in Greece by Psilaset al, 489 non-diabetics older than 50 years were compared with 325 diabetic patients with similar age.<sup>40</sup> The prevalence of PEX was 23.7% in non-diabetic patients and 11 % in diabetic patients (109). The reported prevalence in different parts of the world has varied from 0% to 38% in different populations. In a population-based survey performed by Nouri-Mahdavi et al, a random sample of



people aged 50 or above from Falavarjan city, central Iran, was examined for signs of PEX. 806 eyes in 405 cases (210 women and 195 men) were examined. Seventy-seven eyes of 53 cases showed pseudoexfoliative deposits.<sup>18</sup> According to our data and Nouri's results using Friedman test ( $\alpha=0.05$ ), we conclude that prevalence of PEX in diabetic subjects is lower than non-diabetic subjects at the same age. But Sollosy et al, showed that the incidence of PEX in diabetic subjects was higher than non-diabetic subjects with similar age.<sup>5</sup> In this study it was mentioned that cause of high incidence of PEX in diabetic patients is collagen metabolic changes that was observed in diabetic patients more than other metabolic disorders.

In this study, we did not find statistically significant connections between PEX and any systemic disease that is in agreement with data from the Thessaloniki eye study.<sup>36</sup> In a Swedish study with a very long follow-up (21 years) mortality was estimated for each study interval but the presence of PEX did not influence the risk of death.<sup>15</sup> The only systemic disease associated with PEX at baseline in the present study is bronchial asthma, which was significant ( $p$  value=0.043) and may be associated with oxidative stress.<sup>23</sup> Although Hypertension was more frequent in cases than controls in this study, but difference was not statistically significant. McCarty and Taylor found no significant association between PEX and hypertension, gout, arthritis or diabetes.<sup>16</sup>

## CONCLUSION

The study concludes that PEX is very common in region, increasing with age and more in men. Smoking, occupations involved with sunlight exposure, spring water as water source are possible risk factors for PEX. Glaucoma and cataract are common ocular complications of the syndrome.

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*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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