Pseudoexfoliation Syndrome Association with Aging and Ocular Changes in Cornea, Lens, Retina

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Research Article

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Abstract

Purpose: To examine the 10-year incidence of the pseudoexfoliation syndrome (PEX), possible risk factors of PEX, and its association with aging and ocular changes in cornea, lens, retina within a population-based follow-up study.

Methods: The baseline examination was conducted in 2006 on a random sample of 1,033 adult participants from Kaunas city (Lithuania) population. Out of them 631 participants returned to the follow-up study in 2016. Ophthalmological examination included keratometry, central corneal pachymetry, after diagnostic mydriasis lens opacification was evaluated by LOCS III International classification, PEX was diagnosed by the presence of typical grayish-white exfoliation material on the anterior capsule surface of the lens.

Results: During the 10 years follow-up, the prevalence of the PEX increased from 9.8% to 34.2%. Nuclear cataract was diagnosed the most both in the PEX-group and those without, however, there was no statistically significantly increased risk of developing cataract in those with PEX when compared to those without PEX (OR 1.2; p=0.61). Central corneal thickness (CCT) was thinner in PEX group (529±34μm) and in the eldest group (525±36μm) (p<0.001). Compared to baseline, corneal curvature (CC) became steeper both in the PEX and the no-PEX groups during the follow-up (p=0.013), but the difference didn't reach significance between groups. The biggest part of corneal astigmatism was with-the-rule in no-PEX and PEX groups (37 vs 148; p>0.05). The age, sex and PEX had no influence to age related macular degeneration distribution.

Conclusion: The prevalence of the PEX increased significantly with age. CCT was thinner in PEX group and in elder people. CC was flatter in PEX group.

Introduction

Pseudoexfoliation syndrome (PEX) affects approximately 0.2–30.0% of people older than 60 years of age worldwide [1, 2]. Nordic countries are reported to have the highest PEX prevalence rates [3, 4], as high as 40.6% in those at least 80 years old [4]. Clinically, ocular involvement is described as unilateral from 48.0–76.0% patients. Progression to bilaterally was reported in up to 50.0% of patients within 5 to 10 years after diagnosis [5] and to 71.0% after 12 years [6].

The prevalence of PEX has been found to vary greatly between different studies, raising the possibility of racial and⁄or environmental modulators. PEX has also been linked to changes in central corneal thickness (CCT), steeper corneal curvature (CC) and nuclear lens opacifications [7], but not with age related maculopathy [7]. Age is also a known risk factor for PEX and for senile cataract. Increased lens opacification has been noted to be associated with PEX [8].

While there is a clear tendency for PEX being related to aging, the same cannot be said for PEX and gender [9]. On one hand, Kiliç found a significant relationship between PEX with advancing age and male

gender [10], while the 12-year follow-up of the Reykjavik Eye Study, Iceland, found an association with older age and female sex [6]. We couldn't find any follow-up studies in available data basis which examines PEX and associations of ophthalmological abnormalities in Baltic countries.

In 2006, a population-based epidemiological study on Health, Alcohol and Psychosocial factors In Eastern Europe (HAPIEE) [11], study was conducted in the Hospital of Lithuanian University of Health Sciences. HAPPIE examined the potential associations of ophthalmological and cardiovascular diseases. After 10 years (2016) a follow-up s study was conducted for those willing and able to come back for a follow-up. The aim of this paper was to determine associations of PEX with ocular changes in Lithuanian urban population and identify possible risk factors of PEX after 10 years of follow-up.

Materials And Methods

Study sample / Study population

Respondents of the population-based epidemiological study were residents of Kaunas city (Lithuania) and were part of the ongoing prospective HAPIEE cohort study [11]. During 2006–2008, 7,087 subjects, from Kaunas city (Lithuania), participated in international HAPIEE study. In 2006, out of the 7,087, 1065 individuals participated in ophthalmological substudy. In 2016-17, 686 subjects were investigated in a 10-year follow-up study. The study was approved by the Regional Bioethics committee and was carried out in accordance with the Declaration of Helsinki. During the study, informed consent was obtained from each participant.

At HAPPIE baseline in 2006, ophthalmological examination was carried out on 1,033 participants. Data from 32 respondents were not included due to eye trauma, both eyes being pseudophakic and aphakic, eye globe subatrophy, lens subluxation in vitreus body). Ten years later 631 out of the 1033 participants, 55–83 years-old at mean time, returned for a follow-up examination (the data of 55 respondents were not included in the data analysis due to pseudophakia in both eyes, due to the technical difficulties and uncertainties of evaluating PEX material in the absence of anterior lens capsule after cataract surgery) (response rate 66.4%). The 347 individuals who did not return for follow-up were due to death (n = 164), migration or refusal (n = 183) and 55 were not included due to pseudophakia in both eyes. During the study period were investigated 631 respondents (239 males (37.9%) and 392 females (62.1%)) and their data were compared with baseline study data. For cataract, age-related macular degeneration (AMD), central corneal thickness (CCT), corneal curvature (CC), corneal astigmatism distribution each eye was kept in the analysis. For evaluation of changes and new cases after 10 years we compared same eye of same subjects.

Study instrument

All participants underwent an ophthalmological examination according to a standard examination protocol and same methodology [12–14]. The examination was carried out by two trained and certified

ophthalmologists who had no access to the subjects' medical history.

PEX was diagnosed by slit-lamp examination after diagnostic mydriasis with 1 drop of 1% cyclopentolate. PEX was confirmed as definite by the presence of typical grayish-white exfoliation material on the anterior capsule surface of the lens (complete or partial peripheral band and⁄ or a central shield), other changes associated with PEX such as grayish-white deposits elsewhere in the anterior chamber (iris, corneae), precapsular frosting or haze supported the diagnosis of PEX. PEX was deemed suspect/possible if precapsular frosting or haze were seen. The participants were classified as having PEX if any typical pseudoexfoliation material was present in at least one eye. For statistical analysis, we used data for the respondents with the definite PEX diagnosis as the PEX group. Persons with suspected PEX were grouped together with those without any signs of the PEX.

All study respondents answered to standard questionnaire regarding lifestyle, subjective health and opthalmological pathology.

Ophtalmological examination

For the follow-up study, 631 individuals with 1262 eyes were examined.

Ophthalmological examination included slit lamp biomicroscopy. After diagnostic mydriasis with 1 drop of 1% cyclopentolate, fundus photos centered on the fovea were taken using a Canon CF-60Uvi (Canon Medical Systems, USA).

Lens opacification was evaluated at slit lamp by LOCS III international classification: NO/NC – nuclear opalescence / color (evaluation 0.1 to 6.9), C – cortical, P – posterior subcapsular (evaluation 0.1–5.9) [15]. Cataract was evaluated in 1262 eyes.

Retinal images were graded at Moorfields Eye Hospital Reading Centre in London, UK primarily based on the International Classification for AMD. AMD definition included dry and wet AMD forms. The grading of photographs were carried out by the same graders for both baseline and follow up studies data [16], All images were graded by trained and certified graders.

Altogether, 1262 eyes' had retina images graded, of these, 45 (3.6%) at baseline and 65 (5.2%) at follow-up had ungradable images due to cataract.

Central corneal pachymetry was measured with pachymeter ALCON OCUSCAN RxP, Alcon Laboratories inc., USA, in auto mode, averaging of 10 readings. At the 10-years follow up, CCT was measured in 1262 eyes of which only 2 eyes had no measurements. At baseline examined eyes were selected randomly. For comparing both studies same individuals we have only 304 eyes.

Keratometry was taken using the Auto keratorefractometer ACCUREF-K 9001, SHIN–NIPPON Commerce, inc., Japan. K1, K2, K1 axis, K2 axis, corneal curvature measurements were recorded from keratometry. Corneal astigmatism was calculated as follows: K1-K2 = corneal astigmatism. astigmatism (cylinder (diopters (D)). If cylinder was < 1.0D, it was kept as no corneal astigmatism, if it was ≥ 1.0D it was kept

as corneal astigmatism.. Corneal astigmatism was classified to with-the-rule (ax 90 ° ±30 °), against-the-rule (ax 0 ° ± 30 °), oblique (all the left).

CC and astigmatism were counted in 1182 eyes, data of 80 eyes were missing because we couldn't do measurements cause of dry eye.

Weight and height were measured with a calibrated medical scale, and without shoes or heavy clothes. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared (kg/m2). Normal weight was defined as BMI till 25.0 kg/m^2, overweight as BMI ≥ 25.0–29.99 kg/m^2 and obesity as BMI ≥ 30.0 kg/m^2.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 software. Statistical analysis was performed using software package „IBM SPPS Statistics® 20 for Windows.

Descriptive statistics were applied for various signs in PEX and non-PEX groups. Unilateral and bilateral PEX cases were separated into subgroups. Quantitative variables are presented as median and interquartile range or mean and standard deviation - SD. Categorical data are presented as number (percent).

Data normality detection of continuous variables was checked using *Kolmogorov-Smirnov test*. In case with non-normality, medians and interquartile ranges (IQR) were calculated and *Mann-Whitney U-test* was used to compare continuous data between groups.

Chi square (χ^2) test or *Fisher exact 2-sided test* was used to compare categorical variables. For ordinal data χ^2 linear-by-linear association test was used for confirmation of the linear trend. The comparison of proportions between groups was performed using *z test*.

*McNemar's χ^2 tes*t is used to assess the difference between paired proportions. Quantitative variables were compared with *Wilcoxon test.*

Binary logistic regression analyses were conducted with PEX as predictor controlling for age and gender. Odds ratios (OR) and 95% confidence intervals (CI) of OR were calculated for the risk of new PEX cases and the dependence of risk factors.

Results

In this study 631 participants were examined, among them 392 (62.1%) male and 239 (37.9%) female. The subjects' distribution by sex and occurrence of PEX are shown in Table 1.

Table 1
The distribution of PEX at follow-up survey by gender and affected eye (unilateral, bilateral).

	No PEX, n (%)	PEX, n (%)	p-value	PEX, n (%)		p-value
				Unilateral	Bilateral	
Male	154 (64.4)	85 (35.6)	p > 0.05	35 (41.2)	50 (58.8)	p > 0.05
Female	261 (66.6)	131 (33.4)		51 (38.9)	80 (61.1)	
Total	415 (65.8)	216 (34.2)		86 (39.8)	130 (60.2)	

Baseline and follow-up characteristics of those involved in the ophthalmic study are presented in Table 1. and Table 2. The prevalence of PEX for the baseline cohort (2006–2008) was 9.8% (Table 2.) [12].

During 10 years of follow-up (2016–2017) PEX prevalence increased to 34.2% (216 subject, (85 (39.4%) male and 131 (60.6%) female) (Table 1.). There was no statistically significant difference of PEX frequency between males and females, respectively 35.6% and 33.4% (p > 0.05). Mean age was significantly higher in the PEX group compared to the no-PEX group (73.01 ± 7.97 years vs 68.70 ± 8.16 years, p = 0.001).

Table 2
The distribution of PEX at baseline and follow-up studies.

	No PEX, n (%)	**PEX, n (%)**	**Total, n (%)**	**Unilateral PEX, n (%)**	**Bilateral PEX, n (%)**	**Total, n (%)**	**p value**
Baseline study	569 (90.2)	62 (9.8)	631 (100.0)	37 (5.9)	25 (4.0)	62 (9.8)	**p < 0.01**
Follow-up study	415 (65.8)	216 (34.2)	631 (100.0)	86 (13.6)	130 (20.6)	216 (34.2)	**p < 0.01**

PEX frequency was equal in males and females in age groups, 23.3% of participants aged 55–65 years, 32.1% of those aged 66–75 years and 47.3% of those aged 76–83 years were affected by PEX, the difference between age groups is significant (p < 0.001)(Table 3). PEX significantly increases with aging. Comparing age group 55–65 and 66–75, 55–65 and 76–83, 66–75 and 76–83 the significance was reached (p < 0.05).

Age median in PEX group was higher 74 yrs. versus 68 yrs. without PEX (p < 0.001)(Table 3) and at baseline age medians are 68 yrs. versus 59 yrs. (p < 0.001).

Table 3
The distribution of age groups by PEX at follow-up study.

Age	No PEX, n (%)	PEX, n (%)	p-value
55–65[1]	158 (76.7)	48 (23.3)	**0.001**
66–75[2]	148 (67.9)	70 (32.1)	
76–83[3]	109 (52.7)	98 (47.3)	
Mean (± SD)	68.70 (8.16)	73.01 (7.97)	**0.001**
Median	68.0	74.0	
PEX – pseudoexfoliation syndrome			

A total of 71.3% (154) PEX new cases were diagnosed of those eyes that were available for reexamination (Table 2.).

At baseline, 37 unilateral and 25 bilateral PEX cases were found increasing to 86 unilateral (13.6%) and 130 bilateral (20.6%) by the end of the 10-year follow-up (Table 1. and Table 2.). Twenty (54.1%) cases of unilateral PEX at baseline had progressed to bilateral PEX; nineteen (48.7%) PEX cases in at least one eye at baseline were found to have no signs of the syndrome progression in either eye 10 years later ($p < 0.001$).

PEX risk factors of lifestyle are presented in Table 4.; there was no statistically significant difference between those affected by PEX and those who were in univariate analysis.

Table 4
Distribution of life style and sociodemografic factors in PEX in no-PEX groups.

Risk factors		No PEX, n (%)	PEX, n (%)	p-value
Smoking	Never	285 (68.7)	161 (74.5)	0.128
	Former	86 (20.7)	42 (19.4)	
	Current	44 (10.6)	13 (6.1)	
Alcohol	< 1time/month, never	274 (66.0)	145 (67.1)	0.742
	1–4 time/month	120 (28.9)	63 (29.2)	
	> 1 time/week	21 (5.1)	8 (3.7)	
BMI (kg/m²)	< 25.0	78 (19.2)	33 (15.6)	0.502
	25.0-29.99	150 (36.9)	79 (37.3)	
	≥ 30	178 (43.8)	100 (47.2)	
Education	Primary	32 (7.7)	24 (11.1)	0.334
	Secondary	143 (34.5)	75 (34.7)	
	University	240 (57.8)	117 (54.2)	
Marital status	Single	150 (36.1)	85 (39.4)	0.429
	Married	265 (63.9)	131 (60.6)	

Age, gender, alcohol, BMI and education and marital status didn't increase risk of having PEX.

In multivariate logistic regressions only age for male and female significantly increases the risk of having PEX ($p < 0.001$). Secondary education comparing with primary for men shows tendency for bigger risk of having PEX ($p = 0.08$).

Adjusting by multivariate risk factors, alcohol consumption 1–4 time/month and alcohol consumption > 1 time/week, marital status-married, former and current smokers, normal weight reduced the probability of having the PEX for men, but not significantly.

Adjusting by multivariate risk factors, secondary and university education, normal weight and overweight reduced the probability of having the PEX for women, but not significantly.

Cataract

Of the available 1262 eyes, cataract was diagnosed in 1116 (88.4%) eyes and no cataract in 58 (4.6%) eyes respectively. Prevalence of cataract was significantly higher in the oldest age-group, when comparing to the youngest there is a 43.4% (95% CI 5.939-316.572; $p < 0.001$) increase. Comparing the

youngest and middle age group the risk to have cataract significantly increases 3.4 time (95% CI 1.833–6.330; p < 0.001). Cataract was diagnosed more frequently in female 63.3% than male 36.7% (p = 0.01). There was statistically significantly more cataract diagnosed in no-PEX group when compared to those with PEX (73.4% vs 26.6% p > 0.05). Nuclear cataract was the most common type (70.7%), and there wasn't d reached statistical significance between those with PEX and those without. Mixed cataract was found frequently in no-PEX and PEX groups (72.2% vs 66.7%; p > 0.05)(Table 5.). We found tendency in PEX group to have a bigger risk to have cataract by 21% (95% CI 0.576–2.574; p = 0.61).

Table 5
Cataract distribution in PEX groups at follow - up study.*

	No PEX, n (%)	**PEX, n (%)**	**Total, n (%)**	**p-value**
Cataract	819 (73.4)	297 (26.6)	1116	p > 0.05
Cataract forms:				
Nuclear	591 (72.2)	198 (66.7)	789	p > 0.05
Cortical	2 (0.2)	0	2	
Subcapsular	2 (0.2)	0	2	
Mixed	224 (27.4)	99 (33.3)	323	
* each eye was kept as object.				

Age-related Macular Degeneration

Total number of investigated eyes was 1197. AMD was diagnosed in 937 (78.3%) eyes and no AMD in 260 (21.7%) respectively (Table 6.). At 10-years follow-up, there were 383 new AMD cases (Table 7). There was no statistically significant difference in prevalence of AMD between females and males (female 598 (63.8%) than in male 339 (36.2%), the difference was not significant (p = 0.18). The age didn't have any influence to AMD. PEX had no influence to AMD distribution (Table 6).

Table 6
Age-related macular degeneration distribution in PEX groups at follow-up study.*

	No PEX	PEX	Total, n (%)	p-value
No AMD, n (%)	189 (21.1)	71 (23.7)	260 (100.0)	p = 0.35
AMD, n (%)	708 (78.9)	229 (76.3)	937 (100.00)	
Total, n (%)	897 (100.0)	300 (100.0)	1197 (100.0)	
* each eye was kept as object.				

Table 7
Age-related macular degeneration at baseline and follow-up study.*´ **

	Baseline study, n (%)	Follow-up study, n (%)
No AMD	663 (52.5)	260 (20.6)
AMD	554 (43.9)	937 (74.2)
Total	1262 (100.0)	1262 (100.0)
* each eye was kept as object.		
** same individual eye was compared at baseline and follow-up study.		

Central Corneal Thickness

CCT was measured in 1262 eyes of 631 patients. At follow-up, CCT was significantly smaller in PEX group (529 ± 34μm) comparing with no-PEX group (532 ± 33μm) ($p < 0.001$). CCT became significantly thinner with aging ($p < 0.001$). At follow-up CCT correlated with age. CCT was 537 ± 30 μm in 55–65 years age goup, 533 ± 33 μm in 66–75 years age groups and in the eldest group CCT was thinnest 525 ± 36 μm ($p < 0.001$).The thinnest central cornea was in the eldest age group both for PEX and no-PEX groups respectively (520.63; $p < 0.001$ vs 527.25; $p = 0.006$). After 10 years Pearson Correlation between age and CCT is weak ($r=-0,159$; $p < 0.001$), CCT becomes thinner with age. There was no statistically significant difference between PEX/no-PEX groups in gender and CCT.

Over 10 years, CCT became statistically significantly thinner compared to baseline (539 ± 36 μm vs 531 ± 33 μm, $p < 0.001$. This was driven predominantly by the no-PEX group (at baseline 539 ± 35 μm vs at follow-up 530 ± 31 μm; $p = 0.002$) as not present in in PEX group couldn’t confirm significance (at baseline 539 ± 39 μm vs at follow-up 532 ± 36 μm; $p = 0.280$.

Corneal Curvature

Of the 1182 eyes with corneal curvature (CC) measured, the mean CC was 7.7 ± 0.26 mm (at baseline mean CC 7.6 ± 0.27 mm). Radius of the corneal curvature in males was statistically significantly higher than females (7.8 vs 7.6 mm; $p < 0.001$). At follow up, there was a tendency that CC decreases with age, but not significant ($p > 0.05$). After ten years the cornea became flatter (7.6 vs 7.7 mm; $p < 0.001$), statistically so both in PEX and in no-PEX groups ($p = 0.013$). CC was flatter in PEX group vs no-PEX group at both studies, but couldn't confirm significance.

Corneal Astigmatism

Of the 1182 eyes with relevant measurements, 290 cases of corneal astigmatism were found (Table 8.). Females have more corneal astigmatism (62.8% vs 37.2%, $p = 0.02$). In study population significantly the biggest part of corneal astigmatism was with-the-rule, the tendency was seen and in no-PEX group and PEX groups (Table 8.). In the eldest group (mean age 77.5 ± 6.4) against-the-rule corneal astigmatism was diagnosed the most ($p < 0.001$). At baseline study the biggest part of against-the-rule corneal astigmatism was diagnosed also in the eldest group, but couldn't reach significance.

Table 8
Distribution of corneal astigmatism at follow-up study.**

Astigmatism	No PEX, n (%)	PEX, n (%)	Total, n (%)	p- value
With-the-rule	148 (68.5)*	37 (50.0)*	185 (100.0)	**p = 0.009**
Against-the-rule	54 (25.0)	26 (35.1)	80 (100.0)	
Oblique	14 (6.5)*	11 (14.9)*	25 (100.0)	
Total	216 (100.0)	74 (100.0)	290 (100.0)	
*Statistically significant difference within the groups.				
** each eye was kept as object.				

Discussion

PEX typically affects several structures of the anterior segment of the eye, however there is lack of consistent evidence on PEX incidence and prevalence [17]. PEX prevalence is published to be 0.2–30.0% with increasing prevalence with increasing age around the World. The differences in geographical, ethnic and race features, as well as age and gender distributions of the study participants and methods of diagnosing PEX [2, 4, 9, 18, 19]. Dissemination of PEX varies in different studies: 1.8% in USA [18], 2.3% in west Sydney Australia [20], 3.4% in India [21], 5.7% in Turkey [10], 16,1% in Greece [22], 16.3% in Australia (Aborigines), 16.9% in Middle Norway, 18.0% in Middle Sweden, 22.1% in Finland, Oulu [18], 39.3% in Ethiopia [23].

In Lithuania, PEX prevalence was found to be 43.9%, in 76–83 age group, as high as in Iceland (40.6% in those of 80 years old)[4].

Prevalence of PEX increased with age in all studies [6, 9, 10, 19, 23–26]., this is in agreement with our finding as well and those with PEX are older than those without (72.2 ± 8.1 yrs vs 68.6 ± 8.2 yrs, respectively). Similarly, in Turkey the highest PEX rate was in the 80 years old patients (18.4%) with an increased odds ratio of 45.78 ($p < 0.01$) when compared to the 40–49 age-group [19]. A previous Lithuanian study [13] found that PEX risk increases by 13.5% with every year of age increase. A Swedish study agrees with the age dependent increase, and established the annual incidence of PEX being 1.8% (95% CI 1.3–2.4)[3]. Thessaloniki longitudinal, population-based study found the 12-year incidence of PEX was 19.6% (95% CI, 17.1–22.2)[27]. Icelandic study found that on average there was a 5% increase in risk of developing definite PEX for every decade people older than 50 years (OR = 1.05; 95% CI 1.01–1.09, $p = 0.022$)[7].

Conversely, there are limited data on the incidence of PEX and on factors associated with the development of PEX [28]. This is mainly because few population-based studies in the field of glaucoma and even fewer studies in the field of PEX have re-examined their initial population to collect longitudinal data [28]: The Reykjavik Eye Study (5-year and 12-year follow-up)[6, 29]; the study by Aström and co-workers [3] in Skelleftea, Northern Sweden (21-year follow-up); the Chennai Eye Disease Incidence Study (6-year follow-up)[30] and The Thessaloniki longitudinal, population-based study in Northern Greece (12-year follow-up) are the only prospective longitudinal population- based studies to have provided incidence data for PEX [27]. We couldn't find any follow-up study about prevalence of PEX held in Baltic countries. There are three Baltic states: Lithuania, Latvia and Estonia. Lithuania is situated on the eastern shore of the Baltic Sea in Northern Europe. The prevalence of PEX in Lithuania was found (34.2%) as high as in Iceland (40.6% in those of 80 years old)[4]. There is data from Estonian researches 2004 y, the prevalence of PEX – 35.4% [8] and 2010 y, the prevalence of PEX – 25.5% [31]. The prevalence of PEX in Latvia is 21.6% [32]. The highest prevalence rates of PEX is described in Nordic countries [3, 4]. It was interesting to explore Lithuania's population, whether PEX prevalence is as high as in other Northern countries.

It is established progression of PEX from unilateral to bilateral with aging [6]. In Icelandic study 71.0% of clinically unilateral PEX cases had converted to bilateral over 12 years [6]. In Sweden study 55.0% of unilateral converted to bilateral PEX during 21 years follow-up [3]. In our follow-up study 53.0% of unilateral PEX had progressed to bilateral PEX in 10 years period.

Several studies reported that prevalence of PEX in female is higher than in male [3, 6, 7, 24]. Conversely, Kiliç found a significant relationship between PEX and male gender [10, 32]. In our study, PEX was more common in male 45.6% than in female 42.9%, but the difference between gender groups was not statistically significant. Other studies found no association of PEX with sex [23, 33, 34].

In Saudi Arabian study no significant relation was found between education level, occupation and life style of the patients and prevalence of PEX [34]. In our study secondary education for men showed

tendency for bigger risk of having PEX. The probability of having PEX for men reduced by adjusting by risk factors: alcohol consumption 1–4 time/month and alcohol consumption > 1 time/week, marital status-married, former and current smokers, normal weight, but not significantly. Adjusting by multivariate risk factors, secondary and university education, normal weight and overweight reduced the probability of having the PEX for women, but not significantly.

The Reykjavik Eye Study initially explored potential risk factors for the prevalence of PEX: older age, female sex, increased iris pigmentation, moderate use of alcohol, and asthma were associated with higher prevalence of PEX; the consumption of vegetables and fruit was associated with lower prevalence of PEX. When the same variables the consumption of vegetables and fruit was associated with lower prevalence of PEX [35]. When the same variables were included in a risk factor analysis on the 5-year incidence of PEX, significant associations were found only with age and the consumption of fruit [35]. However, in the risk factor analysis for the 12-year incidence of PEX, there were no statistically significant associations [6]. Being married was shown to be protective for definite PEX in a univariate analysis. However, controlling for the effect of age eliminated this association [7, 27].

In the Thessaloniki Eye Study sex, smoking, alcohol consumption, BMI, CCT didn't show statistical significance [27].

In the Chennai Eye Disease Incidence Study older age, rural residence, illiteracy, pseudophakia and nuclear cataract were significantly associated with the 6-year incidence of PEX [27, 30].

In our study secondary education for men shows tendency for bigger risk of having PEX. Adjusting by multivariate risk factors without excluding gender, former and current smokers, normal weight showed tendency to reduce the probability of having the PEX, but not significantly.

Radius of CC was found to be age-independent and significantly steeper in females than in males [36]. In our study we confirmed that females' CC radius was significantly steeper than for males (7.6 vs 7.8 mm; $p < 0.001$), and that the the cornea became flatter during the 10-years of follow-up (7.6 vs 7.7 mm; $p < 0.001$). Hepsen et al. reported significantly steeper corneal curvature in PEX eyes compared to those without [37]. We couldn't confirm this tendency in our study which is in agreement with another study on this issue [38].

CCT appears to be independent of age and gender. [36] and while our findings for gender was the same, we did find that that CCT became significantly thinner with aging ($p < 0.001$).. Some studies claim that in PEX, CCT values are significantly lower than those in non-PEX eyes [39, 40]. We agree with authors that CCT is smaller in PEX group comparing with no-PEX ($p < 0.006$). On the contrary, Krysik found CCT thicker in PEX group [41]. Many authors report that there is no significant difference in CCT between PEX and no-PEX groups [7, 37, 38, 42–45].

Lens opacification occurs in a high proportion of eyes with PEX and so PEX patients commonly require surgical intervention for their cataract [31] (most commonly nuclear)[46].

Nuclear sclerosis predominated in eyes with PEX compared to those without PEX (57.6% and 36.9%, respectively)[8], confirmed by the findings of the Blue Mountains Eye Study where after 10 years follow-up, eyes with PEX had a significantly greater prevalence nuclear cataract after adjusting for relevant factors (OR = 1.90; 95% CI, 1.04–3.48)[47]. In contrast, while we found a large number of nuclear cataract both in PEX and no-PEX groups, we could not confirm difference in our population. On the contrary, Gunes found that mixed cataract was the most common cataract type in the PEX patients in Turkey [48]. In 30-years follow-up study Ekström and colleague found that PEX was the second most important predictor for cataract surgery after lens opacities, accounting for a 2.38-fold increased risk, male had a lower risk for cataract formation [49]. In our follow-up study in PEX group showed tendency to have higher risk 1.2% to have cataract (95% CI 0.576–2.574; p = 0.61).

In a Turkish population, the prevalence of age-related macular degeneration was found to be significantly higher in PEX group than in those with no-PEX (17.9% vs 9.5%, p = 0.03)[48], but in our study we couldn't confirm this tendency.

Conclusion

During 10 years of follow-up the prevalence of PEX increased from 9.8–34.2%. The frequency of PEX among male and female was the same (p > 0.05). PEX significantly increases with aging. We have found that nuclear cataract was diagnosed mostly, but didn't differ in PEX and no-PEX groups. In PEX group risk to have cataract increased 1.2% (95% CI 0.576–2.574; p = 0.61).

PEX didn't influence distribution of AMD respectively.

CCT significantly was thinner in PEX group and in the eldest PEX group (p < 0.001). There was no differences between genders and CCT.

CC became steeper in no-PEX and PEX groups comparing baseline and follow-up studies (p = 0.013). CC was flatter in PEX group in both studies, but couldn't confirm significance.

The biggest part of corneal astigmatism was with-the-rule in no-PEX and PEX groups. We coudln't find any risk factors which influenced PEX incidence.

Strength And Limitations

The main strength of this study is its population-based prospective study design. Detailed examination by trained and certified operators were carried out using a strict protocol.

The main limitation includes response rate of 66.4%, which makes difficult to reach denominate significance (p < 0.001). Cataract surgery (performed in 8.02% investigated persons; both pseudophakic eyes after 10 years of follow-up), small amount of returned to the follow-up survey respondents may also misrepresent some data [50].

Declarations

Data availability

The data used to support the findings of this study are available from the corresponding author upon request. PEX associations with cardiovascular diseases were discussed in our earlier article [50](PMID: 31956932; DOI: 10.1007/s10792-019-01262-x; https://www.ncbi.nlm.nih.gov/pubmed/?term=rumelaitiene).

Conflicts of Interest

The authors declare that they have no competing interest.

Ethical approval

The study was approved by the Regional Bioethics committee and was carried out in accordance with the Declaration of Helsinki.

Informed consent

Informed consent and consent form for case reports were obtained from all individual participants.

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