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214

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Prevalence of exfoliation syndrome in Estonia and its clinical significance

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UNIVERSITY OF TARTU
PRESS
1632

Department of Medicine, University of Tartu, Estonia.

Dissertation is accepted for the commencement of the degree of *Doctor of Philosophy* in Medicine on June 19th, 2013 by the Council of the Faculty of Medicine, Universty of Tartu, Estonia

Supervisors: Päivi M. Puska MD, PhD, University of Helsinki, Finland

Reviewed by: Pille Taba, MD, PhD Senior Research Fellow, Senior Lecturer, University of Tartu, Estonia

Ruth Kalda, MD PhD Professor of Family Medicine, University of Tartu, Estonia

Opponent: prof. Eija Vesti, University of Turku, Finland

Commencemen: Room 1038, 19 Ravila street, Tartu on October 18th, 2013, at 14.00

ISSN: 1024–395X
ISBN: 978–9949–32–387–6 (Print)
ISBN: 978–9949–32–388–3 (PDF)

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University of Tartu Press
www.tyk.ee

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LIST OF ORIGINAL PUBLICATIONS

1. K. Kaljurand, P. Teesalu. Prevalence of exfoliation syndrome in Estonian population. Eur J Ophthalmology 2010; 20(6): 1012–1017
2. K. Kaljurand, P. Puska. Exfoliation syndrome in Estonian patients scheduled for cataract surgery. Acta Ophthalol Scand 2004; 82: 259–263
3. K. Kaljurand, P. Teesalu. Exfoliation syndrome as a risk factor for corneal endothelial cell loss in cataract surgery. Annals of Ophthalmol 2007; 39(4): 327–333

Contribution of applicant's to original publicatins: Kuldar Kaljurand participated in study design, subject examinations, patient pre- and postoperative examinations and data collection. He participated in data analysis and its interpretation. He is the first author of all papers.

ABBREVITATIONS

ACD	anterior chamber depth
AL	axial length
BSS	balanced salt solution
CCC	continuous capsulorhexis
CCT	central corneal thickness
CI	confidence interval
CV	coefficient of variation
ECD	endothelial cell density
ECM	extracellular matrix
EXG	exfoliation glaucoma
EXM	exfoliative material
EXS	exfoliation syndrome
IOP	intraocular pressure
LOXL	lysyl oxidase-like
mmHg	millitetre of Mercury
OHT	ocular hypertension
OR	odds ratio
OU	opacity units
phaco	phacoemulsification
POAG	primary open-angle glaucoma
SD	standard deviation
VA	visual acuity

1. INTRODUCTION

Exfoliation syndrome (EXS) also called pseudoexfoliation, was first described by the Finnish ophthalmologist J.G.Lindberg in 1917 as small white spots at the papillary border and on the lens capsule, depigmentation of the papillary border and translucency of the iris in cataractous, glaucomatous and normal elderly persons (Lindberg 1917). EXS is an age-related condition with generalised disorder of the extracellular matrix (ECM) characterized by a pathological accumulation of polymorphic fibrillar extracellular material in the anterior segment of the eye (Schlötzer-Schrehardt & Nauman 2006)

Exfoliative material (EXM) appears to be attached to various intraocular tissues such as the lens epithelium, nonpigmented ciliary epithelium, trabecular epithelium, corneal endothelium, vascular endothelial cells and almost all cell types of the iris (Ritch & Schlötzer-Schrehardt 2001)

EXM has also been identified in various tissues of the body, primarily in the connective tissue portion of the visceral organs (Schlötzer-Schrehardt & Nauman 2006) as well as the walls of the short posterior ciliary arteries and vortex veins (Schlötzer-Schrehardt 1991).

Elevated intraocular pressure (IOP) has been reported in eyes with EXS (Arnarsson 2007, 2009; Mitchell et al. 1999; Kozart 1982).

Patients with EXS are twice as likely to convert from ocular hypertension to glaucoma (Leske EMGT 2003) and are more likely to develop glaucoma at all IOPs (Topouzis 2009).

Patients with exfoliative, also known as capsular, glaucoma (EXG) have a greater mean IOP, greater diurnal IOP fluctuation (Konstas et al. 1997), more visual field loss and optic disc damage at diagnosis, poorer response to medication, and greater need for surgical intervention, more rapid progression and a greater proportion of blindness (Ritch 2008).

It has been suggested that increased lens opacification is associated with EXS (Hirvelä 1995; Hietanen 1992). However, it has been difficult to evaluate the direct risk factor for cataract formation, in terms of whether it is high IOP, glaucoma, glaucoma treatment or exfoliative process itself.

EXS is known to be a major risk factor in modern extracapsular cataract surgery and phacoemulsification. The risk of intraoperative problems, such as a poorly dilating pupil, zonular rupture, capsular break, and vitreous loss and postoperative complications including fibrinoid reaction, posterior synechias, cell deposits, and capsule contraction, is higher in eyes with the syndrome that have extracapsular cataract extraction (Skuta et al. 1987; Zetterström et al. 1992; Guzek et al. 1997) or phacoemulsification (Dosso et al. 1997; Hayashi et al. 1998; Scorolli et al. 1998; Shastri & Vasavada 2001).

Other ocular manifestations include dry eye (Kozobolis 1999), lens (and artificial intraocular lens) sub-luxation (Hayashi 1998; Breyer 1999), angle closure and retinal vein occlusion (Ritch 2010).

Specular and electron microscopic studies have revealed both quantitative and qualitative corneal endothelial cell changes in eyes with EXS. EXS eyes

have been found to have a lower endothelial cell density than in non-EXS eyes. Changes in the percentage of hexagonal cells and the coefficient of variation of cell size have been shown when compared to eyes without EXS (Naumann & Schlötzer-Schrehardt 2000; Inoue et al. 2003; Wali et al. 2009). The characteristic tissue alterations predispose to corneal endothelial decompensations which make them vulnerable during intraocular surgery, especially in cataract phacoemulsification.

This clinical study was designed to examine the prevalence of EXS in Estonia and among patients scheduled for cataract surgery. The vulnerability of the corneal endothelium during cataract phakoemulsification in patients with or without EXS was also studied.

2. REVIEW OF THE LITERATURE

2.1. Epidemiology

Although the syndrome has since been discovered throughout the world, there is great variation in the prevalence of EXS in different regions and ethnic groups (Forsius 1988, Karger 2003, Arvind 2003)

These variations may be a true genetic difference related to ethnicity or may be related to examination techniques, diagnostic abilities and criteria, selections of patient subgroups and patient age (Ritch & Schloetzer-Schrehardt 2001).

2.1.1 Prevalence of exfoliation syndrome

Since EXS has been discovered, it has mainly been evaluated as a Scandinavian syndrome. Though the detected occurrence of EXS is worldwide, reported prevalence rates of exfoliation syndrome vary widely in different geographic locations, from 0% of Inuits (Forsius 1979) and 0.9% in Australia (McCarty 2000), 1.7 % in Congo (Kaimbo 2012) and 3.4% in Japan (Miyazaki 2005), 5.5% in France (Colin 1988) and 6.0% in Southern India (Krishnadas 2003), 9.6% in Iran (Nouri-Mahdavi 1999) and 9% in Lithuania (Spečkauskas 2012), 10.7% in Iceland (Arnarsson 2009) and 11.9% in Creece (Anastasopoulos et al. 2011) up to 25.3% in northern Finland (Forsius 1979) and 38% for Navajo Indians (Faulkner 1972). Very low (0.4%) prevalence rates have been reported among the Chinese population (Young 2004). The prevalence of EXS differs remarkably even in different regions and altitudes of one population (Kozobolis 1997, 1999). It also has been suggested that persons living in lower latitudes appear to develop EXS at younger age (Ringvold 1996).

Some years ago Dr. Taylor, on the basis of his study results, debated whether EXS is an environmental disease (Taylor 1979). Interesting data comes from Stein and colleagues, who assessed the risk of EXS by geographic latitude tier. Compared with middle-tier residence, northern-tier residence (above 42°N) was associated with an increased hazard of EXS while southern-tier (below 37°N) was associated with a reduced hazard on EXS. For each additional sunny day annually, the hazard increased by 1.5% in a location with an average level of other climatic factors (Stein 2011). Contrary to those findings, Forsius & Luukka found no EXS in Innuit versus in 20% of Lapps lining at the same latitude (Forsius & Luukka 1973). Kang et al. demonstrated that people of Nordic extraction in the United States were not at increased risk for EXS, (Kang 2012). The lack of clear association with other climate-related disorders of ocular connective tissue (Forsius 2002) suggests that we are dealing with a very different cause for EXS, in which climate might play only a consequential role.

The distribution of EXS between two genders is found to be variable as well.

Some studies have shown EXS to be significantly more prevalent in men (Taylor 1980, Yalaz 1992, Kozobolis 1997, Nouri-Mahdavi 1999) and some find it more prevalent in women (Hiller 1982, Ekström 2008, Åström 2007 I,

Arnarsson 2009), while other studies show no gender difference (Stefanitou 1990; McCarty & Taylor 2000, Arvind 2003, Miyazaki 2005, Jeng 2007, Quiroga 2010).

EXS is an age-dependent disorder in most of studies, the prevalence of EXS increases with age (Karger 2003, Miyazaky 2005, Krause 1988, Åström 2007 II, Arnarsson 2009, Quiroga 2010, Kanthan 2013,) and is seldom found before the age of 50 (Tarkkanen 1962, Forsius 2002). In population studies, patients with EXS have found to be significantly older than those without it (Arnarsson 2007, Arvind 2003, Miyazaki 2005). In a study conducted by Karger and colleagues (Karger 2003) the age-adjusted annual incidence of EXS was 25.9 per 100,000 and it was higher among females than males (32.7 vs 16.9).

2.1.2. Prevalence of glaucoma in subjects with exfoliation syndrome

EXS has been suspected as an independent and strong risk factor for glaucoma. Elevated IOP with or without glaucomatous damage occurs in approximately 25% of subjects with EXS or about 6–10 times the rate in eyes without EXS (Ritch 2001). In a review, Forsius (1988) found the prevalence of glaucoma in EXS to vary around the world considerably, from 0% in the United States to 83% in Argentina. He found roughly one half of EXS eyes have glaucoma. In the Thessaloniki Eye Study, the proportion with glaucoma among subjects with EXS was higher than that for glaucoma among non-EXS participants, 15.2% versus 4.7% respectively (Anastasopoulos 2011). A study by Jeng et al. (2007) found 16% of EXS patients to have glaucoma at the time of diagnosis and that the risk of EXS conversion to EXG is about 60%. Karger et al. (2003) concluded their study with a similar result, 16% of EXS patients had glaucoma and 28% of EXS subjects developed EXG during a 16-year follow-up time. The Blue Mountains Eye Study confirmed the strong relationship between glaucoma and EXS. Subjects with EXS had an increased risk of glaucoma, which was independent of other glaucoma risk factors, including IOP (Mitchell 1999). In another study from Australia McCarty with colleagues found that positive predictive values for glaucoma were 22% in EXS-positives and 12% in EXS-negatives (McCarty 2000). The glaucoma conversion rate has been found to be twice as high in patients with ocular hypertensive (OHT) and EXS as a conversion of OHT without EXS (Grødum et al. 2005).

2.1.3. Prevalence of exfoliation syndrome in patients with glaucoma

Ritch in his review postulate that the prevalence of EXS in glaucoma cohorts is significantly higher than in age-matched non-glaucomatous populations (Ritch 2001). Most population studies report a higher prevalence of EXS among primary open-angle glaucoma (POAG) patients (Arnarsson 2007; Mitchell 1999; Topouzis 2007). The prevalence of EXS among patients with POAG has been reported to vary from 1.4% in the USA (Ball 1988) to 50% in Finland (Hirvelä

1995) and 60% in Norway (Ringvold 1991). In a Finnish population, Hirvelä found one-third of newly diagnosed glaucomas were exfoliative (Hirvelä 1995). In a review, Forsius (1988) found the prevalence of EXS in Finland of patients with glaucoma to be from 24% to 66%. In the study by Åström et al. (2007) 59% of glaucoma patients also had EXS at the age of 87 years. In the Blue Mountains Eye Study, a strong and significant relationship was found between EXS and glaucoma (Mitchell 1999). Glaucomatous damage was present in 14.2% of eyes with EXS compared to 1.7% of eyes without EXS. The age- and gender-adjusted odds ratio was 5.0 (95% CI 2.6–9.6) and this remain unchanged (OR 4.8) after adjustment to glaucoma risk factors and was also relatively unaffected by IOP adjustment (OR 3.7; 95% CI 1.8–7.6,) (Mitchell 1999). Arnarsson and colleagues in the Reykjavik Eye Study found those with EXS to have a four-fold likelihood of having glaucoma compared to those without EXS (Arnarsson 2007).

2.1.4. Heredity

In different studies (Damji 1998; Allingham et al. 2001; Thorleifsson et al. 2007) a genetic component in EXS is suggested. Interesting results from Forsman et al. propose that EXS is consistent with an autsomal dominant trait with incomplete penetrance, where the penetrance is more reduced in males than in females (Forsman 2007). In a milestone study by Thorleifsson et al. two risk variants in the lysyl oxidase-like 1 (LOXL1) gene were identified as being strongly associated with EXS (Thorleifsson 2007). The LOXL1 in one of the enzymes is essential for the formation and maintenance of elastin fibres (Jonasson 2007). LOXL1 protein is a major component of exfoliation deposits and appears to play a role in its accumulation and in concomitant elastotic processes in intra- and extra-ocular tissues of EXS-patients (Ritch 2008, Schlötzer-Schrehardt 2009).

The currently proposed pathogenesis of EXS is a oxidative stress-related, excessive production by elastogenic cells of elastic microfibrils that aggregate into a typical configuration through an enzymatic cross-linking process (Schlötzer-Schrehardt & Naumann 2006).

2.1.5. Exfoliative material

In EXS, the EXM accumulates throughout the anterior segment. There is more than one theory for EXM formation. It has been proposed that the EXM is formed by focally detached corneal endothelial cells with hypertrophized secretory organelles. An abnormal extracellular matrix is synthesized, composed of basement membrane material, microfibrils and EXM fibres. Descemet's membrane appears to be thickened with irregular excrescences and diffuse melanin deposition (Schlötzer-Schrehardt 1993; Naumann & Schlötzer-Schrehardt 2000). Those changes can lead to early corneal endothelial decompensation. Electron- micro-

scopy has shown large aggregates of typical EXM adhering to the corneal endothelium (Naumann & Schlötzer-Schrehardt 2000).

According to another hypothesis, mechanical friction between the iris and the lens, which could lead to micro-fibrillar material being rubbed off of the surface of the anterior lens capsule, where EXM was produced (Ritch 1994). EXM fibrils observed in surface of the corneal endothelial cells may originally come from the lens surface (Prince & Ritch 1986). The friction between the fragile papillary margin of the iris and the lens may cause increased pigment dispersion in EXS eyes (Prince & Ritch 1986) and spreaded melanin granules are then phagocytised by endothelial cells (Naumann & Schlötzer-Schrehardt 2000). A proportion of the subsequently accumulated fibrillar eosinopilic material sticks to the corneal endothelium because of its adhering capabilities (Ringvold 1994). This accumulation of EXM and melanin granules may lead to corneal endothelial decompensation (Naumann & Schlötzer-Schrehardt 2000). At a moment, there is no consensus regarding the location of production and delivery of EXM.

Streeten et al. (Streeten 1986) first described the elastic microfibril theory of pathogenesis, based on similarities between EXM and zonular fibers, and explained EXS as a type of elastosis affecting elastic microfibrils. This fibrogranular material is composed of microfibrillar subunits and is surrounded by an amorphous matrix comprising various glycoconjugates (Streeten 1986; Morrison & Green 1988). Exfoliation fibrils have a characteristic ultramicroscopic appearance of 20–30 nm thickness, with 10 nm subunits and may be 800 to 900 nm long (Seland 1988). Those crossbanded fibrils and filamentous subunits contain predominantly epitopes of elastic fibers such as elastin, tropoelastin, laminin, amyloid P, vitronectin and components of elastic microfibrils (Ovodenko 2007).

Growing evidence implicates oxidative stress and inflammation in EXS pathogenesis. The EXS-specific tissue alterations are caused by a generalised fibrotic matrix process, which has been characterized as a stress-induced elastosis associated with the excessive production and abnormal cross-linking of elastic microfibrils into fibrillar EXM aggregates, (Schlötzer-Schrehardt 2011).

Eagle et al. (1979) were the first to detect EXM outside the eye globe, in the walls of the short posterior ciliary arteries adjacent to the basement membrane of the smooth muscle cells. Exfoliation-like fibres have been detected in skin-biopsy specimens (Streeten 1990) in various peribulbar tissues such as extraocular muscles, walls of wortex veins, orbital connective tissue septa and the optic nerve sheaths of EXS-patients (Schlötzer-Schrehardt 1991). Interestingly, EXM was also found in the clinically unaffected fellow eyes (Schlötzer-Schrehardt 1991). In many studies EXM in autopsy tissue specimens obtained from skin, heart, lungs, liver, kidney and cerebral meninges was revealed in patients with intraocular EXS (Schlötzer-Schrehardt 1992; Streeten et al 1992). According to these findings EXS has been suggested to be an intraocular manifestation of a systemic disorder.

2.2. Clinical picture of exfoliation syndrome

2.2.1. Features of exfoliation syndrome

Exfoliation syndrome is characterized by the development of white, dundruff-like flakes throughout the anterior ocular segments. Exfoliative material is deposited in various tissues: the posterior corneal surface, the pupillary border, the anterior chamber angle, the lens zonules and ciliary processes. EXM on the lens surface appears as a central disc and peripheral band with a biomicroscopically clear intermediate zone (Lindberg 1917, Layden 1974, Schlötzer-Schrehardt 1993).

Pigment dispersion from the iris is known to appear first, before EXM can be detected by biomicroscopy. These clinical signs include the liberation of pigment into the anterior chamber after pupillary dilatation, loss of pigment at the pupillary margin, transillumination of the iris and pigment deposition on the anterior lens capsule, corneal endothelium, iris surface, and the trabecular meshwork (Layden 1974; Prince & Ritch 1986; Schlötzer-Schrehardt 1993).

A pigmentation of the trabecular meshwork is found to be the predominant feature of the EXS (Krause 1973; Layden 1974). A particularly suggestive finding may be pigmentation of the upper portion of the anterior chamber angle or/and specific pigmentation of the irido-corneal angle, known as Sampaolesi's line (Sampaolesi et al. 1988)

2.2.1.1. Vascular changes in exfoliaton syndrome

Vascular changes are pronounced in the eyes with EXS. A fluorescein angiography of the limbal vasculature reveals loss of the regular vascular pattern in the limbus and areas of neovascularisation in advanced cases, as well as congestion of the anterior ciliary vessels (Laatikainen 1971, Raitta & Vannas 1971). Those abnormalities of the iris vessels, loss of radial vessels and obstruction of vessels are shown to cause tissue hypoxia and hypoperfusion that result in neovascularisation of the iris tissue and leakage of fluorescein due to impairment of the blood-aqueous barrier (Vannas 1969; Ringvold & Davanger 1981; Cambiaggi 1988). Ritch et al. found in their prospective study that central retinal vein occlusion is commonly associated with EXS (Ritch 2010). Reduced ocular and cerebral blood flow has been reported by several authors (Harju & Vesti 2001; Yüksel 2001).

2.2.1.2. Corneal endothelium in exfoliation syndrome

It has been suggested that corneal endothelium metabolism is unsettled in eyes with EXS induced a loss of endothelium cells. These endothelial cell changes are induced by altered composition and increased flare intensity of the aqueous humor, caused by a breakdown of the blood-aqueous barrier (Schlötzer-Schrehardt 1992).

In normotensive patients with unilateral EXS Puska with colleagues did not find quantitative or qualitative morphological changes or differences in corneal endothelium between the two eyes. The endothelial cell density (ECD) was, on an average, 3.6 $\pm$11.4% lower in the EXS-eyes but the difference was not significant. They also did not find EXM on the corneal endothelium in any eye (Puska 2000).

On the other hand, Romero-Aroca in his population-based study found that changes such as lower endothelial cell density and low hexagonality percentage with higher coefficient of variation are common findings in patients with EXS, especially in older age groups, and may predispose patients to increased cell loss during cataract surgery, (Romero-Aroca 2011). This study found that complications in cataract surgery were higher in patients with EXS and postoperative corneal oedema was best correlated with a low hexagonality percentage (Romero-Aroca 2011). Among normotensive and nonglaucomatous patients scheduled for cataract surgery, Quiroga and colleagues found a larger percentage of patients (21.3% vs 9.3%), with ECD lower than 2000 cells/mm2, in patients with EXS compared to non-EXS, (Quiroga 2010).

Changes in corneal endothelium have also been more prevalent in normotensive patients, with EXS than in without EXS. Those changes, such as the polymegethism and pleomorphism of corneal endothelial cells, have been discovered in both eyes of patients with unilateral EXS and these changes were essentially the same overtly affected and apparently normal fellow eyes (Wirbelauer 1998). After comparing normotensive EXS eyes to normal eyes without EXS and to eyes with no ocular disease other than senile cataract, in their study, Miyake and colleagues suggested that the corneal endothelial changes are consistent in eyes with EXS and can be considered as an early sign of the disorder, (Miyake 1989).

Also, Inoue found significantly lower corneal endothelial density in EXS eyes compared to non-EXS eyes, and there was no difference between glaucomatous or non-glaucomatous eyes (Inoue 2003).

On the other hand, Østern and Drolsum, in their prospective study among patients with and without EXS who underwent cataract surgery, found no significant difference in ECD in two groups before the surgery or after 6–7 years of follow-up. No significant differences in polymegathism or pleomorphism were asserted. Investigators found no reduction in ECD according to glaucoma status. Also, no clinical signs of corneal decompensation were noted amongst the participants (Østern and Drolsum 2012).

Wali and colleagues concluded that in glaucomatous eyes with EXS keratopathy endothelial cell polymegethism and pleomorphism is more frequently associated with male gender than with cataract. Interestingly, the correlation of pleomorphism and polymegathism was stronger for patients <60 years ($R(2) = 0.7268$, $p = 0.01$) than >60 years old ($R(2) = 0.5805$, $p = 0.01$,) (Wali 2009).

There is also study (Gagnon 1997) in which patients with POAG were compared to those without glaucoma; ECD were found to be significantly lower in patients with glaucoma. Patients receiving three or four topical glaucoma medi-

cations had lower cell counts than those receiving one or two medications (Gagnon 1997). Gagnon and colleagues concluded that in glaucoma patients proposed harmful mechanisms could be direct damage from raised IOP, congenital alteration of the corneal endothelium, toxicity of topical medication or a combination of all of these, (Gagnon 1997).

In patients with advanced EXS, a distinct type of corneal endotheliopathy may occur, which can lead to a corneal endothelial decompensation. In a study on patients with clinically diagnosed EXS and irreversible corneal decompensation by Naumann & Schlötzer-Schrehardt, histological material was obtained from patients undergoing penetrating keratoplasty. Histopathologically corneal buttons showed an abnormal diffuse, irregular thickening of Descemet's membrane and focal accumulations of locally produced EXM. Also, clinically the patients showed diffuse corneal oedema, a pleomorphic and numerically reduced corneal endothelium, and retrocorneal flakes of EXM in some cases (Naumann & Schlötzer-Schrehardt 2000). Investigations, conducted by the same study group in electronic microscopy revealed large clumps of typical EXM that were adhered to the corneal endothelium and masses of EXM were incorporated into the posterior Descemet's membrane (Schlötzer-Schrehardt 1993).

2.2.1.3. Corneal thickness in exfoliation syndrome

Some studies have found that nonglaucomatous and glaucomatous subjects with EXS have thicker corneas compared to those without EXS (Puska 2000; Stefaniotou 1992). Stefaniotou found that subjects with EXS had significantly thicker corneas compared to subjects without EXS, but corneal thickness showed no significant difference between EXS and normal fellow eyes (Stefaniotou 1992). In their study in normotensive eyes with early EXS Puska et al. found higher values of central corneal thickness (CCT) in the exfoliative eyes compared to fellow nonexfoliative eyes (Puska 2000). On the contrarily, Inoue and colleagues found significantly thinner central corneas in patients with EXS compared to non-EXS patients and there was no difference whether affected eye were glaucomatous or not (Inoue 2003). Also Özcura and colleagues found that mean CCT is significantly thinner in nonglaucomatous EXS eyes compared to nonEXS eyes (Özcura 2011). In a large population (N = 1045), in a patients with or without glaucoma, the Reykjavik Eye Study, did not find a significant difference of CCT between subjects with or without EXS, and the result was also the same after adjusting for the effects of age and gender (Arnarsson et al. 2007). In his study Cankaya did not find any significant differences in CCT between normal eyes and EXS eyes with or without glaucoma (Cankaya 2012). Østern and Drolsum had similar results in their study among patients with and without EXS who underwent cataract surgery (Østern and Drolsum 2012).

2.2.2. Clinical course of exfoliation syndrome

While the classic picture of manifest EXS has been written about detail, the early stages of the beginning of EXS have not been well defined. Development of the syndrome from the first pigmentary changes to the full-scale exfoliation syndrome picture is supposed to take 5–10 years (Jerndal 1985).

2.2.2.1. Monocular or binocular involvement

EXS is shown to be a bilateral process, which often has clinically unilateral involvement.

In a study by Romero-Aroca et al. the unilateral prevalence of EXS was 70.9% (Romero-Aroca 2011). Klemetti found that clinically EXS often occurs unilaterally but in up to 41% of cases it may develop in the fellow eye (Klemetti 1988). In a study conducted by Puska (Puska 2002) in 10 year follow-ups 38% had converted to bilateral. No risk factors for conversion to bilateral EXS were found. Åstöm and colleagues found in the group of subjects with unilateral EXS that 55% converted to bilateral EXS during a 21-year follow-up period (Åstöm et al. II 2007). Andrikopoulos and colleagues indicated similar results; bilateral EXS is more frequent than unilateral with the percentage of bilateral EXS rising with progressing age (Andrikopoulos 2009). Unilateral EXS occurs at a younger age than bilateral (Tarkkanen 1962; Klemetti 1988). However, there is a retrospective study, which found a cumulative incidence of conversion to bilateral EXS to be 0.11 at 5 years, 0.36 at 10 years and 0.52 at 15 years (Tarkkanen 2004).

The question has arisen of whether the EXS is histologically a bilateral disorder with asymmetric clinical onset. EXM has been ultrastructurally identified in contralateral eyes that are clinically free of exfoliation (Schlötzer-Schrehardt 1991, Konstas 1993, Prince 1987, Ritch 2010).

2.2.2.2. Ocular hypertension and glaucoma in exfoliation syndrome

The vast majority of studies have found IOP being higher in EXS than in non-EXS eyes (Arvind 2003, Mitchell 1999, Arnarsson 2007, Kozart 1982, Damji 1999), with a few exceptions (McCarty 2000, Krishnadas 2003). The IOP elevation seen in EXS is more likely caused by EXM detaching from the cells that produce it and then floating in anterior segment until it attaches itself in the trabecular meshwork, thereby creating an increased resistance of aqueous humour (Schlötzer-Schrehardt 2006).

The elevation of IOP is well known risk factor for glaucoma. But not all EXS affected eyes develop ocular hypertension or glaucoma: 65.5% of the EXS eyes remained normotensive in study of Klemetti (1988) with follow-up time of 1–23 years. Similar results were detailed in study by Thornburn (1988) in which the presence of EXS in a healthy eye seemed to have no prognostic value for the

development of glaucoma. The essential changes that affect ocular tension are thought to take place in the early phase of the exfoliative process (Hansen & Sellevold 1970) and the risk of developing glaucoma is considered to be highest relatively shortly after the development of fibrillopathy (Aasved 1971)

An Early Manifest Glaucoma Trial study found that in patients with early glaucoma, IOP remained stable without treatment during a 6-year period, regardless of baseline IOP, except for patients with EXG, where IOP increased by almost 1 mmHg annually (Hyman 2010). The Thessaloniki Eye Study produced interesting findings where for screening IOP $\leq$ 20 mmHg the proportion with glaucoma was similar in subjects with and without EXS. For IOP level > 20 mmHg the proportion with glaucoma increased significantly in subjects both with and without EXS, while it was much higher among those with EXS at the same screening IOP (Topouzis 2009). Similar to the prevalence of EXS, the incidence of EXG seems to be an age-dependent disease. Topouzis and colleagues in their study did not find any EXG patient in the group 60 to 64 year age-group, while it was 1% in the 65 to 69 age-group and 2.5% in 80 years and older age-group (Topouzis 2007). This increase in the prevalence of EXG with increasing age was statistically significant. In the Thessaloniki Eye Study, IOP was a significant risk factor associated with both, EXG and POAG (Topouzis 2011). Patients with EXG and POAG have been found to have significantly lower values of CCTcompared with normal subjects of the same age (Alpenza-Dunato 2011), which gives a lower IOP value in Goldmann tonometry. Similar results were reported in several other studies; CCT was significantly thinner in patients with EXG (Gorezis 2008; Özcura 2011) and significantly thicker in cases of ocular hypertension (Gorezis 2008).

Some studies have indicated that the effect of EXS on ocular pathology is more complicated than solely through pressure increase caused by decreased outflow. Puska et al (Puska 1999) in their 3-year prospective study found that in normotensive patients, with unilateral EXS and equal IOP of both eyes throughout the study, the changes in the optic disk were only found in the eye with EXS suggesting the present of a deteriorating factor other than elevated IOP. However, the relationship between glaucomatous damage and IOP seems to be stronger in EXG than in POAG, and EXS has been identified as a major risk factor for open-angle glaucoma (Naumann 1998). Furthermore, EXG is characterised with rapid progression, more resistant to medical treatment and worse prognosis than POAG (Teus MA 1998, Leske et al 2003, Schlötzer-Schrehardt & Naumann 2006, Jonasson 2007).

2.3. Exfoliation syndrome and lens opacification

Although the nature of the relationship is not well understood, increasing evidence has been presented for an association between EXS and cataract formation (Taylor 1979; Hiller 1982; Puska 1994). Objective quantification of lens changes has been a problem due to methodological and instrumental limitations.

In the majority of studies, especially earlier studies, objective methods were not used to measure lens opacity. Raitta & Vesti (1991) and Vesti (1993) used Lens Opacity Meter and found that, at corresponding ages, opacity units were higher in eyes with EXG than in eyes with POAG. Also in a study by Puska & Tarkkanen (2001), the development of lens opacities was followed using the Lens Opacity Meter. At the beginning of the study, the mean lens opacity was 23.5 opacity units (OU) in EXS eyes and 22.9 OU in, initially non-EXS, fellow eyes with no significant difference. After five years, the mean opacity was 30.0 OU and 26.9 OU in EXS and non-EXS fellow eyes, respectively, with a significant difference. In patients who remained unilaterally affected, the EXS eye had a higher opacity value compared to non-EXS eyes at the start of the study and after a five-year follow-up (Puska & Tarkkanen 2001). Hirvelä at al. in a population-based study found that EXS was present in one or both eyes in 22% of the patients with cataract and EXS was found to be a significant risk factor for cataract (Hirvelä 1995). We do have evidence that EXS is a risk factor for lens opacification. Increased lens opacification is suggested to be associated with the EXS in many studies (Layden & Schaffer 1974; Vesti 1993; Puska & Tarkkanen 2001; Romero-Aroca 2011), but these two phenomena have also been linked by age factor.

Due to population ageing in Western countries, there is an increased prevalence of EXS in eyes coming to cataract surgery and an increased prevalence of cataracts in eyes with EXS.

2.3.1. Lens opacification in exfoliation syndrome

The lens depends on the aqueous for its metabolism. In the EXS changes in the composition of the aqueous can intervene to lens metabolism and cause lens opacification. The exact role of high IOPs as a cause of lens opacification in not known, but there is evidence that association between increased IOP and lens opacification do exist (Klein 1997). Also patients on the IOP-lowering treatment have singnificantly greater risk to have nuclear opacities (Leske 2002; Heijl 2002).

There is theory that cataract formation is related to ocular ischemia and that the virtually constant association we have noted clinically between unilateral cataract and asymmetric EXS, the two occurring in the same eye, is indicative of greater ischemia in the involved eye (Ritch & Schlötzer-Schrehardt 2001). Question remains, as to whether this is related phenomenon, or parallel age-related symptoms.

2.3.2. Exfoliation syndrome and subtype of cataract

In clinical and histopathologic studies, the predominant type of cataract in EXS is shown to be a nuclear sclerosis.

In a clinical study of patients scheduled for cataract surgery, Hietanen found that nuclear cataract is a predominant type of cataract in eyes with EXS as compared with patients without EXS, 83% vs 62%, while the frequency of cortical cataract was the same, 15% vs 17%, and that of posterior subcapsular cataract was lower, 2% vs. 22% (Hietanen et al. 1992).

The Reykjavik Eye Study found that EXS was linked to nuclear lens opacification (Arnarsson 2009). Similar results were found in a study by Sekeroglu et al. in which, the most common type of cataract was nuclear in the EXS-group (33.5%) and 24.6% of patients with mature cataract had EXS (Sekeroglu 2008). Identical findings have been reported in studies worldwide, (Obuchowska 2006, Teshome 2004, Benatiya 2006).

In a histopathologic study of intacapsularly removed lenses, anterior cortical (12% vs. 30%), equatorial cortical (49% vs. 65%), posterior (10% vs. 25%) and supranuclear (40% vs. 60%) cataract were found to be less common in EXS than in non-EXS eyes. Nuclear cataract was more prevalent (88% vs. 82%) in EXS eyes. Posterior subcapsular cataract (55% vs. 55%) showed no difference while the anterior subcapsular was slightly less common in non-EXS eyes, (12% vs. 17%,) (Seland & Chylack 1982).

2.3.3. Exfoliation syndrome and cataract surgery

EXS has also been linked to ocular pathologies such as zonular and capsular weakness, poor pupillary dilatation, blood-aqueous barrier breakdown, retinal vein occlusion and corneal endothelium decompensation. These concomitant symptoms can lead to increased risk of surgical complications seen in these patients (Scorolli et al. 1998; Schlötzer-Schrehardt & Naumann 2006, Shingleton 2010). It has been presupposed that in EXS eyes might be at a higher risk of decline in corneal endothelial cell density after cataract surgery.

Corneal endothelial cell loss is a well-known, undesirable side-effect of cataract surgery that can, in severe cases, negatively impact patients' postoperative visual outcomes.

Lundberg and colleagues found the central corneal swelling at postoperative day 1 was strongly correlated with the central corneal cell loss at 3 months $R = 0.785$, $p<0,001$ (Lundberg 2005). Complications in cataract surgery are higher in patients with EXS, and postoperative corneal oedema was correlated with a low hexagonality percentage (Romero-Aroca 2011). Nevertheless, there is an interesting study where after 6–7 years following cataract surgery no significant differences were established in endothelial cell density, pleomorphism, polymegethism and corneal thickness in eyes with or without EXS, with no clinical signs of corneal decompensation (Østern 2012).

2.4. Exfoliation syndrome and systemic diseases

Studies suggest that EXS is not exclusively an ocular condition but rather a systemic-one. EXS material has been identified in different tissues of the body, primarily in a connective tissue of visceral organs (Schlötzer-Schrehardt & Naumann 2006). EXM has been found in various organs of a body such as in the heart, lung, liver, kidney and gall-bladder and also in meninges of patients with ocular EXS (Schlötzer-Schrehardt & Naumann 2006; Streeten 1992). EXS has been associated with transient ischemic attacks, arterial hypertension and myocardial infarction (Repo 1995; Mitchell 1997). EXS has also reported to be a risk factor for coronary artery disease (Andrikopoulos 2009; Citirik 2007; Sekeroglu 2008). Djordjevic-Jocic with colleagues revealed significantly higher frequency of abdominal aortic aneurysm in patients with EXS and EXG than in patients with POAG or cataract (Djordjevic-Jocic et al. 2012). On other hand, Romero-Aroca et al. (2011) and Anastasopoulos et al. (2011) found no connection between EXS appearance and systemic diseases. Åstöm at al. (2007) did not find significant difference in mortality between individuals with or without EXS. In the Thessaloniki Eye Study, Topouzis and colleagues found that vascular diseases and their treatment were associated only with POAG (Topouzis 2011). Tarkkanen et al. (2008), using the Finnish Social Insurance Institution registry, found no difference in the frequency of arterial hypertension or ischemic heart disease in patients with EXG or POAG. This study also reported a significantly lower prevalence of diabetes mellitus in EXS-patients compared to POAG (Tarkkanen et al. 2008). Allingham et al. 2001, nevertheless, found no association between EXS and cardio- and cerebro-vascular disease, arterial hypertension or diabetes mellitus. Similarly to last mentioned study, Spečkauskas in his population-based study found no association between EXS and ischaemic heart disease, arterial hypertension and diabetes mellitus (Spečkauskas 2012).

Although EXS has been associated with a more systemic pathological condition no well-defined association of EXS with a systemic disease has yet been shown.

3. AIMS OF THE RESEARCH

1. To determine the prevalence of EXS in Estonia. To examine differences in related ophthalmological variables, such as IOP and glaucoma, in subjects with EXS and without EXS. To estimate the prevalence of EXS in patients scheduled for cataract surgery.
2. To assess the EXS as a possible risk factor for lens opacification.
3. To compare the influence of various cataract surgery pre-, intra- and post-operative characteristics to corneal endothelium and thickness in patients with or without EXS.

4. DEFINITIONS, SUBJECTS AND METHODS

4.1. Definitions

EXFOLIATION SYNDROME
Exfoliation syndrome was defined as occurrence of biomicroscopically detectable typical white-greyish material on the anterior surface of the lens, and/or at the pupil margin (Puska 2001). Findings of few pigmentary granules on the anterior lens surface, on the iris and on the corneal endothelium without exfoliative material were not defined as EXS.

GLAUCOMA was defined as IOP $\geq$ 21 mmHg with typical glaucomatous changes of the optic disc with or without visual field defects found on the visual field evaluation with Humphrey perimeter. Optic nerve heads were considered glaucomatous on biomicroscopical examination with the Volk lens in the presence of focal or generalized narrowing or disappearance of the neuroretinal rim with an enlarged amount of cupping or pallor (Park 1996).

OCULAR HYPERTENSION was defined as IOP > 21mmHg without optic nerve head changes or visual field defects (Puska 2002).

MATURE CATARACT was defined as a totally opacified lens, either brunescent or white, and was included in the mixed type of cataract.

4.2. Subjects

This thesis is based on the results of three clinical studies. The studies were performed in accordance with ethical standards laid down in the Declaration of Helsinki and informed consent was obtained from all participants. The studies were approved by the Ethics Committee of the University of Tartu.

The studies were conducted in the Eye Clinic of the Tartu University Clinics. All subjects and patients were examined by same investigator, Dr. Kuldar Kaljurand. All patients were operated on by one surgeon, Prof. Pait Teesalu.

4.2.1. Prevalence of exfoliation syndrome in Estonia (I)

A cross-section, population-based study was conducted to determine the prevalence EXS in Estonia. Seven hundred and sixty-six residents, chosen by random sampling from the Estonian Population Database from the city of Tartu, Estonia, were invited to participate in this study. 424 subjects (55.4%) of all samples did participate. All participants were aged fifty years or older and of Finno-Ugric origin. The cohort was divided into decades (50–59; 60–69; 70–80; 81–). All patients underwent a slit-lamp examination before and after pupil dilatation and a thorough ophthalmologic examination. Visual fields were tested with

Humphrey perimeter. Cases with definite or suspicious pathologic findings were directed for further evaluation. The epidemiological data were collected based on an interview with the patient including history of the eye diseases or surgery, family history for glaucoma, history and duration of systemic disease and use of ocular or/and systemic medications.

4.2.2. Exfoliation syndrome in Estonian patients scheduled for cataract surgery (II)

This prospective study comprised 305 consecutive patients (105 male, 200 female) aged 40–93 years (mean 71.5 $\pm$8.6) scheduled for cataract surgery, phacoemulsification with intraocular lens implantation, in the Eye Clinic of Tartu University Clinics. The age group of 70–79 years constitutes 48.8% of all patients. Slit-lamp estimation was performed before and 30–40 minutes after the dilatation of the pupils. Pupil size was measured before and after dilatation. The slit-lamp examination was used to look for localisation of the exfoliation material. In pseudophakic and aphakic fellow eyes, exfoliation material was sought for in the other locations except the lens. The predominant type of lens opacity was recorded. IOP was measured before and after dilatation with the Goldmann applanation tonometer.

4.2.3. Exfoliation syndrome as a risk factor for corneal endothelial cell loss in cataract surgery (III)

In the prospective study 37 consecutive patients (18 male, 19 female) aged 51–85 years (mean 73.5) scheduled for cataract surgery with EXS and 37 patients (16 male, 20 female) aged 43–84 years (mean 68.1) without EXS as a control group underwent a preoperative ophthalmologic examination. The axial length (AL), anterior chamber depth (ACD) and lens thickness were measured and keratometry together with specular microscopy was performed. The intraoperative factors and volume of balanced salt solution (BSS) were recorded. Previous ocular surgery, ocular trauma, high myopia, history of uveitis and abnormalities of the cornea were exclusion criteria for the study. Patients with mature cataract were not included in the study. Postoperative dexamethazone with chloramphenicol (Oftan DexaChlora, Santen) drops were used 5 times daily for 3 weeks, and thereafter 3 times daily for 2 weeks. None of the patients were contact lens wearers in their lifetime.

Table 1. Summary of study subjects and patients

Study	I	II	III
Patients, nr: Age; mean, range, SD (years)	424 70.0 (50–98)	305 75.5 (± 8.6)	37 EXS; 37 nonEXS 73.5 EXS (±8.3); 68.1 nonEXS (±8.0)
Measured	IOP: pre-, postdilatation Pupil: pre-, postdilatation Lens opacification/type of cataract Visual acuity Visual fields	IOP: pre-, postdilatation Pupil: pre-, postdilatation Type of cataract Visual acuity Visual fields	IOP: predilatation Preop; 24h, 1 month postop Pupil: pre-, postop(24h) Type of cataract Visual acuity Visual fields Anterior chamber depth Lens thickness Axial length Keratometry; corneal thickness Morphometric analysis of corneal endothelial cells
Mydriasis	1% cyclopentolate + 10% phenylephrine hydrochloride	1% cyclopentolate + 10% phenylephrine hydrochloride	1% cyclopentolate + 10% phenylephrine hydrochloride

4.3. Methods

4.3.1. Clinical ophthalmological examination

Pupil size was measured before and after dilatation with a special ruler under the same lighting conditions. The presence of EXS was confirmed 30–40 minutes after mydriasis with 1% cyclopentolate and 10% phenylephedrine as typical exfoliative material deposits either on the anterior lens surface, on the pupillary border or on the corneal endothelium and pigment on the anterior lens capsule was recorded. Intraocular pressure was measured before and after dilatation by using the Goldmann applanation tonometer. Visual acuity (VA) was estimated before dilatation using Landolt's acuity charts with lens correction achieving the best VA. The lens was evaluated through dilated pupil using slit-lamp biomicroscopy. The type of cataract (if presented) was recorded as nuclear, cortical, sub- capsular or mixed. Mature cataract was defined as a totally opacified cataract, either brunescent or white, and was included in the mixed type of

cataract. Stereoscopic examination of the vitreous, retina and optic nerve was made at the slit lamp after dilatation with a 90D (Volk) lens. The axial length, anterior chamber depth and lens thickness were measured preoperatively by ultrasonography Humphrey A/B scan system 837, (Humphrey Instruments Inc., San Leandro, California, USA). Preoperative keratometry was performed using a OAP211 keratometer (Carl Zeiss OAP 211, Carl Zeiss, Jena, Germany).

All patients underwent Humphrey automated perimeter (Humphrey Field Analyzer II HFA 750i/GPA, Carl Zeiss Meditec Inc., Dublin, CA USA). The presence of glaucoma, ocular hypertension or other ocular disease and previous intraocular surgery or trauma was registered.

4.3.2. Phacoemulsification

All patients scheduled for cataract surgery underwent phacoemulsification (*phaco*) without complications through a self-sealing limbal tunnel incision.

All operations were made using the same phaco equipment, Protegé, Storz Ophtahlmics (Storz Protégé Microsurgical Systems, Storz instrument company, St.Louis, Mo, U.S.A.), by one experienced surgeon (PT), who was blinded regarding the study participants. Topical anesthesia with 2% oxubrucaine eye drops (Alcain, Alcon) and the temporal approach was used in all cases. After circular continuous capsulorhexis (CCC), phacoemulsification inside the capsular bag was performed. Following initial groove formation into the nucleus, the chopping technique was used. Before CCC and intraocular lens (IOL) implantation, the viscoelastic substance (Celoftal®, Alcon) was injected into the eye. The wound was enlarged up to 5 mm before the implantation of IOL (Bausch&Lomb, model EZE-50). At the end of the operation, the viscoelastic was removed from the anterior chamber as well as from behind the IOL. Evaluated intraoperative factors were overall operation time, elapsed *phaco* time, *phaco* power, overall *phaco* impact (*phaco* time multiplied with *phaco* power) and volume of balanced salt solution (BSS; Bausch&Lomb).

4.3.3. Examination of the corneal endothelial cells

Corneal endothelial cells were photographed and corneal thickness was measured using automatic noncontact specular microscope (Specular Microscope SP-2000P, TOPCON Instrument Corp, made in Japan, Tokyo). This device provides rapid morphometric analysis and has reliable reproducibility (Bovelle 1999; Modis 2002). ECD, average cell area and coefficient of variation (CV; Standard Deviation / average cell size x 100) were recorded in the centre of the cornea and in four paracentral, (superior, inferior, temporal and nasal quadrants) locations. Examinations were made sequentially in a central and fixed paracentral area to analyze regional differences. The positions were placed on the 6 mm diameter circle, each position 3 mm from the centre of the cornea. To determine the endothelial cell density, the endothelial cells were counted in a rectangular

frame placed manually with constant (0.1 x 0.1 mm) area. The frame adjacent cells were marked manually with a mouse and digitized. Only high-contrast and focused endothelial images with sufficient quality and resolutions were noted. Examinations were made preoperatively, on the first postoperative day and 4 weeks after surgery. The 4 week follow-up period was considered to be sufficient because exposure of corneal endothelial cell damage is already detectable in the first postoperative month (Walkow 2000; Wirbelauer 1998; Milla 2005; Østern & Drolsum 2012). All measurements were performed by the same examiner (KK).

4.3.4. Statistical analysis

All data was analyzed using the SAS software package (release 6.12, SAS Institute Inc.). Age and IOP were used as continuous variables. Statistics were performed using the Student *t* test and the Mann-Whitney U test was used to compare differences between the eyes. Pearson's chi-square 2-sided test was used to test the frequencies of lens opacities in the paired eyes. Analyses by subjects were also performed with logistic regression. The 95% confidence intervals of the prevalence were estimated and $p< 0.05$ was selected to denote statistical significance of differences.

5. RESULTS

5.1. Prevalence of exfoliation syndrome in Estonian population (I)

This cross-section population-based study consisted of 424 subjects in which 277 (65.3%) were female and 147 (34.7%) were male. The median age of participants was 70 years (range 50–98 years), in males 71 years (range 51–98 years) and in females 70 years (range 50–93 years). The median age of subjects of EXS was 72 years (range 51–93). Subjects in the EXS group were older than in the non-EXS group but the difference was not statistically significant.

5.1.1. Prevalence of exfoliation syndrome

The overall prevalence of EXS among the study participants in one or both eyes was 25.5% (108); 25.2% (37/147) in male and 25.6% (71/277) in female patients, p = 0.9. The bilateral involvement of EXS was detected in 36 (33.3%) of all EXS cases, and there was no significant difference in appearance of EXS between the two eyes in both genders (p = 0.91, 95% CI 0.7–1.4). The prevalence of EXS increases by age (Table 2).

Table 2. Regression analyses of prevalence of EXS, by age

EXS	Odds ratio	Std. err.	p	[95% CI]
50–59	1.0 (Ref.)			
60–69	3.32	1.58	0.012	1.30–8.44
70–79	5.23	2.40	<0.001	2.12–12.89
80–	5.02	2.51	0.001	1.88–13.41

EXS = Exfoliation syndrome
Std. Err. = Standard error
95% CI = 95% confidence interval
Ref = Reference group

5.1.2. Exfoliation syndrome and intraocular pressure

IOP was higher in the EXS group before and after pupil dilatation (Table 3).

Table 3. IOP before and after pupil dilatation

	IOP (mmHg) [95%] CI		
dilatation:	EXS	non-EXS	p
before	19.6 [18.48–20.63]	17.4 [16.95–17.77]	<0.01
after	19.7 [18.42–20.80]	17.0 [16.67–17.63]	<0.01

mmHg = millimetre of Mercury
IOP = intraocular pressure
non-EXS = without exfoliation syndrome
EXS = exfoliation syndrome.

5.1.3. Prevalence of glaucoma

Glaucoma was found in 70 (16.5%) participants with no difference in appearance between both genders (p = 0.6). Glaucoma was significantly more frequent in the EXS group than the non-EXS group, 35.7% vs. 11.3%, respectively (p <0.05). In logistic regression analysis the prevalence of glaucoma was not age-dependent in our study (Table 4).

Table 4. Regression analyses of prevalence of glaucoma, by age and gender

Glaucoma	Odds ratio	Std. err.	p	[95% CI]
50–59	1.0 (Ref.)			
60–69	0.99	0.42	0.9	0.42–2.31
70–79	2.07	0.80	0.06	0.96–44.4
80–	0.54	0.33	0.33	0.16–1.84
Female	1.0 (Ref.)			
Male	0.63	0.19	0.14	0.35–1.15

Std. Err = Standard error
95% CI = 95% confidence interval
Ref = Reference group

5.1.4. Prevalence of cataract

Any type of lens opsification in one or both eyes was found in 41.5% of male and 40.8% female participants with no statistically significant differences between two eyes and genders. The prevalence of the cataract was detected in 57.0% of cases in the EXS-group compared to 39.5% in the non-EXS group (p = 0.002). Nuclear cataract was more often represented in the EXS-group but was not statistically significant (p = 0.14). Patients with cataract were signifi-

cantly older compared to patients without it and the median age was 74 and 70 years, respectively (p<0,001). In logistic regression analysis, adjusted to age, subjects with EXS have 1.5-fold risk of having cataract compared to the non-EXS group (p = 0.003); both age and EXS have a significant influence on cataract formation (Table 5).

Table 5. Regression analyses of formation of cataract, by EXS and age

Cataract	Odds ratio	Std. err.	p	[95% CI]
EXS	2.03	0.48	<0.01	1.28–3.21
Cataract	Odds ratio	Std. err.	p	[95% CI]
EXS	1.56	0.41	0.09	0.96–2.63
50–59	1.0 (Ref.)			
60–69	2.86	1.23	0.01	1.23–6.64
70–79	11.46	4.75	<0.01	5.08–25.85
80–	29.70	15.37	<0.01	10.78–81.90

Std. Err = Standard error
EXS = Exfoliation syndrome
95% CI = 95% confidence intervall

There were no differences in pupil diameter between two groups before dilatation. Mydriasis was lesser in the non-EXS group but statistically not significantly.

Similar prevalence of systemic diseases was found in both groups of both genders.

There was no difference between the two groups in visual acuity (p = 0.9).

5.2. Exfoliation syndrome in Estonian patients scheduled for cataract surgery (II)

In the whole study group (n = 305, 105 male and 200 female; mean age 71.5 ±8.6 years. EXS was detected in 35.4% of patients scheduled for cataract surgery with 47.2% bilateral and 52.8% unilateral involvement.

In the affected eyes, EXM was noted on the anterior lens capsule of 96.7% eyes (Table 6).

Table 6. Disposition of EXM on the lens anterior capsule

	Central disc	Perferal band	Pupillary border	Posterior corneal surface
EXM	53 (59.6%)	81 (91.0%)	69 (75.0%)	8 (8.7%)

EXM = exfoliation material

EXM was noted only after pupil dilatation in the peripheral part of the lens anterior capsule in 15% of the patients.

Pigment granules were found on the anterior lens surface and posterior corneal surface of 33.7% operative eyes. Only 9.0% of operative eyes without EXS had pigment dusting on the anterior lens capsule and corneal endothelium.

5.2.1. Pre- and postoperative intraocular pressure

In eyes scheduled for cataract surgery, IOP was higher in eyes with EXS than in those without EXS (19.2 $\pm$ 6.5 vs. 17.1 $\pm$ 3.8 mmHg, p = 0.006), and they remained at a higher level after dilatation (18.6 $\pm$ 7.3 vs. 16.4 $\pm$ 4.1 mmHg, p = 0.013).

Ocular hypertension was found in 31 (10.2%) operative eyes of which 16 (51.6%) had EXS and 15 (48.4%) were without EXS.

5.2.2. Prevalence of glaucoma

There was no difference in the mean IOP between patients with EXG or with POAG (20.6 vs. 21.0 mmHg, p = 0.507). EXG embraces 54.4% of all cases of glaucoma.

Forty-five (14.8%) patients had glaucoma in the eye scheduled for cataract surgery; of these, 25 (8.2%) patients had glaucoma in both eyes.

In bilaterally phakic eyes with unilateral EXS (n = 41) glaucoma was recorded in 13 (31.7%) exfoliative and in 6 (14.6%) non-exfoliative eyes.

5.2.3. Type of lens opacification in operative eye

The operative eyes with EXS differed significantly from non-EXS in the predominant type of lens opacity (Table 7).

Table 7. Cataract type in the operative eyes

Type of cataract in operative eye	non-EXS		EXS		p
	N	%	N	%	
nuclear	78	36.8	53	57.6	<0.001
cortical	36	17.0	7	7.6	
subcapsular	43	20.3	7	7.6	
mixed	55	25.9	25	27.2	
total	212	100.0	92	100.0	

Data is missing for one non-EXS patient.
EXS = exfoliation syndrome
non-EXS = without exfoliation syndrome

Nuclear sclerosis was the predominant type of cataract (57.6%) in EXS eyes followed by other type of cataract.

Mature cataract was found in 21 EXS and 12 non-EXS eyes (33 out of 80 mixed cataracts; 41.3%).

Mydriasis was significantly lesser in eyes with EXS (6.4 + 1.1 vs. 7.2 + 0.9 mm, $p < 0.0001$).

The eyes with EXS scheduled for cataract surgery did not differ from non-EXS in visual acuity ($p = 0.099$).

5.3. Exfoliation syndrome as a risk factor for corneal endothelial cell loss in cataract surgery (III)

Thirty-seven consecutive patients with and 37 patients without EXS as a control group scheduled for cataract surgery were studied. Nineteen patients with post-operative corneal oedema, eight from the EXS and 11 from the non-EXS group were not included into analysis because of difficulties in endothelial cell counting on the first postoperative day. Two patients from the EXS group with an endocapsular ring placement were also not included because this surgical maneuver might cause additional damage to endothelium. The mean patient age in the EXS group was significantly older than in non-EXS group, 73.5 (range 51–85) years $\pm$8.3 (SD) and 68.1 (range 43–84) years $\pm$8.0 (SD,) ($p = 0.02$). Patients with EXS had less mydriasis but the difference was not significant (Table 8).

Tabel 8. Pre- and postoperative variables.

Variable	EXS group	non-EXS group	p
n =	27	26	
Age, years	73.5 (±8.3)	68.1 (±8.0)	0.02
Sex, F:M	19:8	20:6	
Pupil, preop ø (mm)	3.6 (±0.6)	3.9 (±0.7)	0.1
Pupil, postop ø (mm)	4.8 (±0.9)	5.0 (±0.9)	0.4
IOP, postop, mmHg	17.6 (±4.5)	16.7 (±2.7)	0.4
IOP, postop (24h)	24.8 (±11.7)	19.7 (±6.0)	0.07
IOP, postop (1 month)	16.5 (±3.4)	17.3 (±5.4)	0.6
ACD, mm	2.98 (±0.4)	2.98 (±0.4)	0.9
Lens thickness, mm	4.4 (±0.6)	4.3 (±0.6)	0.7
Axial length, mm	23.2 (±0.7)	23.4 (±1.2)	0.5
Keratometry	K1 43.5 (±1.6) K2 43.8 (±1.3)	K1 43.3 (±1.2) K2 43.1 (±1.3)	0.09

mm = millimetre
mmHg = millimetre of Mercury
IOP = intraocular pressure
ACD = anterior chamber depth

5.3.1. Preoperative parameters of corneal endothelial cells

Patients in the study and in the control group had similar anterior chamber depts, lens thicknesses, axial lengths and keratometry measured values as well as in pre- and postoperative pupil sizes. IOP was equal in both groups, but with a higher variability in the EXS group (Table 8). There was no significant difference in the pre- and postoperative visual acuity between two groups.

The mean preoperative corneal ECD, average cell area, CV as well as thickness of the cornea did not differ significantly between EXS and non-EXS groups (Table 9). The mean preoperative corneal central ECD was 2543 (±417) in the EXS group and 2594 (±519) in the non-EXS group, the mean paracentral ECD values were 2479 (±422) and 2455 (±475), respectively. Preoperative mean central ECD values were higher than paracentral (the average of superior, inferior, nasal, temporal) cell counts in both groups but not statistically significantly.

Table 9. Pre- and postoperative endothelial cell and corneal thickness variables

variable	region of cornea	Preop EXS	Preop non-EXS	p	Postop 24h EXS (†)	Postop 24h non-EXS (†)	p	Postop 1 month EXS (‡)	Postop 1 month non-EXS (‡)	p
ECD ±SD (cell/mm²)	central	2543 ±417	2594 ±519	0.7	2293 ±438 ($p = 0.04$)	2347 ±449 ($p = 0.05$)	0.9	2083 ±447 ($p < 0.001$)	2344 ±503 ($p = 0.08$)	0.06
	paracentr	2480 ±422	2455 ±475	0.7	2246 ±525 ($p < 0.001$)	2428 ±509 ($p = 0.4$)	0.01	2176 ±486 ($p < 0.001$)	2294 ±546 ($p = 0.04$)	0.09
Average cell area; (μm²)	central	401 ±83	396 ±86	0.5	455 ±102 (p = 0.05)	441 ±90 (p = 0.04)	0.7	500 ±121 (p = 0.001)	441 ±90 (p = 0.07)	0.4
	paracentr	420 ±95	434 ±97	0.8	476 ±156 ($p = 0.002$)	430 ±98 ($p = 0.6$)	0.02	483 ±122 ($p < 0.001$)	454 ±103 ($p = 0.03$)	0.06

variable	region of cornea	Preop EXS	Preop non-EXS	p	Postop 24h EXS (†)	Postop 24h non-EXS (†)	p	Postop 1 month EXS (‡)	Postop 1 month non-EXS (‡)	p
Coef. of variation	central	22.4 ±5.7	24.4 ±7.6	0.3	25.5 ±7.3 (p = 0.09)	26.0 ±5.8 (p = 0.4)	0.8	24.1 ±5.2 (p = 0.2)	23.8 ±7.0 (p = 0.7)	0.8
	paracentr	22.3 ±5.3	23.7 ±6.6	0.08	25.5 ±7.1 ($p < 0.001$)	25.6 ±7.3 ($p = 0.02$)	0.9	24.2 ±6.0 ($p = 0.05$)	24.3 ±5.5 ($p = 0.5$)	0.9
Corneal thickness (mm)	central	0.515 ±0.031	0.520 ±0.035	0.6	0.559 ±0.041 (p < 0.001)	0.553 ±0.046 (p = 0.006)	0.6	0.519 ±0.035 (p = 0.7)	0.523 ±0.042 (p = 0.8)	0.7
	paracentr	0,515 ±0.033	0,524 ±0.035	0.6	0,556 ±0.041 ($p < 0.001$)	0.556 ±0.060 ($p < 0.001$)	0.9	0.520 ±0.036 ($p = 0.3$)	0.527 ±0.038 ($p = 0.5$)	0.2

EXS = exfoliation syndrome
non-EXS = without exfoliation syndrome
ECD = endothelial cell density
SD = standard deviation
paracentr = paracentral
† - *p,* preop vs postop 24h
‡ - *p,* preop vs postop 1 month

5.3.2. First postoperative day

There was a statistically significant difference in the paracentral but not the central endothelial cell loss in the first postoperative day between the EXS and non-EXS patients (Table 9). The decrease of the central ECD was 9.8% ($p = 0.04$) in the EXS and 9.5% ($p = 0.05$) in the non-EXS patients. The decrease of the paracentral ECD was 8.2% ($p < 0.001$) in the EXS and 1.1% ($p = 0.4$) in the non-EXS patients.

The immediate postoperative (24h) increase of CV indicated a temporary heterogenity of endothelial cell size after the surgery that returned near to the baseline value during one month. The increase of CV occurred in the central and paracentral cornea in both group, but the difference between EXS and non-EXS eyes was not significant.

In the paracentral area, but not in the central area, the average cell area was significantly larger in the EXS patients than in the paratsentral area compared to non-EXS patients.

On the first postoperative day the thickness of the central as well as para-central cornea was significantly increased in both groups, indicating oedema, which returned to the baseline level during one month (Table 9).

IOP was higher in the EXS group and it had higher variability, though not statistically significant (24.8 ±11.7 vs. 19.7 ±6.0 mmHg, $p = 0.07$,) (Table 8)

5.3.3. One-month follow-up

The decreases of the mean central and paracentral corneal ECD values in comparison with the preoperative values were 18.1% ($p < 0.001$) and 12.3% ($p < 0.001$) in the EXS group and 11.6% ($p = 0.08$) and 6.6% ($p = 0.04$) in the non-EXS group, respectively. The decrease of ECD was more pronounced in EXS group but the difference between the two groups was not statistically significant (Table 9).

The average cell area was more increased (compensatory to endothelial cell loss) in the EXS group (99 μm2 centrally; 63 μm2 paracentrally) than in the non-EXS (45 μm2 centrally; 20 μm2 paracentrally) group one month postoperatively, but the difference did not reach statistical significance (Table 9).

CV had recovered to the preoperative level after the one month follow-up. The postoperative significant increase of CV only sustained in the paracentral area in the EXS group, but the difference the two groups was not significant (Table 9).

The thickness of the cornea of both groups had returned to the preoperative state one month after the operation (Table 9). In regression analysis we did not find a correlation between corneal thickness and ECD loss in any follow-up time point.

After one-month follow-up IOP was on the preoperative level in both groups. In regression analysis, the pre- and postoperative (24h) IOP, as the main

effect, did not have an influence on central ECD (p = 0.9, p = 0.6 respectively; r2 = 0.47)

5.3.4. Intraoperative parameters

Operation time was similar in both groups.

The consumption of BSS and *phaco* time showed significant differences between the groups; other operation parameters showed no statistically significant difference (Table 10).

Table 10. Operation parameters

Variable	EXS group (±SD)	non-EXS group (±SD)	p
Oper. time, min	12.4 (±4.3)	11.1 (±2.9)	0.2
Phaco power, %	44.0 (±13.2)	41.0 (±16.0)	0.5
Phaco time, sec	92 (±44)	71 (±32)	0.05
Overall *phaco* impact	25.96	20.8	0.2
BSS, mm	26.8 (±7.1)	19.8 (±7.5)	0.001

EXS = patients with exfoliation
nonEXS = patients without exfoliation
SD = Standard Deviation
BSS = balanced salt solution
Overall *phaco* impact = *phaco* power multiplied with *phaco* time

In regression analysis the consumption of BSS and *phaco* time did not have a statistically significant influence to ECD one month after surgery. Regression analysis revealed that *phaco* power had a significant negative impact to ECD (centrally $r^2 = 0.47$, $p = 0.02$; paracentrally $r^2 = 0.39$, $p < 0.001$). There was also a significant influence of overall *phaco* impact (*phaco* power multiplied with *phaco* time) to overall ECD (central, + 4 paracentral) decline ($r^2 = 0.30$, $p = 0.02$). EXS as the main effect or in interaction with *phaco* power did not have an influence on endothelial cell loss ($p = 0.2$), but it had a significant influence on endothelial cell loss in interaction with overall *phaco* impact ($r^2 = 0.27$, $p = 0.05$).

A statistically significant negative association between the age of patients and the postoperative central as well as overall ECD one month after surgery was found in regression analysis ($r^2 = 0.47$, $p = 0.004$ and $r^2 = 0.45$, $p = 0.004$; respectively). The presence of EXS does not have an impact on ECD in interaction with age ($p = 0.7$).

There was also a statistically significant negative association in regression analysis between the preoperative ECD and the change in ECD, indicating that the larger the preoperative cell density, the larger the postoperative cell loss ($r = 0.45$, $p < 0.001$). EXS did not have an influence on postoperative ECD in interaction with preoperative ECD ($p = 0.5$).

6. DISCUSSION

Epidemiological studies are needed in every country in order to obtain evidence-based data about every specific population. This data is important for planning medical and social care.

In the prospective population-based gross-section study, we investigated the prevalence of EXS in Estonia. Additionally, we looked at the IOP-level of participants, prevalence of glaucoma, lens opacity, and subtype of cataract. We evaluated the coexistence of EXS with systemic conditions. We also compared patients with EXS to those without EXS on different parameters.

Secondly, we examined the prevalence of EXS in patients scheduled for cataract surgery. This study addressed several clinical aspects such as frequency of EXS and glaucoma, pre- and postoperative IOP, mydriasis and the type of lens opacity in cataract patients.

Thirdly, the potential clinical impact of EXS in cataract phacoemulsification to corneal morphology was investigated.

6.1. Advantages and limitations

The advantages of these studies include the random population sample, the relatively high prevalence of EXS in this population and the prospective nature of these investigations. Our population-based study subjects were randomly chosen from the Estonian Population Database. In the prevalence study of EXS in patients scheduled for cataract surgery and in a study of EXS as risk factor for corneal endothelium, all participants were consecutive patients, without any pre-selection.

One deficiency of this investigation is that the information about systemic conditions was self-reported. Other limitations include the relatively low proportion of the oldest age-group and the lack of opportunity to examine immobile persons. Theoretically those persons could be more commonly affected; therefore, EXS may be somewhat underrepresented in this investigation. However, Krause et al. (1988), in their study conducted in elderly houses found a similar prevalence of EXS as aged matched non-institutionalized individuals.

6.2. Prevalence of exfoliative syndrome in the Estonian population

The reported prevalence of EXS in different populations varies extensively in the literature ((from 0% of Inuits (Forsius 1979), up to 22.4% in Finland (Krause 1988)). It is a well-known fact that EXS is common in Nordic countries. Worldwide prevalence varies greatly and it is difficult to distinguish distinct geographical distribution. The difference between many of these studies may be a true genetic difference related to ethnicity or may be related to exami-

nation techniques, diagnostic abilities and criteria, use of mydriatics, sampling methods and age distribution (Ritch & Schloetzer-Schrehardt 2001).

In our study of the Estonian population, the prevalence of EXS was 25.5% in subjects fifty years and older, which is the same as in Finland. Forsius in his two different studies on the prevalence of EXS in Finland found prevalence from 21% up to 25.3% in northern Finland (Forsius 1979; 1988). Forsman in her population-based study in the subisolate island of southern Finland found prevalence of EXS to be 8.1% in subjects over 50 years of age which increased to 18.4% for subjects over 70 years of age (Forsman 2007). The similar prevalence rates in our and in the Finnish studies are not surprising as both nations, Finland and Estonia, are of Finno-Ugric origin. Studies have revealed varying gender difference in prevalence of EXS. We did not find any difference in the gender distribution (25.6% in female and 25.2% in male, $p = 0.9$) of EXS, which is in accordance with many studies (Forsius 1988; Arvind 2003; McCarty 2000; Miyazaki 2005; Krishnadas 2003). Some investigators have reported a male preponderance (Nouri-Mahdavi 1999; Forsman 2007; Kozobolis 1997) but some also reported female preponderance (Karger 2003; Mitchell 1999; Åström & Lindén 2007; Arnarsson 2007; Ekström & Alm 2008). Although EXS occurs worldwide the prevalence among different geographic and racial populations and even inside the same ethnic populations varies considerably. At the moment, to our knowledge, commonly accepted methodology and diagnostic criteria for the definition of EXS do not exist. A lack of uniformly manageable epidemiologic studies does not facilitate estimating the true differences of prevalence of EXS and taking into consideration the influence of the possible impact of climate, socio-economic situation and cultural differences of different populations.

Distribution of EXS for bilateral vs. unilateral cases is highly variable in reported cases (Nouri-Mahdavi 1999; Kozobolis 1997; Kozart & Yanoff 1982) the percentage of bilateral involvement varies from ¼ to ¾. Most studies indicate that EXS is basically a bilateral syndrome although the clinical presentation is often unilateral. In a prospective 10-year follow-up study, Puska (Puska 2002) found that 38% of unilateral EXS cases had converted to bilateral. Arnarsson et al. had similar results in their study: 71% of clinically unilateral cases had converted to bilateral in 12 years (Arnarsson 2012). We found bilateral involvement of EXS in 33.3% of cases in our study. There was no significant difference in the appearance of EXS between the two eyes in both genders. In our study, subjects with the bilateral involvement of EXS, compared to unilateral, were not significantly older, which is similar to other studies (Kozart & Yanoff 1982; Arvind 2003).

As in many studies (Karger 2003; Arvind 2003; McCarty & Taylor 2000; Miyazaki 2005; Krause 1988; Kozobolis 1997; Mitchell 1999; Damji 1999; Åström 2007; Anastasopoulos 2011) if not in all, we found that the prevalence of EXS significantly increases with age. In the Thessaloniki Eye Study, in a large population ($N = 2554$), they found that participants with EXS were significantly older than nonEXS participants, (mean age 73.8 vs 70.4 years, $p < 0.0001$)

(Anastasopoulos 2011). In our study the median age of the participants of EXS was higher than that of the non-EXS participants, but the difference was not significant. Age in our study profoundly increases the prevalence of EXS, but also substantially affects other ophthalmological variables and is therefore an important confounder to consider.

In a review, Forsius reported the frequency of EXS in patients with cataract to vary from 0.3% in Poland, 3% in France, 9% in American Indians (New Mexico) up to 18% in Norway and 33% in Finland (Forsius 1988). EXS syndrome has been known to be associated with a greater prevalence of cataract, though the exact aetiology of this association is not known (Puska & Tarkkanen 2001; Schlötzer-Schrehardt & Naumann 2006; Young 2004; Arvind 2003; Taylor 1979; Hiller 1982; Puska 1994; Puska & Tarkkanen 2001). Findings in our study are in strong agreement with the above-mentioned studies, as we found a significantly different prevalence of cataract was detected in 57% of cases in the EXS group compared to 39.5% in the non-EXS group ($p = 0.002$). Also, in agreement with these studies, we found patients with cataract to be significantly older than patients without it; the median age was 74 and 70 years respectively and the prevalence of cataract increased with age. Moreover, the regression analysis in our study showed that EXS adjusted for age had a significant impact on cataract formation. Patients with EXS have a 1.5-fold age-adjusted risk of cataract. However there are studies were connections between EXS 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 EXS (Arnarsson 2009; McCarty 2000).

We found a tendency for nuclear cataract prevalence in the EXS group, which is similar to findings in earlier studies (Young 2004; Arvind 2003; Hietanen 1992). Recently published data from The Blue Mountains Eye Study found significantly greater prevalence of nuclear cataract in eyes with EXS and this association persist after adjustment for age, gender, smoking, diabetes, steroid use, myopia, socioeconomic status and open-angle glaucoma, (Kanthan 2013). In the Reykjavik Eye Study nuclear cataract, like EXS, was also shown to be highly age-related but causally not related to EXS (Arnarson 2007). Moreover, in the same study, nuclear lens opacification in EXS patients compared to non-EXS patients was highly significant until it was adjusted to age (Arnarson 2007). On the other hand, Krishnadas and colleagues found that EXS was associated with posterior subcapsular and cortical cataract, (Krishnadas 2003). The causative relationship between EXS and different types of cataract needs further clarification.

In our population-based study, we found a significant relationship between IOP and EXS. IOP in our study was significantly higher in eyes with EXS compared with the non-affected eye, before as well as after pupil dilatation. Similarly, Åström & Lindén, in their population based study found that in participants with unilateral EXS IOP is significantly higher in the affected eye, but there was no difference between the mean IOP of the non-EXS eyes in subjects

with unilateral EXS and the IOP of eyes in those with no EXS in either eye (Åström & Lindén 2007). They also found that IOP > 22 mHg was in 17% of EXS eyes and 3.0% in the non-EXS eyes. One reason for the elevated IOP in EXS 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 & Naumann 1995).

In the Thessaloniki Eye Study subjects with EXS compared to those with no EXS had higher percentage of IOP > 22 mmHg. This finding was mainly explained by the higher proportion with glaucoma among EXS participants. In this study investigators concluded that patients with EXS, compared to non-EXS, had significantly higher mean IOP, but after excluding glaucoma patients the IOP was only 0.6 mmHg higher ($p = 0.05$) in EXS-positives (Anastasopoulos 2011). However, there is a large population-based study from Australia (N = 5147), in which no significant relationship was found between IOP and EXS (McCarty & Taylor 2000). Similar conclusions were made by investigators in the Aravind Comprehensive Eye Survey study (Krishnadas 2003).

According to existing evidence, the elevation of IOP is a well-known risk factor for glaucoma (Le et al. 2003; Heijl, EGTS 2002). In the Collaborative Initial Glaucoma Treatment Study (CIGTS) investigaros found the mean IOP at baseline significantly higher in the EXG patients compared to POAG patients (Musch 2012). In a study conducted by McCarty and colleagues strong relationship between EXS and glaucoma was found after checking for age; although not highly sensitive, EXS was found to be a specific predictor of glaucoma status (McCarty & Taylor 2000).

In earlier studies, the prevalence of glaucoma in eyes with EXS has been found to vary considerably, from 7% in the USA (Kozart & Yanoff 1982) to 22.7% in Norway (Aasved 1971), 13.0% in the India (Arvind et al 2003) up to 61% in Finland (Tarkkanen 1962). It has been suggested that patients with EXS have the IOP-independent risk of glaucoma. In the Thessaloniki Eye Study the proportion with glaucoma among EXS participants was 15.2% while the proportion with glaucoma among non-EXS participants was 4.7% and in multivariate analysis, the presence of EXS was a risk- factor for glaucoma (Topouzis 2011). Investigators have evaluated the relationship between EXS and glaucoma after adjusting for IOP in Blue Mountains Eye Study (Mitchell 1999) and found subjects with EXS to have 2- to 3-fold independent risk of glaucoma. Åström et al. (2007) in their study with long (21 years) follow-up found, that EXS increases the risk of glaucoma four fold. In a prospective 10-year follow-up study, Puska found conversion to EXG in 32% in the initially EXS and 38% in the initially non-EXS fellow eyes, while POAG developed only in 3.5% of the nonEXS eyes. When initial IOP was removed from the model, the pupillary dilatation values ($RR = 0.488$; $p = 0.03$) and the differences in IOP between fellow eyes ($RR = 1.224$; $p = 0.01$) were associated with conversion to EXG (Puska 2002). In the Thessaloniki Eye Study where increased likelihood of

glaucoma development at the same IOP was investigated, it was found that the proportion with glaucoma for screening IOP < 20 mmHg was similar in subjects with or without EXS. For IOP level > 20 mmHg the proportion with glaucoma increased highly in subjects both with and without EXS, while it was much higher among those with EXS at the same screening IOP (Topouzis 2009). The previously mentioned studies showed that only a certain number of subjects with EXS develop glaucoma. The association of EXS with IOP, its differences, and their links to glaucoma development require additional, properly designed, prospective, population-based investigations.

The prevalence of glaucoma has been found to be high in Northern Europe (Ringvold 1996; Ekström 2008). Hirvelä and colleagues found the prevalence of glaucoma to be in 12% of inhabitants aged 70 years or older in Finland (Hirvelä 1994). Åstöm and colleagues (Åström I 2007) found a relatively high prevalence of glaucoma in their population study in age group of 80 years (3.2%) and in group 87 years (11.8%), with 4.0% and 20.5% in non-EXS and EXS groups respectively. The results of our study are in agreement with those findings, as glaucoma was significantly more frequent in the EXS group than in non-EXS group, 35.7% vs 11.3% respectively. In our population study, the glaucoma was found in 16.5% of participants. As all participants in our population-based study were of Finno-Ugric origin and relatively high prevalence of EXS, the findings could reflect true, relatively high, prevalence of glaucoma in the Estonian population. Exfoliative glaucoma seems to the prevalent type of glaucoma in the Estonian population as 50% of all glaucoma patients involved in the study had EXS. This is in agreement with findings in Sweden (Åström I 2007) where exfoliation syndrome in 59% of all glaucoma cases was found. In the CIGTS POAG subjects (58.0 years) were significantly younger on average than those with EXG (65.1 years,) (Musch et al. 2012). The high prevalence of glaucoma in our study could also be explained by the fact that 73.8% of participants were 60 years or older and the median of the age of the sampling was 70 years.

However, in the Reykjavik Eye Study Arnarsson and colleagues (Arnarsson 2007) did not find EXS to be a risk factor for glaucoma although they did find higher IOP in EXS eyes. Ekström and Alm found in their study that EXS alone is not associated with glaucoma and there is no indication of interaction between EXS and increased IOP (Ekström & Alm 2008).

The role of EXS in glaucoma development seems to be unclear and further investigations are needed to clarify this issue. It is known that the prevalence of glaucoma as well as EXS increases with age (Mitchell 1999; Åström II 2007). Nevertheless, the prevalence of glaucoma was not age-dependent in our study, which is not in accordance with many earlier studies (Karger 2003; Åström 2007). One potential explanation for this finding could be the relatively small number of patients in the age group 80 years and older. Low participation rates among subjects aged 80 years and older is a common problem in population-based studies, including herein.

EXS is found to be associated with elastic tissue changes (Schlötzer-Schrehardt U & Naumann GO 2006), vascular morbidity (Mitchell 1997), coronary

heart disease (Sekeroglu 2008) and arterial hypertension (Miyazaki 2005). Visontai et al. found decreased cardiovagal regulation in patients with EXS (Visontai 2008). However, in our study we did not find statistically significant connections between EXS and any systemic disease that is in agreement with data from the Thessaloniki Eye Study (Anastasopoulos 2011). In a Swedish study with a very long follow-up period (21 years) mortality was estimated for each study interval but the presence of EXS did not influence the risk of death (Åström 2007). In Finnish population-based registry survey, no difference in frequency of arterial hypertension or ischaemic heart disease was noted between patients with POAG and EXG but the frequency of diabetes mellitus was lower among patients with EXG (Tarkkanen 2008). Ultrastructural and immunohistochemical studies suggest that EXS involves the abnormal accumulation of elastin fibres, extracellular matrix and proteoglycans (Streeten 1992; Uusitalo 1993). Biochemical analysis will be required to resolve questions about the disturbance of systemic metabolism in EXS-positive subjects, and its connections with systemic conditions.

In regression analysis, EXS did not have an impact on visual acuity, in this population-based study, which is in agreement with previous investigations (Puska & Tarkkanen 2001; Hietanen 1992). Also in CIGTS the mean visual acuity at baseline between POAG and EXG patients were not significant (Musch 2012). However, in the study of lens opacity in unilateral EXS Puska (Puska 1994) found significantly decreased vision in EXS-positive's compared to EXS-negative's, while the eyes did not differ in refraction and lens opacity.

As with Allingham and colleagues (Allingham 2001), we did not find an association between EXS and age-related macular degeneration.

6.3. Exfoliation syndrome in patients scheduled for cataract surgery

We found EXS in a 35.4% of cases in patients scheduled for cataract surgery, either in the operative or fellow eye. 47.2% of cases were bilaterally and 52.8% were unilaterally affected. In bilaterally phakic patients EXS was found in 30.2% of the operative eyes, 55.4% being bilaterally and 44.6% being unilaterally affected. Those figures are within the same range as earlier reported in Finland among a similar study group, 26.5%, (Hietanen 1992). An even higher frequency of EXS, 42%, has been reported in Sweden in patients undergoing cataract surgery (Olivius et al. 1989). In a review, Forsius (Forsius 1988) reported the frequency of EXS in patients with cataract to vary from 0.3% in Poland, 3% in France, 9% in American Indians (New Mexico) up to 18% in Norway and 33% in Finland. Interestingly, in our study among patients scheduled for cataract surgery the prevalence of EXS was significantly higher in males in the age group of 50–59 years (22.2% vs. 12.5%), 60–69 years (35.7% vs. 24.1%) and 70–79 years (40.0% vs. 26.5%), while the prevalence was higher in females in the age group of 80–89 years (42.2% vs. 29.4%), but there was not a signifi-

cant difference in the overall prevalence of EXS in the study population. The effect of age and gender on variables linked to EXS is shown, but the question remains open regarding different division of EXS in different age groups. Among patients scheduled for cataract surgery, there was a clear increase in the frequency of EXS from 17.6% in the age group of 50–59 years up to 38.6% in the age group of 80–89 years.

Age is a significant risk factor for senile cataract and the incidence of cataract increases with age (Taylor 1979; Hiller 1982; Krause 1988; Kozobolis 1997, Forsius 1988; Ringvold 1991; Hietanen 1992; Sekeroglu 2008; Obuchowska 2006). In a cross-sectional population study, Hirvelä and colleagues recognised that almost two thirds of the population of 70 years of age or older had lens opacities. The prevalence of cataract increased with age from 44.6% in the 70- to 74-year-old age group to 97.6% of persons in the 85- to 89-year-old age group (Hirvelä 1995). In earlier studies, EXS is also shown to be a strongly age-dependent disorder, which is seldom found before the age of 50 years (Tarkkanen 1962; Krishnadas et al. 2003). We did not find any patient <50 years to have EXS. Also, Karger found an incidence rate of 2.8 per 100,000 in the age group of 40 to 49 years (Karger et al. 2003). In another study from Sweden, frequency od EXS was lower in the age group of 50–59 years (2.9%) in patients scheduled for cataract surgery but similar to our results in age-group of 80–89 years (39.2%,) (Olivius et al. 1989). It is a well known fact that the prevalence of EXS rises with age (Arnarsson 2007; Anastasopoulos 2011) and can play a role in cataract formation. It is not substantiated with natural aging alone. A larger prevalence figure of EXS in patients scheduled for cataract surgery could be explained with a higher mean age but there can be a specific pathological background. In our study of patients scheduled to cataract surgery 35.4% had EXS in the operative eye. This high percentage indicates a strong relationship between EXS and cataract. Increased lens opacification has also been noted as being associated with EXS in numerous previous studies (Taylor 1979; Hiller et al. 1982; Puska 1994). Puska & Tarkkanen in their elegant prospective study found a significant increase in opacity of the lens during a 5-year follow-up in EXS and non-EXS subjects but the increase was significantly higher in EXS eyes compared to non-EXS eyes. They found similar cluster of changes in patients who remained unilaterally affected; the lens opacity values were higher in the EXS eye compared to the fellow non-EXS eye at the end of the five-year follow-up (Puska & Tarkkanen 2001). Kanthan and colleagues in the Blue Mountain Eye Study, in a large population (3654), found similar associations between EXS at the baseline and 10-year incidence of the cataract surgery. After excluding eyes with glaucoma, the association of EXS cataract surgery remained significant (Kanthan 2013). In the Thessaloniki Eye Study, the cataract surgery was more likely to reported in EXS participants (21%) then in non-EXS (11,%) ($p = 0.05$), adjusted for age and sex. This association remained significant after the exclusion of participants with glaucoma and/or glaucoma treatment (Anastasopoulos 2011). Furthermore, when the analysis was repeated using person-specific data, similar associations were observed between EXS

and cataract surgery. On the other hand, no significant associations were observed between EXS at baseline and the long-term progression of the different cataract type, including nuclear, (Kanthan 2013). An association between EXS and cataract is biologically feasible, as in the EXS eyes the blood-aqueous barrier is impaired (Küchle 1996) and the rate of aqueous flow through the anterior chamber is lower compared to the non-EXS eyes (Johnson 1982) but lens metabolism depens on the aqueous. Further investigations are needed to clarify the genomic and proteomic background and connections of these two pathologies.

In our study, among patients scheduled for cataract surgery, the predominant type of lens opacity in the operative eyes with EXS differed significantly from those without EXS (Table 7). In both clinical and histopathological studies, the predominant type of cataract in EXS has been shown to be nuclear sclerosis, while cortical and supranuclear cataracts are less common and severe in EXS (Seland & Chylack 1982, Hietanen 1992, Sekeroglu 2008, Kanthan 2013). This finding was confirmed in the present study, 57.6% of all eyes with EXS scheduled for cataract surgery had nuclear cataract, which is similar with findings of earlier studies (Young 2004; Arvind 2003; Hietanen 1992). We found the same trend in our population-based cross-sectional study. Also, in a Finnish cross-sectional population-based study, stepwise logistic regression analysis indicated that the only risk factor for cortical cataract to be age and the risk factors for nuclear sclerosis to be age and exfoliation (Hirvelä 1995). In recently published long-term follow-up data from The Blue Mountains Eye Study suggest that the presence of EXS is associated with an increased risk of nuclear cataract (OR 1.90; 95% CI 1.04–3.48) and cataract surgery (Kanthan et al 2013). The finding that posterior subcapsular cataract is more common in patients without EXS than in those with it (Seland & Chylack 1982; Hietanen et al. 1992; Puska 1994) was confirmed in our study (19.7% vs. 6.5%). On the other hand, Krishnadas and colleagues (Krishnadas 2003) found that EXS was associated with posterior subcapsular and cortical cataract. Nuclear cataract, like EXS, was also shown to be highly age-related but not causally related to EXS in the Reykjavik Eye Study (Arnarsson 2007). The relationship between EXS and different types of cataract needs further investigations. Both conditions, EXS and cataract, can have similar pathophysiological backgrounds as oxidative stress (Schlötzer-Schrehardt 2010) and decreased antioxidant defence (Erdurmuş 2011). A relatively high percentage of mature cataracts (11%) were found in this material in comparison to 1.7% in an earlier study, (Hirvelä 1995). The economic situation in Estonia can explain the high percentage of mature cataracts to some extent, but 2/3 of patients (21 out of 33) had EXS of those patients. Sekeroglu and colleagues found same trend, 24.6% of all mature cataracts had EXS, in their study (Sekeroglu 2008).

The operative eyes with and without EXS preoperatively did not differ in pupil diameter (4.0 vs. 4.2 mm, $p = 0.139$), but mydriasis was less in eyes with EXS than in those without EXS (6.4 vs. 7.2 mm, $p < 0.0001$). The poorer response to mydriatics in eyes with EXS compared to those without EXS was confirmed in this study (Tarkkanen 1986; Puska 1995). Similarly to our find-

ings in patients scheduled for cataract surgery, Wirbelauer (Wirbelauer et al. 1998) and Shastri (Shastri et al 2001) found significantly poorer mydriasis in EXS-eyes. Insufficient mydriasis is important risk-factor in cataract phacoemulsification, especially in patients with EXS due to weak zonules and possible subluxation of the lens (Skuta 1987). Odds ratio for intra-operative complications (vitreous loss, capsular break, zonular break) is estimated to be 5.1 for EXS that is present as opposed to when it is absent (Scorolli 1998).

In regression analysis EXS did not have an impact on visual acuity in patients scheduled for cataract surgery, which is in agreement with previous investigations (Puska & Tarkkanen 2001; Hietanen 1992).

In the present study, the mean preoperative IOP was significantly higher in the operative eyes with EXS than in those without it (19.2 +6.5 vs. 17.1 +3.8 mmHg, $p = 0.006$). After pupil dilatation, IOP remained at a higher level in eyes with EXS when compared to eyes without EXS (18.6 + 7.3 vs. 16.4 + 4.1 mmHg, $p = 0.013$). In earlier studies conducted on patients scheduled for cataract surgery, the findings are similar; there are tendency to higher IOP in patients with EXS compared those without it (Hietanen 1992; Shastri 2001; Shingleton 2003; Teshome 2004; Sekeroglu 2008). However, Wirbelauer in his two different studies found no difference between those two groups in pre- and postoperative IOPs in cataract patients (Wirbelauer 1998; 1998b).

Also, in our study, glaucoma was significantly more frequent in eyes with exfoliation (27.8%) than in those without it (9.6%). In earlier studies, the prevalence of glaucoma in eyes with EXS has been found to vary considerably, roughly half of the EXS eyes being glaucomatous (Aasved 1971; Karger et al. 2003; Tarkkanen 1962). In a study conducted by Hietanen and colleagues, in patients scheduled for cataract surgery, a history of glaucoma was recorded in 33.8% of patients with EXS and in 10.1% of non-EXS patients ($p < 0.001$). Thirty-one percent of patients with EXS and 7% of patients without EXS had medical treatment for high IOP preoperatively. Irrespective of their treatment, a trend to higher preoperative IOP was seen in patients with EXS compared to those without it (Hietanen 1992).

In our study forty-five (14.8%) patients had glaucoma in the eye scheduled for cataract surgery, and of these 25 (8.2%) patients had glaucoma in both eyes. Four (1.3%) patients had glaucoma only in the fellow eye. As in our population-based study, in patients scheduled for cataract surgery glaucoma was significantly more frequent in eyes with EXS than in those without it. Of all glaucoma cases, EXG embraced 54.4% (in an operative eye 63.3%). The figure is similar to that reported earlier in Northern Europe (Tarkkanen 1962; Ringvold et al.1991; Hirvelä et al. 1995).

EXS as a risk factor for glaucoma is wellknown fact and it warranted in our study. We found in bilaterally phakic eyes with unilateral EXS ($n = 41$) glaucoma was recorded in 31.7% EXS and in 14.6% non-EXS eyes. Similar results had Hirvelä and colleagues in their study were they found that persons with EXS in one or both eyes, glaucoma was found in 27%, and in 8% in the non-EXS group (Hirvelä 1995). Hyman and colleagues found in the Early Manifest

Glaucoma Trial that eyes with EXG have significantly higher IOPs compared to POAG (Hyman et al. 2010). Similar findings had Konstas in his study, in comparison with POAG, patients with EXG had higher untreated IOP and higher IOP with medical therapy (Konstas 1993), and EXG patients have greater diurnal IOP fluctuations (Konstas 1997). The influence of IOP and its fluctuation for cataract formation merit further investigations.

Somewhat surprisingly, in our material we found no difference in the mean IOP between patients with EXG or with primary open-angle glaucoma (20.6 vs. 21.0 mmHg, $p = 0.507$). OHT was found in 31 (10.2%) operative eyes of which 16 (51.6%) eyes were affected and 15 (48.4%) were without exfoliation, with do difference between two groups. Nevertheless, Arvind found the prevalence of OHT to be significantly higher in the EXS-positives (Arvind 2003). Also Anastasopoulos with colleagues in the Thessaloniki Eye Study found significant percentage of EXS-positives having IOP $\geq$ 22 mmHg compared to those without EXS (Anastasopoulos 2011).

The presence of EXS and EXG found to be unfavourable prognostic factors in cataract surgery (Naumann 1998).

6.4. Exfoliation syndrome as a risk factor for corneal endothelial cell loss in cataract surgery

Several studies in normotensive patients with senile cataract have demonstrated quantitative or qualitative morphological changes in corneal endothelium in patients with EXS (Wirbelauer 1998; Wirbelauer 1997; Inoue 2003). In a similar patient's group, Miyake et al. observed a decrease of hexagonality and an increased coefficient of variation (Miyake 1989). Observations of these studies suggest that the corneal endothelial changes represent a consistent finding in eyes with EXS and in patients with EXS keratopathy only moderate rise in IOP or intraoperative factors can lead to the corneal decompensation. Those potential changes can be amplified by insufficient mydriasis and zonular instabilities. On the other hand, Puska et al. (Puska 2000) did not find quantitative or qualitative morphological changes in corneal endothelium in comparing the cornea in both eyes of normotensive patients with unilateral EXS.

Previous studies have found that corneal endothelial cells have decreased cell density, an increased the coefficient of variation of the cell area, and decreased the percentage of hexagonal cells with increasing age (Abib 2000; Inoue 2003). Physiological reduction in endothelial cells due to ageing has been estimated to be 0.5–0.6% per year with a gradual increase in polymegethism and pleomorphism (Bourne 1994; 1997). Age has been found to be an important variable to relevant to ECD in cataract surgery (Inoue 2002; Küchle 2000).

Stefaniotou et al. found significantly lower cell density in the EXS group than in the controls, which had no ocular disease other than senile cataract, but there was no difference between the eyes with EXS and normal fellow eyes (Stefaniotou 1992). Wirbelauer in two different studies of normotensive patients

scheduled for cataract surgery found a significant reduction of total ECD in patients with EXS (Wirbelauer 1997; 1998). Regional morphometric data revealed reduced ECD in central and paracentral region in patients with EXS compared to non-EXS patients, which suggests diffuse endothelial cell reduction in central and paracentral areas in patients with EXS (Wirbelauer 1998). Moreover, in patients with EXS without previous surgery on the other eye the endothelial variables revealed a similar pattern with reduced total ECD compared to controls (Wirbelauer 1998). Inoue with colleagues found also that ECD was significantly lower in patients with EXS, but they did not place significant difference between the pleomorphism and the coefficient of variation in the cell area in the EXS-patients and controls (Inoue 2003). Our results suggest, contrarily to some mentioned previous studies, that preoperative ECD do not differ significantly in cataractous patients with or without EXS, centrally (2543 vs 2593 resp), or paracentrally (2480 vs 2455 resp). Preoperatively, we did not find differences in the coefficient of variation and hexagonal cells between two groups. This is in accordance with recent study conducted by Cankaya and colleagues (Cankaya 2012). In a study by Puska and colleagues in non-glaucomatous, normotensive subjects, similar to our results, found that eyes with or without EXS did not differ in ECD and in the coefficient of variation of cell size or pleomorphism (Puska et al 2000). Also, Østern & Drolsum did not find significant differences in ECD, pleomorphism and polymegethism between two, EXS *vs* non-EXS, groups (Østern & Drolsum 2012).

There is no consensus in data from literature about the direct harmful impact of EXM on corneal endothelial cells.

In the first postoperative day, we found a statistically significant difference in paracentral but not in central endothelial cell loss between the EXS and non-EXS groups. The decrease of the central ECD was 9.8% in the EXS group and 9.5% in the non-EXS group, while it was 8.2% in the EXS and 1.1% in the non-EXS group paracentrally. Similar to our findings, Wirbelauer found central and paracentral cell loss occurred more homogenously over the entire cornea in the EXS group, reducing the ECD by 10.6% and 11.3%, while the similar decrease was 6.1% and 12.2%, respectively, in the non-EXS group (Wirbelauer 1998). Our findings are in line with the results of Wirbelauer, (Wirbelauer 1998) who found a similar total decrease of ECD without a significant difference between two groups. This endothelial cell loss reflects an immediate surgical effect, and stabilization with mild decrease of the ECD was observed at the end of one-month follow-up in both groups.

One month after the surgery, ECD was more affected centrally as well as paracentrally in the EXS group than the non-EXS group but not statistically significantly. In the operated eyes, the total ECD was significantly lower in EXS and non-EXS patients compared to preoperative with not a significant difference between the two groups, which is in accordance with Wirbelauer et al. (Wirbelauer 1998). Compared to our results, Wirbelauer (Wirbelauer 1998) found a similar extent of postoperative decrease of ECD at the end of the follow-up. Also, in a study, by Østern & Drolsum with a long follow-up time (6–7 years),

with relatively large number of cataract patients at the end of the follow-up (45), they found no pre- and postoperative differences in ECD, between EXS and non-EXS group, in the end of follow-up (Østern & Drolsum 2012).

Walkow and colleagues conducted a study, on normotensive non-EXS patients, where they evaluated the possible effect of the location of the corneoscleral tunnel incision on total and localized endothelial cell loss after phacoemulsification. They found no significant differences in the central or in the area localized in the quadrant of the positions of the corneal surgical site (Walkow 2000). This finding consequentially supports our results after a one-month follow-up that ECD during cataract phacoemulsification is homogenously affected, despite of differences in the first postoperative day.

In our study, in patients scheduled for cataract surgery, as in a number of previous investigations (Scorolli 1998; Shingleton 2003; Pohjalainen 2001) patients with EXS were significantly older than the controls. To evaluate the influence of aging and EXS to ECD, we performed regression analysis with age and EXS as covariates. After one month of regression analysis, we found significant negative association between the age of patients and the postoperative central as well as overall ECD ($r2 = 0.47$, $p = 0.004$; and $r2 = 0.45$, $p = 0.004$, respectively). We found that in both groups, in patients with or without EXS, age was the most significant factor associated with higher cell loss during cataract surgery independently from EXS or other variables. In elderly people, the overlapping synergy of aging and EXS can lead to pronounced metabolic interferences of corneal endothelium and stroma and further studies are needed to clarify this issue.

Puska found that eyes with EXS had higher values for CCT than the fellow non-EXS eyes in normotensive patients with unilateral EXS (Puska 2000). On the contrary, Inoue in a study with EXS patients, with or without glaucoma, found CCT in the EXS eyes to be significantly thinner than that of the non EXS control patients, regardless of the presence of glaucoma (Inoue 2003). Ozcura et al in a study in EXS patients, with or without glaucoma, who were compared to age-matched non-EXS patients, found that the mean CCT was significantly thinner in all EXS and nonglaucomatous EXS eyes compared to controls. Ozcura also found that the mean CCT reading did not differ between EXS and non-EXS fellow eyes (Ozcura 2011). Stefaniotou et al. in turn found significantly thicker corneas in the EXS group than in the controls and, similarly to last mentioned study, there was no difference in patients with unilateral EXS between the eyes with EXS and normal fellow eyes (Stefaniotou 1992). In our study, the mean preoperative CCT values did not differ significantly between the EXS and non-EXS group, which is in accordance with Cankaya et al. and Østern & Drolsum study (Cankaya 2012; Østern & Drolsum 2012). No significant differences between groups in CCT were found during the follow-up to our study.

In the first postoperative day, a significant increase of the CCT was recorded in EXS and non-EXS eyes due to corneal oedema but there was no significant difference between values of CCT at baseline and after one month. Similar findings had Ventura and colleagues in their non-EXS study group where all patients had significant corneal swelling on the first postoperative day which

was restored to preoperative values by 3 and 12 months, even in patients in whom significant endothelial cell loss occurred (Ventura 2001). Similar to many other studies (Inoue 2003; Ventura 2001), we did not find a correlation in regression analysis between endothelial cell loss and CCT in any follow-up time point. However, Lundberg in the study on nonEXS patients, found a strong correlation between corneal swelling in the first postoperative day and ECD loss after phacoemulsification cataract surgery (Lundberg 2005). There is no consensus in literature regarding the potential influence of EXS on CCT. Moreover, the results of different studies are contradictory. We can conclude, based on the results of our study that the presence of EXS, in cataract phacoemulsification, does not significantly affect CCT.

During cataract phacoemulsification the relationship between endothelial cell loss and morphometric parameters of the eye as well as parameters of surgical procedure has been evaluated in several studies. Different preoperative factors can have unequal power of significance in patients with and without EXS in interaction with intra- and postoperative factors. Walkow and colleagues found the age to be an important factor to cell loss only with correlation with lens thickness and longer operation time (Walkow 2000). They also found a significant correlation between endothelial cell loss and axial length, but not between endothelial cell loss and anterior chamber depth. Contrarily, Küchle et al. found a significant relationship in cataract surgery between ACD and endothelial cell loss in patients with EXS but not between AL and ECD (Küchle 2000).

In our study, no correlation between AL, ACD, keratometry, lens thickness and pre- and postoperative ECD was found not in EXS or in non-EXS group. Although a shallow anterior chamber and short axial length could dispose a reduction of endothelial cells in cataract surgery, we believe that surgeon technique and the *phaco* settings used are more important. We found, in regression analysis, in our study that the age of the patient was the most significant factor associated with higher cell loss during cataract surgery independently from EXS or other preoperative variables.

Wirbelauer in his study did not find differences in *phaco* power between EXS and nonEXS-patients, and *phaco* power did not have an influence to ECD in his study (Wirbelauer 1998). Contrary to results of mentioned study, we found in our study, among intraoperative parameters, that the *phaco* power was significant variable for ECD loss and, similarly, the presence of EXS did not affect ECD in regression analysis.

Walkow and colleagues in their study found *phaco* time to be the most significant intraoperative factor in endothelial cell loss (Walkow 2000). In our study, there was a significant difference between the two groups in *phaco* time, which could be explained by more cautious surgical technique in EXS eyes due to insufficient mydriasis and zonular weakness. In our study, we also measured volume of balanced salt solution used during the operation and found that it was used significantly more in EXS-cases, which can also partly be explained with longer *phaco* time. The overall operation time was also longer in our study in EXS-cases but not significantly. Wirbelauer, contrarily, did not find differences

in *phaco* time in EXS and non-EXS-patients, and this variable did not have an influence to ECD in their study (Wirbelauer 1998). Similar to the last mentioned study, we did not find a direct relationship between *phaco* time and ECD, but time became significant in interaction with *phaco* power. Moreover, in regression analysis EXS in interaction with overall *phaco* impact (phaco time multiplied with power) had a significant influence on endothelial cell loss. This indicates that EXS in high *phaco* impact cases (e.g. hard nucleus) significantly increases the risk of endothelial cell loss.

In patients scheduled for cataract surgery, the mean preoperative IOP was significantly higher in the operative eyes with EXS than in those without it. Hietanen found the same trend in her study in patients scheduled in cataract surgery (Hietanen 1992). Patients with EXS also have tendency to have elevated postoperative IOP and IOP spikes (Pohjalainen 2001; Levkovitch-Verbin 2008). Similar to other studies (Pohjalainen 2001; Lagreze 1996), we found a significant rise of IOP in the first postoperative day, which returned to the baseline value over the course one month.

Pohjalainen and colleagues in their study where they compared postoperative IOP of EXS versus non-EXS patients after phacoemulsification found normalised pressure as soon as one week after the cataract surgery with no differences between two groups (Pohjalainen 2001). Levkovitch-Verbin and colleagues found a similar reduction of postoperative IOP elevation in EXS eyes (Levkovitch-Verbin 2008). Results from our study confirm those findings that patients with EXS have a tendency towards a postoperative rise of the IOP but not significantly compared to the control group. The IOP postoperative peak is transient, with not a significant difference between two groups and it does not have a significant influence on endothelial cell damage. However, there is a study from Germany in which Wirbelauer with colleagues did not find, in similar patient groups, a significant IOP rise in the first postoperative day in EXS or in non-EXS patients (Wirbelauer 1998b). They also found a similar decrease of postoperative IOP, compared to preoperative, in both exfoliative and nonexfoliative groups after 1 and 6 month follow-ups (Wirbelauer 1998b). In our study, in one month after surgery, there was postoperative decrease of IOP (compared to pre-operative) in EXS-group but it did not reach statistical significance. There is a retrospective study which comprised of the analysis of 1,122 eyes with EXS and found long-term IOP reduction, 7-years follow-up, after cataract removal on EXS eyes with or without glaucomatous changes (Shingleton 2008). Also Damji et al. found in their prospective study that IOP decreases more in EXS-positives after cataract phacoemulsification compared to control eyes without EXS. This effect was more pronounced in glaucoma patients and persists for at least 2 years (Damji 2006). Regression analysis of our data showed that pre- and postoperative IOP did not have an effect on ECD in both groups, which is in accordance with most previous studies. The results of our study confirmed that perioperative IOP fluctuation in patients with EXS do not affect corneal endothelium compared to non-EXS patients.

7. CONCLUSIONS

1. Our cross-sectional population-based study showed the high prevalence of EXS in Estonia and that it increases with age. The overall prevalence of EXS was 25.5%, which is at the same level as Nordic countries. In a regression analysis, adjusted for age, we found significant, 1.5-fold, impact of EXS on cataract formation.
2. Patients with EXS have tendency to have higher IOP compared to non-EXS patients. Glaucoma was significantly more frequent in the EXS group compared to non-EXS patients.
3. We found EXS in 35.4% of eyes in patients scheduled for cataract surgery. This finding is also similar to that reported earlier in Northern Europe.
4. We found string relationship. The results of our study are in agreement that nuclear cataract is prevalent in patients with EXS. We found strong relationship between EXS and cataract.
5. We found the age to be the most important parameter in endothelial cell loss in patients with and without EXS. Exfoliation syndrome independently did not affect ECD in regression analysis. *Phaco* power was the most affective intraoperative variable to endothelial cell loss. Although endothelial cell loss was more expressed in the EXS group than in the non-EXS group, the statistically significant negative correlation was only determined in interaction with the overall *phaco* impact.

The widespread prevalence of EXS in Estonia requires attention in everyday clinical practice to diagnose and treat patients with ocular hypertension, glaucoma and cataract in time. EXS can be easily overlooked as in 15% of patients EXS was noted only after pupil dilatation. Demands for high quality cataract surgery do not allow us to underestimate the potential complications caused by EXS. An experienced surgeon using a highly adhesive viscoelastic agent should operate on eyes with a hard nucleus and EXS.

SUMMARY IN ESTONIAN

Eksfoliatsiooni sündroomi levimus Eestis ja selle kliiniline tähendus

Sissejuhatus:
Eksfoliatsiooni sündroom (EXS), tuntud ka pseudoeksfoliatsiooni nime all, on east sõltuv krooniline haigusseisund, mida iseloomustab fibrillaarse ekstratsellulaarse materjali produktsioon ja progresseeruv kuhjumine silmamuna eesmises segmendis. Silma vaatlusel on nähtav silma eesmises segmendis miniatuurset kõõma meenutav materjal, mis tüüpiliselt sadeneb läätse eesmisele pinnale, pupillaaräärisele ja eeskambri nurka. Iseloomulik on ka pupillaaräärise depigmentatsioon. Esimesena kirjeldas seda fenomeni ja käsitles teaduslikel alustel Soome oftalmoloog John G. Lindberg. Eksfoliatiivset materjali on leitud ka väljaspool silmamuna: tagumistel tsiliaararterites ja vorteksveenides aga ka vistseraalsete organite sidekoes.

Tõusnud silma siserõhk on sage tüsistus EXS-i esinemisel. EXS-patsientidel on mitmekordne risk haigestuda püsivasse okulaarsesse hüpertensiooni ja glaukoomi.

Avatud eeskambri nurgaga glaukoomi koosesinemisel EXS-ga nimetatakse haigust eksfoliatiivseks glaukoomiks. Seda haigust iseloomustavad sagedasemad ja suuremas ulatuses silma siserõhu kõikumine, ning märksa agressiivsem haiguse kulg. Samuti on iseloomulik tõrksam allumine medikamentoossele ravile kui sagedasem vajadus kirurgilise ravi järele.

On täheldatud katarakti sagedasemat esinemist EXS-patsientidel. Tuleb siiski tunnistada, et selgeid põhjuslikke seoseid ei ole tõestatud kuna tegu on mõlemal juhul east sõltuva seisundiga. Küll on EXS-i puhused muutused nagu halvasti laienev pupill, zinni jätkete ja läätse kapsli nõrkus riskifaktoriteks intraoperatiivsete tüsistuste nagu kapsli rebenemine ja klaaskeha hernia tekkel.

Uuringud on näidanud kvantitatiivseid ja kvalitatiivseid muutusi silma sarvkesta endoteelis. EXS-positiivsetel on leitud sarvkesta endoteeli rakkude tihedus olema madalam võrrelduna EXS-negatiivsetega. On sedastatud muutusi rakkude heksagonaalsuses ning tõusnud on rakkude suuruse variatsiooni koefitsient. Need iseloomulikud muutused on predispositsiooniks endoteelirakkude kahjustusele silmakirurgias, sealhulgas ka katarakti operatsioonil.

Epidemioloogia:
Kuigi EXS esinemine on ülemaailmne võib täheldada selle esinemissageduse küllalt suur erinevust eri piirkondade vahel. Siiani läbiviidud uuringud ei ole teostatud ühetaolise metoodikaga ja seetõttu on keeruline eri uuringutest saadud andmeid omavahel võrrelda.

Avastamisest alates on EXS-i, seoses sealse sagedasema esinemisega, peetud nn Skandinaavia sündroomiks. Esinemissagedus varieerub 0% inuiitidel 1,7%-ni Kongos, 3,4%-st Jaapanis 5,5%-ni Pranstusmaal, 9,0%-st Leedust 11,9%-ni Kreekas kuni 25,3%-ni soomlastel. Erinevad uuringud on leidnud ka küllalt

erinevat EXS-i esinemist eri sugupoolte vahel. Mitmetes uuringutes on viidatud võimalikule geneetilisele predisponeeritusele EXS-i esinemisel.

Eksfoliatiivne materjal:
Praeguste seisukohtade kohaselt on EXS-i puhul tegu elastsete mikrofibrillide moodustumisega mis agregeeruvad tüüpiliseks konfiguratsiooniks üle ensümaatilise ristseotuse. Eksfoliatiivse materjali (EXM) koostises on elastiini, tropoelastiini, laminiini, amüloid P, vitronektiini ning elastsete mikrofibrillide komponente. Eksfoliatiivse materjali (EXM) tekke ja migratsiooni kohta on erinevad teooriad. Migratsiooni-teooria järgi on EXM tekkinud mittepigmenteeritud ripslihase epiteelis ja iirise veresoonte seintes ja ladestub siis läätse kapslile ja mujale silma eesmises segmendis. Paikse tootmise teooria järgi toimub EXM-i teke kohapeal.

Kliiniline pilt:
EXS-i iseloomustab spetsiifilise valkja, kõõma meenutava, helbelise materjali moodustumine üle kogu silma eesmise segmendi. EXM ladestub iirise äärisele, eeskambri nurka ja sarvkest endoteelile. EXM ladestub ka läätse eeskapslile moodustades seal spetsiifilise tsentraalse diski ja perifeerse vöö. Esineb ka pigmendi dispersiooni iirise tagumiselt lestmelt, olles sellega eeskambri nurga pigmenteerumise peamiseks põhjuseks. EXS-ga kaasnevad ka silma eesmise segmendi vaskulaarsed muutused peamiselt iirisel ja limbuse piirkonnas põhjustades hüpoperfusiooni ja hüpoksiat.

Eelnevad uuringud on andnud küllalt vastukäivaid andmeid sarvkesta endoteeli rakkude tiheduse kohta EXS-positiivsetel. On näidatud EXS-positiivsetes silmades sarvkesta endoteeli rakkude tiheduse olema madalam võrrelduna EXS-negatiivsetega. Samas ei ole erinevust rakutiheduses võrrelduna sama patsiendi EXS-negatiivse kaassilmaga. On ka mitmeid uuringuid kus ei ole leitud mingeid erinevusi EXS-positiivsete ja -negatiivsete vahel. Analoogselt endoteeli rakkude tihedusele on andmed vasturääkivad ka sarvkesta paksuse osas. On leitud nii õhemaid kui paksemaid sarvkesti EXS-positiivsetel võrrelduna EXS-negatiivsetega.

EXS on praeguste teadmiste järgi organismi süsteemne protsess millel esineb peamiselt silmapoolne haaratus. Tegemist on histoloogiliselt kahepoolse aga kliiniliselt sageli ühepoolselt väljendunud protsessiga. Diagnoosimise hetkel on EXS leitav kolmandikul patsientidest. Uuringus, milles jälgiti unilateraalse esinemisega patsiente kümne aasta jooksul, leiti protsessi muutus kahepoolseks 38%-l juhtudest. Sealjuures ei tuvastatud mingeid protsessi mõjutavaid riskifaktoreid.

Enamus uuringutes, vaid üksikute eranditega, on tuvastatud olulistelt kõrgem silma siserõhk EXS-positiivsetel võrrelduna EXS-negatiivsetega. Tõusnud silma siserõhk on hästi tuntud glaukoomi riskifaktor. Samas mitte kõikides EXS-positiivsetes silmades ei ole silma siserõhk tõusnud ja ei kujune välja glaukoomi. Siiski tõstab EXS-i esinemine glaukoomi haigestumise riski 4–6 korda.

On tõendeid, mis viitavad EXS-i olulisele rollile katarakti moodustumisel. Silma läätse ainevahetus on otseselt sõltuv silmasisesest vesivedelikust ja selle metabolismist. Tõusnud või kõikuval silma siserõhul võib olla siin oluline roll katarakti moodustumisele kaasaaitamisele.

Nii histoloogilised kui kliinilised uuringud on näidanud, et sagedamini esinevaks katarakti alatüübiks EXS-positiivsetel on nukleaarne katarakt.

EXS ja katarakti kirurgia:
EXS-i puhused sümptomid nagu halvasti laienev pupill, lõdvad zinni jätked, rabedam läätsekapsel tõstavad lõikustüsistuste riski ning võivad mängida olulist rolli lõikuse lähi- ja kaugtulemustele. Samuti on vigastusaltim sarvkesta endoteel.

EXS ja süsteemsed haigused:
EXM sarnast materjali on leitud EXS-positiivsetel vistseraalsete organite sidekoes. EXM-i on leitud südamest, kopsudest, maksast, sapipõiest ja neerudest aga ka peaaju veresoonte seintest. EXS-positiivsetel on leitud kõrgem transitoorsete isheemiliste atakkide, arteriaalse hüpertensiooni ja müokardi infarkti esinemissagedus. Samas on uuringuid kus selliseid seoseid leitud ei ole. EXS süsteemne tähendus vajab täiendavaid süstemaatilisi uuringuid.

Käesoleva teadustöö eesmärgiks:
- oli teada saada EXS-i esinemissagedus Eesti populatsioonis, hinnata silma siserõhku ja glaukoomi esinemist EXS-ga ja EXS-ta isikutel; hinnata EXS-i esinemist katarakti lõikuseks saabunutel,
- hinnata EXS-i kui potentsiaalset riskifaktorit läätse tuhmumisel,
- katarakti lõikuse, fakoemulsifikatsiooni, pre- intra- ja postoperatiivsete muutujate mõju sarvkesta endoteelile ja sarvkesta paksusele EXS-ga ja EXS-ta patsientidel.

Uurimistöö aluseks olevates uuringud viidi läbi Helsingi Deklaratsiooni printsiipe silmas pidades. Kõik uuringud said kinnituse Tartu Ülikooli Eetikakomiteelt. Kõik osalenud andsid kirjaliku teavitatud nõusoleku uuringus osalemiseks.

Kõik uuritavad vaadati läbi ühe uurija, Kuldar Kaljurand, poolt. Kõik lõikused viis läbi prof. Pait Teesalu fakoemulsifikatsiooni meetodil. Lõikuse käigus paigaldati läätse kapslikotti intraokulaarne kunstlääts.

Eksfoliatsiooni sündroomi esinemissagedus Eestis:
Populatsiooni-põhine, läbilõike uuring viidi läbi juhusliku valimi alusel, (Eesti Rahvastikuregister) Tartu linna elanike hulgas. Uuritavad olid viiskümmend aastat või vanemad ja jaotatud kümne aasta kaupa gruppidesse. Kõik patsiendid olid soome-ugri päritolu. Osales 424 isikut, kellest 65,3% olid naised ja 34,7% olid mehed. Uuringus osalemiseks nõusoleku andnud isikutele teostati oftalmoloogiline läbivaatus Tartu Ülikooli Silmakliinikus. EXS-i esinemine ja, olemasolul, katarakti alatüüp sedastati müdriaasi järgselt.

Eksfoliatsiooni sündroomi esinemine katarakti operatsiooniks saabunuil:
Prospektiivne uuring viidi läbi 305 katarakti lõikuseks saabunud eelselektsioonita patsiendi hulgas. Katarakti fakoemulsifikatsiooni-meetodil läbiviidud lõikus viidi läbi Tartu Ülikooli Silmakliinikus. Lõikuspäeva hommikul läbisid kõik uuritavad põhjaliku oftalmoloogilise läbivaatuse. Silma siserõhk ja pupilli läbimõõt mõõdeti enne ja pärast müdriaasi samades valgustingimustes. EXS-i esinemine ja katarakti alatüüp sedastati müdriaasi järgselt.

Eksfoliatsiooni sündroom kui riskifaktor sarvkesta endoteeli kahjustuseks katarakti kirurgias:
Prospektiivne, kohort-uuring milles osales 37 EXS-positiivset ja kontrollgrupis 37 EXS-negatiivset patsienti viidi läbi Tartu Ülikooli Silmakliinikus katarakti operatsiooniks saabunuil. Eelnev silma trauma või operatiivne ravi, suur lühinägevus, uveiit anamneesis ning sarvkest muud anomaaliad olid aluseks patsiendi uuringusse mittearvamisele. Kõikidel uuritavatel mõõdeti optilise telje pikkus, eeskambri sügavus, läätse paksus ning teostati keratomeetria. Sarvkesta paksus ning endoteeli rakutihedus mõõdeti peegel-mikroskoobi abil. Endoteelist tehti ülesvõte 0,1x0,1 mm alal ning loendati rakkude hulk, hinnati rakkude suurust ning määrati variatsiooni koefitsient. Ülesvõtted tehti viies positsioonis: tsentraalselt, üleval, all, nasaalsel ja temporaalsel 6 mm diameetriga alal. Sel kombel hinnati sarvkesta paksust ja endoteeli rakkude seisundit lõikuse eelselt, vahetult lõikusele järgneval päeval ja ühe kuu möödumisel lõikusest. Lõikuse eelselt sedastati katarakti alatüüp.

Tulemused:
EXS-i levimus Eestis on 25,5% viiskümmend aastat ja vanematel isikutel. Kahepoolne haaratus sedastati 33,3%-l EXS-positiivsetest. EXS-i esinemissagedus tõusis eaga oluliselt. Puudus sugudevaheline erinevus EXS-i esinemisel. EXS-positiivsetel oli oluliselt kõrgem silma siserõhk nii enne kui pärast pupilli laiendust. Glaukoom diagnoositi 16,5%-l uuringus osalejatest ning glaukoom oli oluliselt sagedamini EXS-positiivsetel, vastavalt 35,7% ja 11,3%. Erinevalt EXS-st ei olnud glaukoomi esinemine east sõltuv. Läätse muutused esinesid 41,5%-l patsientidest, olulise erinevusega EXS-positiivsete (57,0%) ja EXS-negatiivsete (39,5%) vahel. Regressiooni analüüsil andis EXS, east sõltumata, 1,5-kordse riski katarakti tekkeks. Populatsiooniuuringus ei olnud erinevust nägemisteravuses eri gruppide vahel.

Katarakti operatsiooniks saabunuil esines EXS 35,4%-l juhtudest. Kahepoolne haaratus esines 47,2%-l patsientidest. Viieteistkümnel protsendil patsientidest oli EXS sedastatav vaid läätse eeskapslil perifeerse vööna ja nähtav vaid maksimaalses pupilli laienduses. Müdriaas oli oluliselt väiksem EXS-positiivsetes silmades. Oodatavalt oli EXS-positiivsetel kõrgem silma siserõhk võrreldes EXS-negatiivsetega, mis säilis ka müdriaasi järgselt. Opereeritavates silmades esines kaashaigusena glaukoom 14,8%-l juhtudest ja neist 54,4%-l oli tegu eksfoliatiivse glaukoomiga. Opereeritavates silmades oli EXS-positiivsetel domineerivaks katarakti alatüübiks nukleaarne katarakt samal ajal kui EXS-nega-

tiivsetel olid eri alatüübid märksa ühtlasemalt jaotunud. 41,3%-l kõikidest küpsetest kataraktidest olid EXS-positiivsed.

Katarakti lõikuseks saabunuil ei olnud olulisi erinevusi lõikuseelses sarvkesta endoteeli rakutiheduses kahe uuringugrupi vahel. Keskmine tsentraalne rakutihedus oli vastavalt 2543 (+417) ja 2594 (+519) EXS-positiivsetel ja -negatiivsetel. Keskmine üldine paratsentraalne rakutihedus oli vastavalt 2479 (+422) ja 2455 (+475) EXS-positiivsetel ja -negatiivsetel. Esimesel postoperatiivsel päeval oli kahe grupi vahel oluline erinevus paratsentraalse endoteliaalse rakutiheduse muutuses, vastavalt 8,2% ja 1,1% EXS-positiivsetel ja -negatiivsetel. Tsentraalses osas olid gruppidevahelised muutused ühtlasemad. Esimesel postoperatiivsel päeval oli sedastatav oluline variatsiooni koefitsiendi tõus mõlemas grupis, mis viitas lõikuse varasele mõjutusele ja sarvkesta endoteeli ajutisele heterogeensusele, ning taandus lõikuseelsele tasemele ühe kuu möödudes. Esimesel lõikusjärgsel päeval oli sarvkesta paksus tõusnud kõigis mõõdetud punktides ja ilma oluliste gruppidevaheliste erinevusteta. Tegu oli samuti vahetu lõikuse mõjuga sarvkestale ning turse taandus lõikuseelsele tasemele ühe kuu möödudes mõlemas grupis ilma oluliste gruppidevaheliste erinevusteta. Ühe kuu möödudes oli tsentraalse ja paratsentraalse endoteeli rakutiheduse langus vastavalt 18,1% ja 12,3% EXS-positiivsetel ja 11,6% ja 6,6% EXS negatiivsetel. Rakutiheduse langus oli väljendunum EXS-positiivsetel kuid mitte statistiliselt oluliselt. Samuti oli kompensatoorselt endoteeli rakkude vähenemisele tõusnud endoteeli rakkude pindala kuid jällegi mitte oluliste erinevustega eri gruppide vahel. Silma siserõhk oli taandunud lõikuseelsele tasemele mõlemas grupis. Regressiooni analüüsil ei omanud ei lõikuse eelsed ega vahetud lõikuse järgsed (24h) silma siserõhu näitajad olulist rolli sarvkesta endoteeli rakkude muutuses ei EXS-positiivsetel ega -negatiivsetel.

Operatsiooni kestus oli sarnane mõlemas grupis. Intraoperatiivsetest parameetritest oli EXS-positiivsetel oluliselt pikem *phaco*-aeg ja suurem balansseeritud soolalahuse kulu. Regressioonianalüüsil ei omanud siiski kumbki näitajatest eraldivõetuna olulist rolli lõikustulemustele. Küll aga omas olulist toimet endoteeli rakkudele *phaco*-jõud ja seda mõlemas grupis ilma olulise erinevuseta eri gruppide vahel. Samuti omas olulist toimet lõikustulemusele summaarne *phaco*: (*phaco*-jõud korrutatud *phaco*-ajaga). EXS eraldiseisvana või koos *phaco*-jõuga ei omanud regressiooni analüüsil olulist toimet sarvkesta endoteeliele, küll aga koos summaarse *phaco*'ga ($r2 = 0,27$, $p = 0,05$).

Patsiendid EXS-positiivsete grupis olid oluliselt vanemad kui patsiendid EXS-negatiivsete grupis ning regressiooni analüüs näitas olulist negatiivset korrelatsiooni kõrgema vanuse ja endoteeli rakkude kahjustuse vahel. Koosmõjus eaga ei omanud EXS olulist rolli endoteeli rakkude muutustes.

Järeldused:

1. Populatsiooniuuring osutas kõrgele (25,5%) EXS esinemissagedusele Eestis ja on east sõltuv patoloogia. EXS-i esinemissagedus on samas suurusjärgus Soome ja teiste Põhjamaade näitajatega. Regressiooni analüüsil on neil 1,5-kordne risk katarakti moodustumiseks.

2. EXS-positiivsetel on tendents omada kõrgemat silma siserõhku võrreldes EXS-negatiivsetega. EXS-positiivsetel esineb oluliselt sagedamini glaukoomi.
3. EXS-i kõrge esinemissagedus katarakti operatsiooniks saabunuil. Kõrged koosesinemise näitajad EXS-i ja katarakti vahel.
4. Nukleaarne katarakt on levinuim alatüüp EXS-i ja kataratki koos esinemisel.
5. Kõrgem iga on olulisim riskifaktor sarvkesta endoteeli rakkude kahjustumisel katarakti lõikuse käigus nii EXS-positiivsetel kui -negatiivsetel. Phacojõud on olulisim intraoperatiivne endoteeli rakke kahjustav faktor. EXS eraldivõetuna ei oma olulist rolli endoteeli rakkude kahjustumisel küll aga koos summaarse phaco'ga.

REFERENCES

1. Aasved H. The frequency of fibrillopathia epitheliocapsularis (so-called senile exfoliation or pseudoexfoliation) in patients with open-angle glaucoma. Acta Ophthalmol (Copenh) 1971; 49(2): 194–210.
2. Abib FC, Barreto Junior J. Behavior of corneal endothelial density ovar a lifetime. J Cataract Refract Surg, 2000; 27: 1574–1778.
3. Alpenza-Dunato Z, Novak-Stroligo M, Kovacević D, Caljkusić-Mance T, Corneal thickness in pseudoexfoliative glaucoma, Coll Antropol 2011; 35(2): 303–304.
4. Allingham RR, Loftsdottir M, Gottfredsdottir MS, Thorgeirsson E, Jonasson F, Sverisson T, Hodge WG, Damji KF, Stefánsson E. Pseudoexfoliation syndrome in Icelandic families. Br J Ophthalmol 2001; 85(6): 702–707.
5. Anastasopoulos E, Topouzis F, Wilson MR, Harris A, Pappas T, Yu F, Koskosas A, Founti P, Coleman AL, Characteristics of pseudoexfoliation in the Thessaloniki Eye Study, J Glaucoma 2011; 20:160–166.
6. Andrikopoulos GK, Mela EK, Georgakopoulos CD, Papadopoulos GE, Damelou AN, Alexopouos DK, Gartaganis SP. Pseudoexfoliation syndrome prevalence in Greek patients with cataract and its association to glaucoma and coronary artery disease. Eye (Lond) 2009; 23(2): 442–447.
7. Arnarsson AM, Epidemiology of exfoliation syndrome in the Reykjavik Eye Study, Acta Ophthalmol. 2009; 87 Thesis 3: 1–17.
8. Arnarsson AM, Damji KF, Sverrisson T, Sasaki H & Jonasson F. Pseudo-exfoliation in the Reykjavik Eye Study: prevalence and related ophthalmological variables. Acta Ophthalmol Scand 2007; 85: 822–27.
9. Arnarsson A, Sasaki H, Jonasson F. Twelve-year incidence of exfoliation syndrome in the Reykjavik Eye Study. Acta Ophthlmol 2012; doi: 10.1111/j.1755-3768.2011.02334.x.
10. Arvind H, Raju P, Paul PG, Baskaran M, Ve Ramesh S, George RJ, McCarthy & Vijaya L. Pseudoexfoliation in south India. Br J Ophthalmol 2003; 87: 1321–23.
11. Åström S & Lindén C. Incidence and prevalence of pseudoexfoliation open-angle glaucoma in northern Sweden: I. Baseline report. Acta Ophthalmol Scand 2007; 85: 828–31.
12. Åström S, Stenlund H & Lindén C. Incidence and prevalence of pseudo-exfoliations and open-angle glaucoma in nortern Sweden: II. Results after 21 years of follow-up. Acta Ophthalmol Scand 2007; 85: 832–837.
13. Ball SF. Exfoliation syndrome prevalence in the glaucoma population of South Louisiana. Acta Ophthalmol (Copenh) 1988; 66 (Suppl 184): 93–98.
14. Benatiya Andaloussi I, Touiza E, Daoudi K, Bouayed MA, Bhallil S, Elmasbahi I, Abdellaoui M, Tahri H. Pseudoexfoliation syndrome in Moroccan patients with cataract scheduled for surgery. Bull Soc Belge Ophtalmol 2006; (300): 57–64.
15. Bourne WN, Nelson LR, Hodge DO. Continued endothelial cell loss ten years after lens implantation. Ophthalmology 1994; 101: 1014–1022.
16. Bourne WM, Nelson LR, Hodge DO. Central corneal endothelial cell changes over a ten-year period. Invest Ophthalmol Vis Sci 1997; 38(3): 779–782.
17. Bovelle R, Kaufman SC, Thompson HW, Hamano H. Corneal thickness measurements with the Topcon SP-2000P specular microscope and an ultrastructural pachymeter. Arch Ophthalmol. 1999; 117:868–870.

18. Breyer DK, Helmeking H, Gerke E. Late dislocation of the capsular bag after phacoemulsification with endocapsular IOL in pseudoexfoliation syndrome. Ophthalmologe 1999; 96(4): 248–251.
19. Cambiaggi A. Is the exfoliation syndrome a contraindication for the use of IOL in cataract surgery? Acta Ophthamol Suppl 1988; 184: 123–125.
20. Cankaya AB, Anayol A, Özcelik D, Demirdogen E, Yilmazbas P. Ocular response analyzer to assess corneal biomechanical properties in exfoliation syndrome and exfoliaton glaucoma. Graefes Arch Clin Exp Ophthalmol. 2012; 250: 255–260.
21. Citirik M, Acaroglu G, Batman C, Yildiran L, Zilelioglu O. A possible link between the pseudoexfoliation syndrome and cornary disease. Eye 2007; 21: 11–15.
22. Colin J, Le Gall G, Le Jeune B, Cambrai MD, The prevalence of exfoliation syndrome in different areas of France, Acta Ophthalmol Suppl 1988; 184: 86–89.
23. Damji KF, Bains HS, Stefansson E, Lftsdottir M, Sverrisson T, Thorreirsson E, Jonasson F, Gottfredsdottir M, Allingham RR. Is pseudoexfoliation syndrome inherited? A review of genetic and nongenetic factors and a new observation. Ophthalmic Genet 1998; 19: 175–185.
24. Damji KF, Bains HS, Amjadi K, Dohadwala AA, Valberg JD, Chevrier R, Gould LF, Zackon DH, Addisson DJ. Familial occurrence of pseudoexfoliation in Canada. Can J Ophthalmol 1999; 34(5): 257–65.
25. Damji KF, Konstas AAG, Liebmann JM, Hodge WG, Ziakas NG, Giannikakis S, Mintsioulis G, Merkur A, Pan Y, Ritch R. Intraocular pressure following phacoemulsification in patients with and without exfoliation syndrome: a 2 year prospective study. Br J Ophthalmol 2006; 90: 1014–1018.
26. Djordjevic-Jocic J, Jovanovic P, Bozic M, Tasic A, Rancic Z. Prevalence and early detection of abdominal aortic aneurysm in pseudoexfoliation syndrome and psedoexfoliation glaucoma. Curr Eye Res 2012; 37(7): 617–623.
27. Dosso AA, Bonvin ER, Leuenberger PM Exfoliation syndrome and phacoemulsification. J Cataract Refract Surg 1997; 23: 122–125.
28. Eagle RC, Font RL, Yanoff M, Fine BS. Proliferative endotheliopathy with iris abnormalities. The iridocorneal endothelial syndrome. Arch Ophthalmol 1979; 97: 2104–2111.
29. Ekström C. Insidence of open-angle glaucoma in central Sweden. Acta Ophthalmol 2008; 86: 747–754.
30. Ekström C & Alm A. Pseudoexfoliation as a risk factor for prevalent open-angle glaucoma. Acta Ophtalmol 2008; 86: 741–46.
31. Erdurmuş M, Yağci R, Atiş Ö, Karadağ R, Akbaş A, Hepşen IF. Antioxidant status and oxidative stress in primary open angle glaucoma and pseudoexfoliative glaucoma. Curr Eye Res 2011; 36: 713–718.
32. Faulkner HW. Pseudoexfoliation of the lens among the Navajo Indians. Am J Ophthalmol 1972; 72: 206–207.
33. Forsius H. Exfoliation-material in various ethnic populations. Acta Ophthalmol Scand (Suppl) 1988; 66: 71–85.
34. Forsius H. Prevalence of pseudoexfoliation syndrome of the lens in Finns, Lapps, Icelanders, Eskimos and Russians. Trans Ophthalmol Soc UK, 1979; 99(2): 296–298.
35. Forsius H & Luukka H. Pseudoexfoliation iof the anterior capsule of the lens in Lapps and Eskimos. Can J Ophthalmol 1973; 8:274–277.

36. Forsius H, Forsman E, Fellman J, Eriksson AW. Exfoliation syndrome: Frequency, gender distribution and association with climatically induced alterations on the cornea and conjunctiva. Acta Ophthalmol Scand 2002; 80: 478–484.
37. Forsman E, Cantor RM, Lu A, Eriksson A, Fellman J, Järvelä I, Forsius H. Exfoliation syndrome: prevalence an inheritance in a subsiolate of the Finnish population. Acta Ophthalmol Scand 2007; 85: 500–507.
38. Gagnon MM, Boisjoly HM, Brunette I, Charest M, Amyot M. Corneal endothelial cell density in glaucoma. Cornea 1997; 16(3): 314–318.
39. Gorezis S, Christos G, Stefanitou M, Moustakis K, Skyrlas A, Kitsos G. Comparative results of central corneal thickness measurements in primary open-angle glaucoma, pseudoexfoliation glaucoma and ocular hypertension. Ophthalmic Surg Lasers Imagining 2008; 39(1): 17–21.
40. Grødum K, Heijl A, Bengtsson B. Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. Ophthalmology 2005; 112(3): 386–390.
41. Guzek JP, Holm M, Cotter JB et al. Risk factors for intraoperative complications in 1000 extracapsular cataract cases. Ophthalmology 1997; 94: 461–466.
42. Hansen E, Sellevold OJ. Pseudoexfoliation of the lens capsule. 3. Ocular tension in eyes with pseudoexfoliation. Acta Ophthalmol (Copenh) 1970; 48(3): 446–454.
43. Harju M, Vesti E. Blood flow of the optic nerve head and peripapillary retina in exfoliation syndrome with unilateral glaucoma or ocular hypertension. Graefes Arch Clin Exp Ophthalmol 2001; 239(4): 271–277.
44. Hayashi H, Hayashi K, Nakao F, Hayashi F Anterior capsule contraction and intraocular lens dislocation in eyes with pseudoexfoliation syndrome. Br J Ophthalmol 1998; 82: 1429–1432.
45. Heijl A, Leske MC, Bengtsson B, Hyman L, Hussein M; Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol 2002; 120(10): 1268–1279.
46. Hietanen J, Kivelä T, Vesti E & Tarkkanen A Exfoliation syndrome in patients scheduled for cataract surgery. Acta Ophthalmol Scand 1992; 70: 440–446.
47. Hiller R, Sperduto RD, & Krueger DE. Pseudoexfoliation, intraocular pressure, and senile lens changes in a population-based survey. Arch Ophthalmol 1982; 100: 1080–1082.
48. Hirvelä H, Luukinen H & Laatikainen L. Prevalence and risk factors of lens opacities in the elderly in Finland. A population-based study. Ophthalmology 1995; 102: 108–117.
49. Hirvelä H, Tuulonen A & Laatikainen L. Intraocular pressure and prevalence of glaucoma in elderly people in Finland; a population-based study. Int Ophthalmol 1994; 18: 299–307.
50. Hyman L, Heijl A, Leske MC, Bengtsson B, Yang Z. Early Manifest Glaucoma Group. Natural history of intraocular pressure in the early manifest glaucoma trial: A 6-year follow-up. Arch Ophthalmol 2010; 128(5): 601–607.
51. Inoue K, Okugawa K, Oshika T, Amano Shiro. Morphological study of corneal endothelium and corneal thickness in pseudoexfoliation syndrome. Japanese J Ophthalmology, 2003; 47(3): 235–239.
52. Inoue K, Tokuda Y, Inoue Y, Oshika T, Inoue J. Corneal endothelial cell morphology in patients undergoing cataract surgery. Cornea 2002; 21:360–363.
53. Jeng SM, Karger RA, Hodge DO, Burke JP, Johnson DH, Good MS. The risk of glaucoma in pseudoexfolation syndrome. J Glaucoma 2007; 16(1): 117–121.

54. Jerndal T. The initial stage of the exfoliation syndrome. Acta Ophthalmol Suppl 1985; 172: 65–66.
55. Johnson DH, Brubaker RF. Dynamics of aqueous humor in the syndrome of exfoliation with glaucoma. Am J Ophthalmol 1982; 93(5):629–634.
56. Jonasson F. Solving the enigma of exfoliation glaucoma: a breakthrough in glaucoma research. Acta Ophtalmol Scand 2007; 85: 808–809.
57. Kaimbo W, Kaimbo D, Pseudoexfoliation syndrome in Congolese patients. J Fr Ophthalmol 2012; 35(1): 40–45.
58. Kang JH, Loomis S, Wiggs JL, Stein JD, Pasquale LR. Demografic and geographic features of exfoliation glaucoma in 2 Uniated States-based prospective cohorts. Ophthalmology 2012; 119(1): 27–35.
59. Kanthan GL, Mitchell P, Burlutsky G, Rochtchina E, Wang JJ. Pseudoexfoliation syndrome and the long-term incidence of cataract and cataract surgery: The Blue Mountains Eye Study. Am J Ophthamol 2013; 155: 83–88.
60. Karger RA, Jeng SM, Johnson DH, Hodge DO, Good MS. Estimated incidence of pseudoexfoliation syndrome and pseudoexfoliation glaucoma in Olmsted County, Minnesota. J Glaucoma 2003; 12: 193–97.
61. Klein BE, Klein R, Moss SE. Incident cataract surgery: The Beaver Dam Eye Study. Ophthalmology. 1997; 104: 573–580.
62. Klemetti A. Intraocular pressure in exfoliation syndrome. Acta Ophthalmol Suppl 1988; 184: 54–58.
63. Konstas AGP, Mantziris DA, Stewart WC. Diurnal intraocular pressure in untreated exfoliation and primary open-angle glaucoma. Arch Ophthalmol 1997; 115(2): 182–185.
64. Konstas AG, Jay JL, Marshall GE, Lee WR. Prevalence, diagnostic features and response to trabeculectomy in exfoliation glaucoma. Ophthalmology 1993; 100(5): 619–627.
65. Kozart DM & Yanoff M. Intraocular pressure status in 100 consecutive patients with exfoliation syndrome. Ophthalmology 1982; 89: 214–18.
66. Kozobolis VP, Detorakis ET, Tsilimbaris MK,, Vlachonikolis IG, Tsambarlakis IS, Pallikaris IG. Correlation between age-related macular degeneration and pseudoexfoliation syndrome in the population on Crece(Grete). Arch of Ophtahalmol 1999; 117: 664–669.
67. Kozobolis VP, Detorakis ET, Tsopakis GM. Evaluation of tear secretion and tear film stability in pseudoexfoliation syndrome. Acta Ophthalmol Scand 1999; 77: 406–409.
68. Kozobolis VP, Papatzanaki M, Vlachonikolis IG, Pallikaris IG & Tsambarlakis IG. Epdemiology of pseudoexfoliation in the island of Crete (Greece). Acta Ophthalmol Scand 1997; 75: 726–29.
69. Krause U, Alanko HI, Kärnä J, Miettinen R, Larmi T, Jaanio E, Ollila O-I & Takala J. Prevalence of exfoliation syndrome in Finland. Acta Ophthalmol Scand 1988; 184: 120–122.
70. Krause U, Helve J, Forsius H. Pseudoexfoliation of the lens capsule and liberation of iris pigment. Acta Ophthalmol (Copenh) 1973; 51(1): 39–46.
71. Krishnadas R, Nirmalan PK, Ramakrishnan R; Thulasiraj RD; Katz J, Tielsch JM, Friedman DS; Robin AL. Pseudoexfoliation in Rural Population of Southern India: The Aravind Comprehensive Eye Survey. Am J Ophthalmology 2003; 135: 830–37.

72. Küchle M, Vinores JJ, Mahlow J, Green WR. Blood-aqueous barrier in pseudoexfoliation syndrome: evaluation by immunohistochemical staining of endogenous albumin. Graefes Arch Clin Exp Ophthalmol 1996; 234(1): 11–18.
73. Küchle M, Viestenz A, Martus P, Händel A, Jünemann A, Naumann GO. Anterior chamber depth and complications during cataract surgery in eyes with pseudoexfoliation syndrome. Am J Ophthalmol 2000; 129: 281–285.
74. Laatikainen L. Fluorescein angiographic studies of the peripapillary and perilimbal regions in simple, capsular and low-tension glaucoma. Acta Ophthalmol Suppl 1971; 111: 3–83.
75. Lagreze WD, Bomer TG, Funk J. Effect of surgical technique on the increase in intraoulr pressure after cataract extraction. Ophthalmic Surg Lasers 1996; 27: 169–173.
76. Layden WE, Shaffer RN, Exfoliation syndrome. Am J Ophthalmol 1974; 78(55): 835–841.
77. Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthamol Vis Sci2003; 44(9): 3783–3789.
78. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E, Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Opthamlol. 2003; 121(1): 48–56.
79. Leske MC, Wu SY, Nemesure B, Hennis A, Barbados Eye Studies Group. Risk factors for incident nuclear opacities. Ophthalmology 2002; 109(7): 1303–1308.
80. Levkovitch-Verbin H, Habot-Wilner Z, Burla N, Melamed S, Goldenfeld M, Bar-Sela SM, Sachs D. Intraocular pressure elevation within the first 24 hours after cataract surgery in patients with glaucoma or exfoliation syndrome. Ophthalmology 2008; 115: 104–108.
81. Lindberg JG. Kliniska undersökningar över depigmenteringen av pupillarranden och genomlysbarheten av iris vid fall av åldersstarr samt i normala ögon hos gamla personer. Thesis, Helsingfors. Translation into English 1979. Clinical investigations on depigmentation of the pupillary border and translucency of the iris. Acta Ophthalmol Scand (Suppl) 1917; 190.
82. Lundberg B, Jonsson M, Behndig A. Postoperative corneal swelling correlates strongly to corneal endothelial cell loss after phacoemuslification cataract surgery. Am J Ophthalmol 2005; 139(6): 1035–1041.
83. McCarty CA & Taylor HR. Pseudoexfoliation syndrome in Australian adults. Am J Ophthalmol 2000; 129: 629–33.
84. Milla E, Verges C, Cipres M. Corneal endothelium evaluation after phacoemulsification with continous anterior chamber infusion. Cornea. 2005; 24:278–282.
85. Mitchell P, Wang JJ, Hourihan F. The relationship between glaucoma and pseudoexfoliation. The Blue Mountain Study. Arch Ophthalmol 1999; 117: 1319–1324.
86. Mitchell P, Wang JJ, Smith W. Association of pseudoexfoliation syndrome with icreased vascular risk. Am J Ophthalmol 1997; 124: 685–687.
87. Miyake K, Matsuda M, Inaba M, Corneal endothelial changes in pseudoexfoliation syndrome. Am J Ophthalmol 1989; 108: 49–52.
88. Miyazaki M, Kubota T, Kubo M, Kiyohara, Iida Mituo, Nose Y & Ishibashi T. The prevalence of pseudoexfoliation syndrome in a Japanise population. J Glaucoma 2005; 14: 482–484.

89. Modis L Jr, Langenbucher A, Seitz B. Corneal endothelial cell density and pachymetry measured by contact and noncontact specular microscopy. J Cataract Refract Surg. 2002; 28:1763–1769.
90. Morrison JC, Green WR. Light microscopy of the exfoliation syndrome. Acta Ophthalmol Suppl 1988; 184: 5–27.
91. Musch DC, Shimizu T, Niziol LM, Gillespie BW, Cashwell LF, Lichter PR. Clinical characteristics of newly diagnosed primary, pigmentary, and pseudoexfoliative open-angle glaucoma in the Collaborative Initial Glaucoma Treatment Study. Br J Ophthalmol, 2012; 96(9): 1180–1184.
92. Naumann GO, Schlötzer-Schrehardt U. Keratopathy in pseudoexfoliation syndrome as a cause of corneal endothelial decompensation: a clinicopathologic study. Ophthalmology, 2000; 107(6): 1111–1124.
93. Naumann GO, Schlötzer-Schrehardt U, Küchle M. Pseudoexfoliation syndrome for the comprehensive ophthalmologist. Intraocular and systemic manifestations. Ophthalmology 1998; 105(6): 951–968.
94. Nouri-Mahdavi K, Nosrat N, Sahebghalam R & Jahanmard M. Pseudoexfoliation syndrome in central Iran: a population-based survey. Acta Ophthalmol Scand 1999; 77: 581–84.
95. Obuchowska I, Bryl-Przybylska A, Mariak Z. Pseudoexfoliation syndrome in patients scheduled for cataract surgery. Klin Oczna 2006; 108(10–12): 397–400.
96. Olivius EOP, Nordell SI, Wålinder PE. Fibrinoir reaction after extracapsular cataract extraction and its relatonship to exfoliation syndrome – a prospective study. Eur J Implant Ref Surg 1989; 1: 5–8.
97. Østern AE, Drolsum L. Corneal endothelial cell 6–7 years following cataract surgery in patients with pseudoexfoliation syndrome. Acta Ophthalmol 2012; 90: 408–411.
98. Østern AE, Saethre M, Sandvik G, Råen M, Drolsum L. Posterior capsular opacification in patients with pseudoexfoliaton syndrome: a long-term perspective. Acta Ophthalmol 2012; Mar 9. doi: 10.1111/j.1755-3768.2011.02380.x.
99. Ozcura F, Aydin S, Dayanir V. Central corneal thickness and corneal curvature in pseudoexfoliation syndrome with and without glaucoma. J Glaucoma 2011; 20: 410–413.
100. Ovodenko B, Rostagno A, Neubert TA, Shetty V, Thomas S, Yang A, Liebmann J, Ghiso J, Ritch R. Proteomic analysis of exfoliation deposits. Invest Ophthlalmol Vis Sci 2007; 48(4): 1447–1457.
101. Park KH, Tomita G, Liou SY, Kitazawa Y. Correlation between peripapillary atrophy and optic nerve damage in normal-tension glaucoma. Ophthalmology 1996; 103(11): 1899–1906.
102. Pohjalainen T, Vesti E, Uusitali RJ, Laatikainen L. Intraocular pressure after phacoemulsification and intraocular lens implantation in nonglaucomatous eyes with and without exfoliation. J Cataract Refract Surg 2001; 27: 426–431.
103. Prince AM, Ritch R. Clinical signs of the pseudoexfoliation syndrome. Ophthalmology 1986; 93(6): 803–807.
104. Prince AM, Streeten BW, Ritch R, Dark AJ, Sperling M. Preclinical diagnosis of pseudoexfoliation syndrome. Arch Ophthalmol 1987; 105(8): 1076–1782.
105. Puska PM. Unilateral exfoliation syndrome: conversion to bilateral exfoliation and to glaucoma: a prospective 10-year follow-up study. J Glaucoma 2002; 11(6): 517–524.

106. Puska P. Lens opacity in unilateral exfoliation syndrome with or without glaucoma. Acta Ophthalmol (Copenh) 1994; 72: 290–296.
107. Puska P. The amount of lens exfoliation and chamber-angle pigmentation in exfoliation syndrome with or without glaucoma. Acta Ophthalmlol Scand 1995 73(3): 226–232.
108. Puska P, Vesti E, Tomita G, Ishida K, Raitta C. Optic disc changes in normotensive persons with unilateral exfoliation syndrome: a 3-year follow-up study. Graefes Arch Clin Exp Ophthalmol 1999; 237(6): 457–462.
109. Puska P, Tarkkanen A. Exfoliation syndrome as a risk factor for cataract development. Five-year follow-up lens opacities in exfoliation syndrome. J Cataract Refract Surg 2001; 27: 1992–1998.
110. Puska P, Vasara K, Harju M, Setälä K. Corneal thickness and corneal endotheilium in normotensive subjects with unilateral exfoliation syndrome. Graefe's Arch Clin Exp Ophthalmol 2000; 238: 659–663.
111. Quiroga L, Lansingh VC, Samudio M, Peňa FY, Carter MJ. Characteristics of the corneal endothelium and pseudoexfoliation syndrome in patients with senile cataract. Clin & Exp Ophthalmol 2010; 38: 449–455.
112. Raitta C, Vannas S. Fluoresceinangiographic features of the limbus and perilimbal vessels. Eye Ear Nose Throat Mon 1971; 50(1): 20–23.
113. Raitta C, Vesti E. The effect of sodium hyaluronate on the outcome of trabeclectomy. Ophthalmic Surg 1991; 22(3): 145–149.
114. Repo LP, Suhonen MT, Teräsvirta ME, Koivisto KJ. Color Doppler imagining of the ophthalmic artery blood flow spectra of patients who have had a transient ischemic attack. Correlations with generalized iris transluminance and pseudoexfoliation syndrome. Ophthalmology 1995; 102(8): 1199–1205.
115. Ringvold A. Epidemiology of glaucoma in northern Europe. Eur J Ophthalmol 1996; 6: 26–29.
116. Ringvold A. Corneal endothelial involvement in pseudoexfolation syndrome. Arch Ophthalmol 1994; 112: 297–298.
117. Ringvold A, Blika S, Elsås T, Guldahl J, Brevik T, Hesstvedt P, Hoff K, Høisen H, Kjørsvik S, Rossvold I. The middle-Norway eye-screening study. II. Prevalence of simple and capsular glaucoma. Acta Ophthalmol (Copenh) 1991; 69(3): 273–280.
118. Ringvold A, Davanger M. Iris neovascularisation in eye with pseudoexfoliation syndrome. Br J Ophthalmol 1981; 65(2): 138–141.
119. Ritch R. Perspective on exfoliation syndrome. J Glaucoma 2001; 10(5 Suppl 1): S33–35.
120. Ritch R. The management of exfoliative glaucoma. Progress in Brain Research 2008; 173: 211–224.
121. Ritch R. Exfoliation syndrome and occuldable angles. Trans Am Ophthalmol Soc. 1994; 92:845–944.
122. Ritch R, Prata TS, de Morales CG, Vessani RM, Costa VP, Konstas AG, Liebmann JM, Schlötzer-Schrehardt U. Association of exfoliation syndrome and central retinal vein occlusion: a ultrastructural analysis. Acta Ophthalmol 2010; 88(1): 91–95.
123. Ritch R & Schloetzer-Schrehardt UM. Exfoliation syndrome. Surv Ophthalmol 2001; 45: 265–315.
124. Romero-Aroca P, Masip-Serra R, Martinez-Salcedo I, Salvat-Serra M, Fernández-Ballart J, Bautista-Pérez A. High prevalence of pseudoexfoliation syndrome and

its complications in Tarragona in northeast Spain. Eur J Ophthalmol 2011; 21(5): 580–588.
125. Sampaolesi R, Zarate J, Croxato O, The chamber angle in exfoliation syndrome. Clinical and pathological findings, Acta Ophthalmol Suppl 1988; 184: 48–53.
126. Schlötzer-Schrehardt U. Genetics and genomics of pseudoexfoliation syndrome/ glaucoma. Middle East Afr J Ophthalmol 2011; 18: 30–36.
127. Schlötzer-Schrehardt U. Molecular pathology of pseudoexfoliation syndrome/ glaucoma – new insights from LOXL1 gene associations. Exp Eye Res 2009; 88(4): 776–785.
128. Schlötzer-Schrehardt U. Oxidative stress and pseudoexfoliation glaucoma. Klin Monbl Augenheilkd. 2010; 227: 108–113.
129. Schlötzer-Schrehardt UM, Dörfler S, Naumann GO. Corneal endothelial involvement in pseudoexfoliation syndrome. Arch Ophthalmol 1993; 111(5): 666–674.
130. Schlötzer-Schrehardt U, Koca MR, Naumann GO, Volkholz H. Pseudoexfoliation syndrome. Ocular manifestation of a systemic disorder? Arch Ophthalmol 1992; 110: 1752–1756.
131. Schlötzer-Schrehardt U, Küchle M, Naumann GO. Electron-microscopic identification of pseudoexfoliation material in extrabubular tissue. Arch Ophthamol, 1991; 109(4): 565–570.
132. Schlötzer-Schrehardt U & Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol 2006; 141(5): 921–37.
133. Schlötzer-Schrehardt U, Naumann GO. Trabecular meshwork in pseudoexfoliation syndrome with and without open-angle glaucoma. A morphometric, ultrastructural study. Invest Ophthalmol Vis Sci 1995; 36: 1750–1764.
134. Scorolli L, Scorolli L, Campos EC, Bassein L, Meduri RA. Pseudoexfoliation syndrome: a cohort study on intraoperative complications in cataract surgery. Ophthalmologica, 1998; 212(4): 278–280.
135. Sekeroglu MA, Bozkurt B, Irkec M, Ustunel S, Orhan M, Sarabasi O. Systemic associations and prevalence of exfoliation syndrome in patients scheduled for cataract surgery. Eur J Ophthalmol 2008; 18(4): 551–555.
136. Seland JH, Chylack LT Jr. Cataract in the exfoliation syndrome (fibrillopathia epitheliocapsularis). Trans Ophthalmol Soc U.K. 1982; 102(3): 375–379.
137. Seland JH. The ultrastructural changes in the exfoliation syndrome. Acta Ophthalmol Suppl 1988; 184: 28–34.
138. Shastri L & Vasavada A. Phacoemulsification in pseudoexfoliation syndrome. J Cataract Refract Surg 2001; 27: 1629–1637.
139. Shingleton BJ, Heltzer J, O'Donaghue MW. Outcomes of phacoemusification in patients with and without pseudoexfoliation syndrome. J Cataract Refract Surg. 2003; 29: 1080–1086.
140. Shingleton BJ, Laul A, Nagao K, Wolff B, O'Donoghue M, Eagan E, Flattem N, Desai-Bartoli S. Effect of phacomulsification on intraocular pressure in eyes with pseudoexfoliation: single-surgeon series. J Cataract Refract Surg 2008; 34: 1834–1841.
141. Shingleton BJ, Marvin AC, Heier JS, O'Donoghue MW, Laul A, Wolff B, Rowland A. Pseudoexfoliation: High risk factors for zonule weakness and concurrent vitrectomy during phacoemulsification. Cataract Refract Surg. 2010; 36(8):1261–9

142. Skuta GL, Parrish PK II, Hodapp E et al. Zonular dialysis during extracapsular cataract extraction with implantation of posterior chamber lens. Arch. Ophthalmol 1987; 105: 632–634.
143. Spečkauskas M, Tamošiūnas A, Jašinskas V. Association of ocular pseudoexfoliation syndrome with ischaemic heart disease, arterial hypertension and diabetes mellitus. Acta Ophthalmol. 2012; 90(6): e470–475.
144. Stefaniotou M, Kalogeropoulos C, Razis N, Psilas K. The cornea in exfoliation syndrome. Doc Ophthalmol. 1992; 80: 329–333.
145. Stefaniotou M, Petroutsos G, Psilas K. The frequency of pseudoexfoliation in a region of Greece (Epirus). Acta Ophthalmol Scand 1990; 68: 307–309.
146. Stein JD, Pasquale LR, Talwar N, Kim DS, Reed DM, Nan B, Kang JH, Wiggs JL, Richards JE. Geographic and climatic factors associated with exfoliation syndrome. Arch Ophthalmol 2011; 129: 1053–1060.
147. Streeten BW, Gibson SA, Dark AJ. Pseudoexfoliative material contains an elastic microfibrillar-associated glycoprotein. Trans Am Ophthalmol Soc 1986; 84: 304–320.
148. Streeten BW, Dark AJ, Wallace RN, Li ZY, Hoepner JA. Pseudoexfoliative fibrillopathy in the skin of patients with ocular pseudoexfoliation. Am J Ophthalmol 1990; 110: 490–499.
149. Streeten BW, Li ZY, Wallace RN, Eagle RCJ, Keshgegian AA. Pseudoexfoliative fibrillopathy in visceral organs of a patient with pseudoexfoliative syndrome. Arch Ophthalmol 1992; 110: 1757–1762.
150. Zetterström C, Olivestedt G, Lundvall A. Exfoliation syndrome and extracapsular cataract extraction with implantation of posterior chamber lens. Acta Ophthalmol Scand 1992; 70: 85–90.
151. Tarkkanen A. Pseudoexfoliation of the lens capsule. A clinical study of 418 patients with special reference to glaucoma, cataract and changes of the vitreous. Acta Ophthalmol Suppl 1962; 71: 1–98.
152. Tarkkanen AH. Exfoliation syndrome. Trans Ophthalmol Soc U K 1986; 105: 233–236.
153. Tarkkanen A, Reunanen A, Kivelä T. Frequency of systemic vascular diseases in patients with primary open-angle glaucoma and exfoliation glaucoma. Acta Ophthalmol 2008; 86(6): 598–602.
154. Tarkkanen A, Kivelä T. Cumulative incidence of converting from clinically unilateral to bilateral exfoliation syndrome. J Glaucoma 2004; 13(3): 181–184.
155. Taylor HR. The environment and the lens. Br J Ophthamol. 1980; 64(5): 303–310.
156. Taylor HR. Pseudoexfoliation, an environmental disease? Trans Ophthal Soc U.K. 1979; 99: 302–307.
157. Teshome T, Regassa K. Prevalence of pseudoexfoliation syndrome in Ethiopian patients scheduled for cataract surgery. Acta Ophthalmol Scand 2004; 82(3): 254–258.
158. Teus MA, Castejon MA, Calvo MA, Pérez-Salaíces P, Marcos A. Intraocular pressure as a risk factor for visual field loss in pseudoexfoliative and in primary open-angle glaucoma. Ophthalmology 1998; 105(12): 2225–2230.
159. Thorburn W. The outcome of visual function in capsular glaucoma. Acta Ophthalmol Suppl 1988; 184: 132–137.
160. Thorleifsson G, Magnusson KP, Sulem P, Walters GB, Gudbjartsson DF, Stefansson H, Jonsson T, Jonasdottir A, Jonasdottir A, Stefansdottir G, Masson G, Hardarson GA, Petrusson H, Arnarsson A, Motellebipour M, Wallerman O,

Wadelius C, Gulcher JR, Thorsteindottir U, Kong A, Jonasson F, Stefansson K. Common sequence in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science 2007; 317: 1397–1400.
161. Topouzis F, Harris A, Wilson MR, Koskosas A, Founti P, Yu F, Anastasopoulos E, Pappas T, Coleman AL. Increased likelihood of glaucoma at the same screening intraocular pressure in subjects with pseudoexfoliation: the Thessaloniki Eye Study. Am J Ophthalmol 2009; 148(4): 606–613.
162. Topouzis F, Wilson MR, Harris A, Anastasopoulos E, Yu F, Mavroudis L, Pappas T, Koskosas A, Coleman AL. Prevalence of open-angle glaucoma in Greece: the Thessaloniki Eye Study. Am J Opthlamol 2007; 144(4): 511–519.
163. Topouzis F, Wilson MR, Harris A, Founti P, Yu F, Anastasopoulos E, Pappas T, Koskosas A, Salonikou A, Coleman AL. Risk factors for primary open-angle glaucoma and pseudoexfoliative glaucoma in the Thessaloniki Eye Study. Am J Ophthalmol 2011; 152(2): 219–228.
164. Uusitalo M, Kivelä T, Tarkkanen A. Immunoreactivity of exfoliation material for the cell adhesion-related HNK-1 carbohydrate epitope. Arch Ophthalmol 1993; 111: 1419–1423.
165. Vannas A. Fluorescein angiography of the vessels of the iris in pseudoexfoliation of the lens capsule, capsular glaucoma and some other forms of glaucoma. Acta Ophthalmol Suppl 1969; 105: 1–75.
166. Ventura AC, Wälti R, Böhnke M. Corneal thickness and endothelial density before and after cataract surgery. Br, J Ophthalol. 2001; 85: 18–20.
167. Vesti E. Development of cataract after trabeculectomy. Acta Ophthalmol (Copenh) 1993; 71(6): 777–781.
168. Visontai Z, Horvath T, Kollai M, Hollo G. Decreased cardiovagal regulation in exfoliation syndrome. J Glaucoma 2008; 17: 133–138.
169. Wali UK, Bialasiewicz AA, Rizvi SG, Al-Belushi H. In vivo morphometry of corneal endothelial cells in pseudoexfoliation keratopathy with glaucoma and cataract. Ophthalmic Res, 2009; 41(3): 175–179.
170. Walkow T, Anders N, Klebe S. Endothelial cell loss after phacoemulsification: relation to preoperative and intraoperative parameters. J Cataract Refract Surg. 2000; 26:727–732.
171. Wirbelauer C, Anders N, Pham DT, Wollensack J. Corneal endothelial cell changes in pseudoecxfoliation syndrome after cataract surgery. Arch Ophthalmol 1998; 116(2): 145–149.
172. Wirbelauer C, Anders N, Pham DT, Holchbach A, Wollensak J. [Early postoperative endothelial cell loss after corneoscleral tunnel incision and phacoemulsification in pseudoexfoliation syndrome]. Ophthalmologe 1997; 94: 332–336.
173. Wirbelauer C, Anders N, Pham DT, Wollensak J, Lagua H. Intraocular pressure in nonglaucomatous eyes with pseudoexfoliation syndrome after cataract surgery. Ophthalmic Surg Lasers 1998b; 29(6): 466–471.
174. Yalaz M, Othman I, Nas K, Eroğlu A, Homurlu D, Cikintas Z, Ashouri A, The frequency of pseudoexfoliation syndrome in the eastern Mediterranean area of Turkey. Acta Ophthamol (Copenh), 1992; 70(2): 209–213.
175. Young AL, Tang WW & Lam DSC. The prevalence of pseudoexfoliation syndrome in Chinese people. Br J Ophthalmol 2004; 88: 193–95.
176. Yüksel N, Karabas VL, Arslan A, Demirci A, Cağlar Y. Ocular hemodynamics in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Ophthlamology 2001; 108(6): 1043–1049.

177. Özcura F, Aydin S, Dayanir V. Central corneal thickness and corneal curvature in pseudoexfoliation syndrome with and without glaucoma. Journal of Glaucoma 2011; 20(7): 410–413.

ACKNOWLEDGEMENTS

This work was carried out in the Eye Hospital of Tartu Univesity Clinics. Studies conducted in thesis are based on teamwork with my mentors whom I wish to express my sincere gratitude. I would like to acknowledge:

Docent Päivi Puska, my supervisor, for her true mentorship and kind patience throughout the long process. I highly appreciate her constructive criticism and knowledge about the art of writing scientific paper. I am very greatful for the opportunity to work together with doctor with big heart and endless empathy;

Professor Pait Teesalu for his support and opportunity do perform all this clinical work in Eye Hospital of Tartu University Clinics. I appreciate his way to focus on basic, not forgetting forest behind the trees;

Timo Pessi and Kristiina Rajaleid for statistical analyses and valuable advices;

All patients, who participated in the study for their cooperation;

And last but not least, I would like to cherish my family.

CURRICULUM VITAE

Name: Kuldar Kaljurand
Date of birth: June 10, 1967
Citizenship: Estonia
Address: Eye Clinic of Tartu University Hospitals, J.Kuperjanovi 1
Tartu, 51003 Estonia
Telephone: +3727319750
Fax: +3727319754
E-mail: Kuldar.Kaljurand@kliinikum.ee

Education:

2000 – 2004	PhD student, Faculty of Medicne, University of Tartu
1997 – 2000	Residentship of ophthalmology, Eye Clinic of Tartu University Hospital
1995 – 1997	Internship, Tartu University Hospital
1985 – 1995	Faculty of Medicine, University of Tartu
1974 – 1985	Jüri Secondary School

Language skills: estonian, english, russian, finnish

Professional employment:
2005 – ophthalmologist, Eye Clinic of Tartu University Hospital
2005 – senior assistent, Department of Ophthalmology, University of Tartu

Main interest of research:
Exfoliation syndrome – Prevalence in Estonia and significance in glaucoma and cataract management

ELULOOKIRJELDUS

Nimi: Kuldar Kaljurand
Sünniaeg: 10.06.1967
Kodakondsus: Eesti
Aadress: TÜ Silmakliinik, SA TÜK Silmakliinik, J.Kuperjanovi 1 Tartu, 51003 Eesti
Tel: +3727319750
Faks: +3727319754
E-post: Kuldar.Kaljurand@kliinikum.ee

Hariduskäik:

2000–2004	doktorantuur Tartu Ülikool
1997–2000	residentuur TÜK Silmakliinik
1995–1997	internatuur TÜ Maarjamõisa Haigla
1996 IX–XII	Helsinki Ülikool
1985–1995	Tartu Ülikool, arstiteaduskond ravi eriala
1974–1985	Jüri Keskkool

Keeleoskus: eesti, inglise, vene, soome

Teenistuskäik:
2005 – arst-õppejõud, SA Tartu Ülikooli Kliinikum, Silmakliinik
2005 – vanemassistent, Department of Ophthalmology, University of Tartu

Teaduslik ja arendustegevus:
Glaukoomi sümptomaatikasse kuuluva eksfoliatsiooni sündroomi levimus Eestis ja selle kliiniline tähendus glaukoomi ja katarakti kirurgias.

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