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REVIEW

# Monitoring and management of the patient with pseudoexfoliation syndrome: current perspectives

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**Abstract:** Pseudoexfoliation syndrome (PES) is a complex and age-related systemic disorder characterized by the progressive accumulation and granular deposition of pseudoexfoliative material in various intraocular and extraocular tissues. The diagnosis of PES is so important because it is a major risk factor for complications during cataract surgery and the most frequent cause of secondary glaucoma. In addition to ocular complications, PES is related with numerous systemic abnormalities, for which the list is growing steadily. Therefore, management and monitoring of patients with PES are crucial. The aim of this paper was to review current perspectives on monitoring patients with PES and addressing management of ocular and systemic associations of this clinically important and biologically fascinating disease.

**Keywords:** management, monitoring, pseudoexfoliation syndrome, cataract, pseudoexfoliation glaucoma

## Introduction

Pseudoexfoliation syndrome (PES) is a complex and age-related systemic disorder characterized by the progressive accumulation and granular deposition of abnormal extracellular whitish pseudoexfoliative material (PXM) in various intraocular and extraocular tissues. PXM is composed of amyloid, laminin, collagen, elastic fibers, and basement membrane, and the same material seen in ocular tissue has been shown in other parts of the body, such as the heart, liver, kidneys, lungs, cerebral meninges, vessel walls, and skin, indicating PES is a diffuse disease with ocular and systemic manifestations.[1–3]

In 1917, Lindberg first described exfoliation syndrome after observing the presence of whitish-gray material deposited on the pupillary border in approximately half his patients with chronic glaucoma.[4] Subsequently, in 1926, Vogt named this disease "capsular glaucoma", because he believed that this whitish material could originate from peeling of the anterior lens capsule.[5] Later, in 1954, the term "pseudoexfoliation syndrome" was used by Dvorak-Theobald, who observed the deposition of PXM on the lens capsule, ciliary body, and zonules.[6]

Also known as "Viking disease", PES principally affects northern Europeans and especially Scandinavians, although it has been reported in all population types and races.[7] In all populations, the prevalence of the disease increases markedly with aging.[7] Occurrence is negligible in the middle-aged population (49–54 years), but it increases to 5% in Americans aged 75–85 years and to 6.25% for elderly Australian subjects aged 85 years or older.[7–9]

Even though the exact etiology and pathogenesis of PES are not fully understood, we know that multiple factors play roles in its pathogenesis. Geographic and environmental factors together with genetic predisposition may explain the different

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prevalence of the disease worldwide. The pathological process in intraocular and extraocular tissues is characterized by the chronic and progressive accumulation of PXM, which is either the result of excessive production and/or insufficient breakdown, and is regarded as pathognomonic of PES, based on its unique light-microscopy and ultrastructural criteria.[1,10] This is supported by common gene variants in LOX1 at locus 15q22 coding a pivotal enzyme that serves as both a cross-linking enzyme and a scaffolding element, which ensures spatially defined deposition of elastin.[11] LOX1 also regulates the prompter of elastin.[12] Therefore, it has been proposed that PES is a kind of elastosis that results from the overproduction of elastic microfibrillar components, such as fibrillin 1.[11–13]

In patients with PES, almost all tissue of the anterior segment of the eye is involved, with important implications for patient management. Characteristic alterations in the anterior ocular segment may predispose the eye to a broad spectrum of intraocular complications, such as increased IOP, cataract formation, zonular instability, phacodonesis, blood–aqueous barrier dysfunction, melanin dispersion, posterior synechiae, and keratopathy (Table 1).[10,14] Also, these pathological alterations may explain the markedly increased intraoperative and postoperative complications in patients with PES who undergo intraocular surgery. These ocular complications include posterior capsular rupture and vitreous loss, zonular dehiscence, intraocular hemorrhage, corneal edema and decompensation, severe postoperative inflammation, IOP spikes, synechiae, capsular phimosis, secondary cataract, and intraocular lens (IOL) subluxation (Table 1).[10,14–16]

**Table 1** Possible clinical and surgical complications in patients with pseudoexfoliation syndrome

| Tissue involvement | Clinical complications | Surgical complications |
|---|---|---|
| Lens, ciliary body, zonules | Cataract<br>Zonular instability<br>Phacodonesis<br>Lens subluxation/dislocation<br>Angle-closure glaucoma (due to pupillary/ciliary block) | Posterior capsular rupture<br>Vitreous loss<br>Zonular dialysis<br>IOL decentration<br>Capsular phimosis<br>Secondary cataract |
| Iris | Iris rigidity<br>Poor mydriasis<br>Melanin dispersion<br>Blood–aqueous barrier defect (pseudouveitis)<br>Capillary hemorrhage<br>Posterior synechiae | Miosis<br>Poor surgical access<br>Intra/postoperative hyphema<br>Severe postoperative inflammation<br>Posterior synechiae<br>Pupillary block |
| Trabecular meshwork | Intraocular hypertension<br>Open-angle glaucoma | Postoperative IOP elevation |
| Cornea | Endothelial decompensation<br>Endothelial migration/proliferation | Endothelial decompensation |
| Posterior segment | Retinal vein occlusion | |

**Abbreviations:** IOL, intraocular lens; IOP, intraocular pressure.

The aim of this paper is to review current perspectives on monitoring patients with PES and addressing management of ocular and systemic associations of this clinically important and biologically fascinating disease.

## Clinical findings and early recognition

Accurate diagnosis and early recognition of the disease are critical to reduce the operative complications associated with PES. PES can involve almost all the tissues of the anterior segment of the eye, with important implications in managing these patients. Ultrasound-biomicroscopy investigations on morphological alterations of the anterior segment of eyes with PES have demonstrated abnormalities of the zonules, lens thickening, shallow central anterior-chamber depth, and occludable angles.[17,18] In unilateral PES patients, similar morphological alterations have been observed in affected and fellow eyes.[19] Another clinical study examining patients with unilateral PES via anterior-segment optical coherence tomography revealed that eyes with PES had narrower anterior-chamber angle, decreased angle widening during pupillary movements, and increased iridolenticular contact and iris convexity compared to eyes of healthy subjects.[20] Fellow eyes also shared similar features to some degree.[20]

A definitive diagnosis can be made only by observing PXM on the anterior lens surface with a dilated pupil. On the other hand, the classic biomicroscopy illustration of "target-like" lens depositions represents a late stage of the disease that is preceded by a long, chronic, and preclinical course. As the precapsular layer of the lens becomes thicker, the focal defects begin in the mid-peripheral zone with abrasive movements of the iris, starting often in the upper nasal quadrant (mini-PES), which further extend and become confluent with the classic biomicroscopy illustration of manifest PES.[10] Although the recognition of this delicate layer requires an experienced controller, there are some clinical hints that help alert the ophthalmologist to the early stages of PES. The main anterior-segment structures that can be affected in PES and the clinical findings observed in these structures are outlined in the following sections.

### Lens

The deposition of whitish PXM on the anterior lens surface is the most consistent and hallmark diagnostic feature of PES.

The classic pattern consists of three distinct zones of PXM deposition that may become visible when the pupil is fully dilated: a relatively homogeneous central disk-shaped zone corresponding roughly to the pupil diameter, a granular, often layered, peripheral zone, and a clear intermediate zone (Figure 1).[7] The clear intermediate zone results from the rubbing of the iris over the lens surface during pupillary movement.

## Iris

Iris changes are an early and well-recognized clinical feature in PES. PXM is most prominent at the pupillary border, next to the lens. The deposition of PXM at the pupillary margin and on the iris sphincter with pigment loss in pupillary ruff is frequent and one of the hallmark signs of PES.[21] Loss of iris pigment and deposition throughout the anterior segment are reflected in iris sphincter–region transillumination, loss of the pupillary ruff, pigment dispersion in the anterior chamber after pupillary dilation, pigment accumulation, and increased trabecular meshwork pigmentation.[22] Iris vascular abnormalities are also characteristics in PES that are often narrowed and may become obliterated, and cells of vessel walls can become completely degenerated in advanced stages of PES.[7]

## Cornea

Scattered flakes of PXM can be present on the endothelial surface on the cornea. Pigment accumulation on the cornea may cause diffuse and aspecific pigmentation on the central endothelium, rarely having the pattern of a Krukenberg spindle. More frequently, pigment is deposited on Schwalbe's line, with one or several undulating pigmented lines (Sampaolesi line) observed in the peripheral cornea anterior to Schwalbe's line, and this is an early sign of PES.[7,21]

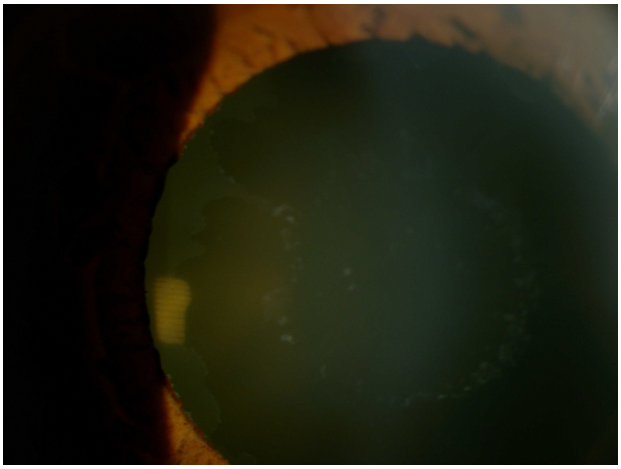

**Figure 1** Slit-lamp examination shows pseudoexfoliation material on the lens surface in distinct zones: a central disk, peripheral zone, and clear intermediate zone.

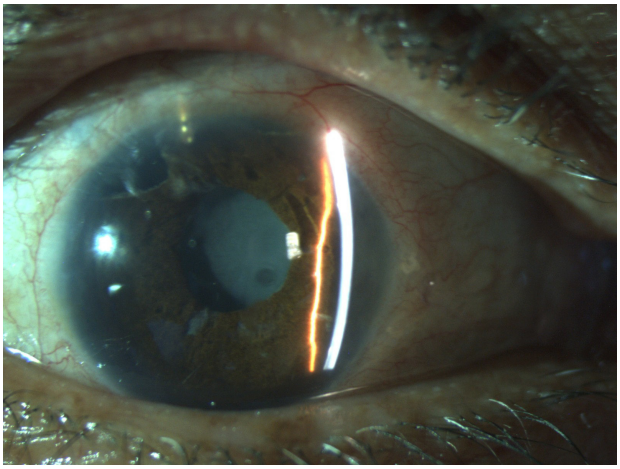

**Figure 2** Lens subluxation is observed in a patient who underwent trabeculectomy surgery due to pseudoexfoliation glaucoma.

## Other tissue

PXM can be detected earliest on the ciliary processes and zonules, which are often frayed and broken. The deposition of PXM on the zonules leads to weakening of the zonules and increased incidence of zonular dialysis and spontaneous subluxation or dislocation of the lens in advanced cases with PES (Figure 2).[7,21]

The trabecular meshwork shows moderate–excessive pigmentation in PES. Increased trabecular pigmentation is a prominent sign of PES, and occurs in almost all cases with clinically evident disease.[7,21] Furthermore, PXM can be found on the vitreous face, on vitreous strands when the face is ruptured, on the posterior lens capsule, and on IOLs after cataract extraction.

# Monitoring and management of associated pathologies

The diagnosis of PES is so important, since it is a major risk factor for complications during cataract surgery and the most frequent cause of secondary glaucoma. In addition to ocular complications, it is known that PXM can be found in various extraocular tissues and is related to numerous systemic abnormalities, for which the list is growing steadily. As such, management and monitoring of patients with PES are crucial, in particular for the conditions outlined in the following section.

## Cataract

PES represents an independent additional hazard for the development of lens opacification and cataract progression, most commonly of a nuclear type.[23,24] Moreover, cataract is the most common cause of patients with PES requiring

surgical intervention. The results of the Reykjavik Eye Study, which included 1,045 subjects who were followed up for 12 years, revealed that eyes with PES at baseline were more likely to have cataract surgery during the 12 years.[25] Another population-based 30-year follow-up study found that PES was a strong predictor of cataract surgery, accounting for a 2.38-fold increased risk in multivariate analysis.[26] Furthermore, it has been shown that lens-densitometry values of affected and even unaffected eyes of patients with clinically unilateral PES are significantly higher than those of healthy eyes.[27] However, the exact pathophysiology of the association between PES and cataractogenesis is not clear yet. On the other hand, it has been emphasized that oxidative stress, ocular ischemia, aqueous hypoxia, increased growth-factor levels, and reduced protection against ultraviolet light by lower levels of ascorbic acid in aqueous humor can contribute to this association.[28–30] Also, changes in the iris vasculature and blood–aqueous barrier in PES may influence the composition of aqueous humor and subsequently may affect lens metabolism, resulting in cataract formation.[24]

PES is not only associated with increased risk of cataractogenesis. It is also well known that patients with PES are much more prone to higher risks of complications during and even after cataract extraction.[7,31] These complications can occur from poor pupillary dilation, zonular fragility leading to intraoperative or postoperative IOL dislocation and vitreous loss, postoperative IOP spikes potentiating glaucomatous damage, capsular phimosis, prolonged and heightened intraocular inflammation, postoperative corneal decompensation, and secondary cataract.[14–16] On the other hand, advances in techniques and instruments for cataract surgery have improved markedly, and operative management of cases with PES and even overall outcomes for patients with PES who undergo cataract surgery could be similar to those for non-PES patients with the appropriate preoperative, intraoperative, and postoperative approaches.[32,33]

## Preoperative management

The first step begins with preoperative evaluation to manage or reduce the increased risks associated with PES. As usual, clinicians should start with the patient's history. From this, clinicians can learn a history of trauma that can suggest an additional increased risk of zonular fragility and/or lens subluxation with vitreous loss in association with PES zonulopathy. The patient history may also be informative about the usage of antiprostate drugs and anticoagulants, which might require additional care regarding surgery. Since complications occur generally with advanced PES cases, cataract surgeries may be preferred in the early stages of the disease to avoid increased late-stage zonular fragility and harder nuclei.

The clinical signs of PES can be identified by slit-lamp examination. Biomicroscopy evaluation after mydriasis has high sensitivity and specificity to recognize the presence of PXM over the lens surface and iris, even at early stages of PES. Furthermore, slit-lamp biomicroscopy should include rigorous assessment of the degree of preoperative pupillary dilation, degree of cataract, phacodonesis, and corneal endotheliopathy.

Also, hints of zonular fragility should be evaluated, in order to assess the risk of complications during cataract surgery. The classic clinical finding of reduced zonular integrity is phacodonesis with eye movements and sometimes a reduction in anterior-chamber depth, owing to a forward shift of the lens. The reported incidence of phacodonesis and/or lens subluxation changes from 8.4% to 10% in patients with PES.[34,35]

It is also important to provide maximum pupillary dilation in patients with PES. Eyes with PES usually show inadequate pupillary dilation, owing mainly to the rigidity and fibrosis caused by iris sphincter–muscle involvement. Sometimes, posterior synechiae can also be observed, and this further reduces response to mydriatic medications.[36] The maximum degree of pupil dilatation should be considered preoperatively to ensure adoption of appropriate surgical measures. Preoperative administration of nonsteroidal anti-inflammatory agents may also help to maintain maximum achievable pupil dilation during cataract surgery.[37,38]

Corneal assessment should be kept in mind in patients with PES before cataract surgery. Specular microscopy studies in eyes with and without PES have shown that eyes with PES have decreased endothelial cell counts with altered endothelial morphology compared to healthy eyes, which may potentiate complications of cataract surgery.[39–41] Therefore, preoperative evaluation of variations in corneal endothelial cell density and morphology is important in patients with PES.

## Intraoperative management

In the era of phacoemulsification, PES still represents a relevant challenge for the surgeon. During cataract surgery in eyes with PES, surgeons have to cope with two main problems: poorly dilated pupils and zonular fragility. A poorly dilated pupil not only makes a small and difficult capsulorhexis and increases the risk of iris prolapse but also increases surgical risk, due to poor visualization of the lens

during the surgery. Therefore, adequate pupil dilation is important before initiating capsulorhexis or phacoemulsification. If adequate pupil dilation cannot be achieved with preoperative dilating eyedrops, intraoperative techniques should be considered. Intraoperative usage of highly viscous cohesive ophthalmic viscosurgical devices (OVDs) or a combination of two different OVDs with different rheological properties (soft-shell technique) can help to overcome this issue and protect the cornea endothelium.[42] Additionally, for cases with posterior synechia, synechiae should be lysed with a blunt spatula and could also be mechanically stretched using two iris manipulators. However, careful and gentle manipulations are required, due to the ischemic fragile iris in PES. If sufficient pupil dilation cannot be achieved with OVDs, surgeons can stretch the pupil with instruments such as iris hooks or pupillary rings to maintain pupil size throughout the surgery.[43] After adequate pupil dilation, surgeons can further reduce the stress on the capsular bag by performing a larger-diameter capsulorhexis. A sufficiently large and well-centered circular continuous capsulorhexis allows the subsequent surgical steps to be made much more easily and minimizes the risk of capsular bag damage. As postoperative capsular bag contraction (phimosis) may produce additional zonular stress and increase the risk of IOL dislocation, creating a large capsulorhexis is very important for minimizing capsular contraction.[44,45]

Zonular fragility is another difficulty during surgery of cases with PES. The degree of zonular fragility can be assessed as soon as the surgeon initiates the capsulorhexis. Difficulties with puncturing the anterior capsule are the first sign of diminished anterior-capsule tension. In such cases, a 25-gauge sharp needle bent at the tip might help to make the initial capsulotomy by applying minimum pressure to the zonular apparatus. Depending on the severity of zonular weakness, surgeons can use capsular tension rings (CTRs) and/or capsular retractors to support the capsular bag during surgery. When zonular instability or phacodonesis is noted at any time during surgery, a CTR can be placed to stabilize the capsular bag and minimize further zonular loss. However, attention should be paid to the placement of a CTR, as early CTR placement can trap the lens cortex and then make subsequent cortical cleaning difficult and stressful on the capsular bag. Additionally, surgeons should ensure that the capsular bag is intact before inserting a CTR, because it can prolapse thorough a capsular rent into the vitreous cavity and require vitrectomy for removal.[44] It has been reported that CTRs reduce intraoperative complications of cataract surgery in eyes with PES, suggesting the usage of CTRs in cases of mild zonulopathy and phacodonesis.[46,47] If more extensive zonular instability is present, CTRs alone might not be enough to prevent intraoperative or postoperative dislocation of the IOL–capsular bag complex. In such cases, capsule retractors can be used during all steps of hydrodissection and phacoemulsification, followed by the implantation of a modified CTR sutured to the sclera to assure anteroposterior stability of the IOL–capsular bag complex.[35,48]

Phacoemulsification for cases with PES is not different from other complicated cataract cases. A zonule-friendly horizontal and vertical chopping technique provides the least zonular stress and has advantages in the setting of a small pupil. It is helpful to work in the central anterior chamber, thus avoiding the capsular periphery. Zonular stress can be minimized by gentle two-instrument rotation of the nucleus.[49] Vitreous prolapse from a zonule defect may be present prior to surgery or may occur at any time during surgery. In such cases, limited anterior vitrectomy and using a cohesive OVD tamponade can help to complete the cataract and cortex removal. Also, care in minimizing anterior-chamber swallowing by liberal use of OVDs and filling the anterior chamber with an OVD before removing the eye can help to reduce the risks further.[49,50] Early recognition of vitreous prolapse, intraocular aqueous misdirection, and positive posterior pressure is also important.[51]

Lens-cortex removal in PES may be challenging and more difficult than nucleus and epinucleus removal, in particular in the presence of a CTR, which can trap the cortex. On the other hand, removing the cortex can be reliably achieved without disturbing the zonules, given close attention to signs of instability symptoms and slight modifications to surgical technique. Liberal and repeated cortical hydration and the use of viscodissection to separate the cortex from the capsule may help soften cortex material and facilitate aspiration.[49] Slow-motion careful tangential stripping of the cortex from anterior and posterior capsules under low-flow conditions in combination with gentle centripetal traction can improve control.[52]

The choice of IOL to be implanted in PES patients is related to assessment of the condition and the future risk of capsular instability. The ideal IOL placement is within a capsular bag. In the presence of zonular weakness, a single-piece or three-piece acrylic IOL may be implanted according to the surgeon's preference following a CTR implant. A one-piece IOL requires less manipulation and carries a lower risk of damage to the capsules and zonules, and thus is the preferred IOL in patients for whom it is acceptable. Considering the risk of capsule contraction and

IOL instability, toric IOLs and multifocal IOLs constitute a possible cause of early or late unsatisfactory visual results. Similarly, any IOL placed within the sulcus should not be used in PES patients, because of the probability of decentralization and posterior dislocation.[35] If a complete capsular diaphragm is missing, an anterior-chamber IOL should not be implanted, considering the risk of glaucoma and corneal decompensation secondary to endothelial cell abnormalities in cases with PES.[35,49]

## Postoperative management

Despite excellent cataract surgery, some postoperative difficulties can occur in patients with PES because of abnormalities in ocular structures. Therefore, careful postoperative monitoring is important in these patients. In addition, difficulties encountered during surgery, increased operating time, and additional manipulations can increase the risk of postoperative complications.

Increased postoperative inflammation, which is attributed to the breakdown of the blood–aqueous barrier that accompanies ischemic iris changes, is expected in PES. In the preoperative period, patients with PES exhibit an aqueous protein concentration at baseline levels several times higher than those measured in PES-free cataracts. In the preoperative period, baseline aqueous protein concentrations of patients with PES are several times higher than those without PES.[53,54] Also, due to the prolonged and complicated surgery, iris manipulations, and possible vitreous loss, severe postoperative fibrinous uveitis is more common in these patients.[55] It is also expected that intensive and prolonged inflammation with breakdown of the blood–aqueous barrier may complicate the postoperative course of cases with PES and increase the risk of posterior synechia, capsular contraction, and cystoid macular edema.[35] Fortunately, it has been shown that postoperative usage of topical nonsteroidal anti-inflammatory drugs reduces the amount of aqueous protein release and the percentage of patients showing increased macular thickness.[56]

Another more common postoperative complication in PES is anterior-capsule contraction and phimosis, which occur especially in the presence of a smaller capsulorhexis and can lead to postoperative IOL decentration and dislocation (Figure 3).[45,57] A neodymium:YAG laser can be used for the treatment of phimosis by making radial laser incisions through the circumferential anterior capsule bag, releasing the centripetal traction on the anterior capsule and zonules.[49] In the presence of a dense phimotic anterior capsule–contraction band, radial incisions can be performed surgically. However, laser or surgical capsulotomy should be performed as soon as the capsular gap begins to shrink to prevent worsening of zonular damage.[35,58]

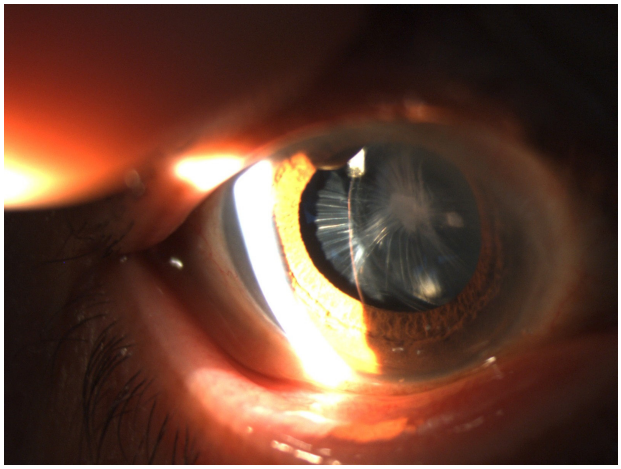

**Figure 3** Postoperative intraocular lens dislocation due to anterior capsular phimosis in a patient with pseudoexfoliation syndrome.

## Elevated IOP and glaucoma

PES is currently considered the most common identifiable reason for open-angle glaucoma (OAG), and the proportion of patients with glaucoma among those with PES varies, as shown in the different population-based studies in Table 2.[59–64] The frequency of PES-associated secondary OAG can be higher than the primary form of the disease.[10,65] Pseudoexfoliation glaucoma (PEG) is a common cause of blindness worldwide and tends to be more progressive and serious compared to primary OAG (POAG).[66] The worse prognosis of PEG could be associated with the clinical characteristics of PEG, ie, typically related to higher IOP levels, greater diurnal fluctuations in IOP, and marker IOP spikes.[66–68] Fortunately, in all populations, the majority of patients with PES do not have glaucoma. It is not exactly understood why some

**Table 2** Proportion of glaucoma among cases with pseudoexfoliation syndrome in different populations

| Location | Proportion of glaucoma among cases with PES | Population-based research |
|---|---|---|
| Greece | 15.2% | Thessaloniki[55] |
| Australia | 14.2% | Blue Mountains[8] |
| Iceland | 12% | Reykjavik[57] |
| India | 7.5% | Aravind Comprehensive[58] |
| India | 5.5% | Andhra Pradesh[59] |
| South Africa | 2.8% | Temba glaucoma[60] |

**Abbreviation:** PES, pseudoexfoliation syndrome.

patients with PES develop glaucoma while the majority will probably never have glaucoma. However, it has been hypothesized that trabecular obstruction and localized damage can be the causative factor for chronic elevations in IOP and the development of PEG.[69] PXM blocks gaps in the trabecular meshwork, promoting the accumulation of pigment and debris, and this causes obstruction of channels throughout which aqueous normally outflows into Schlemm's canal. Pigment liberation from peripupillary iris-pigment epithelium and its accumulation in the anterior-chamber angle is a well-known risk factor for increased IOP and glaucoma development, and may be a possible explanation of this association.[70]

To date, there has been no evidence suggesting that patients with PES with normal-range IOP need special monitoring or management to prevent glaucoma development.[71] In addition, genetic testing with LOXL1 would not be useful in predicting glaucoma development among subjects with PES.[72] On the other hand, with regard to monitoring and IOP evaluation, one needs to keep in mind that IOP presents with higher fluctuation in cases with PES.[66–68,73] As such, a single IOP measurement in PES cases might not represent their IOP values.

On the other hand, individuals with the presence of PXM have a significantly higher prevalence of ocular hypertension and glaucoma compared to non-PES subjects.[44,69,71] Patients with PES and IOP above the normal limit have double to triple the risk of glaucoma development compared to non-PES subjects with IOP above the normal limit.[74,75] Additionally, it has been shown that PES is an important independent risk factor for glaucoma development in cases with ocular hypertension.[75] The Early Manifest Glaucoma Trial (EMGT) study revealed that ocular hypertension in eyes with PES was found to have an HR of 2.12 with regard to glaucoma progression.[76]

If PEG develops in patients with PES, long-term monitoring and management, including diurnal pressure monitoring and examinations at shorter intervals, are usually required. However, monitoring and management of PEG are more difficult than POAG, and PEG has a higher incidence of progression.[77] Eyes with PEG usually respond poorly to medical therapy and need surgical treatment.[77,78] If medical treatment is not sufficient to manage PEG, subsequent interventions are needed. However, gonioscopy should be done to evaluate the iridocorneal angle, particularly in cases where damage is progressive and high IOP or intermittent periods of elevated IOP are observed. The angle could be narrow or might have progressive narrowing, not only as result of a maturing cataract but also due to zonular laxity with secondary anterior-lens movement. In such cases, a mixed mechanism may exist for the development and progression of glaucoma, and the individual can benefit from laser iridotomy or early cataract extraction. The main medical, laser, and surgical treatment options that can be used in the treatment of patients with PEG are outlined in the following sections.

## Medical management

Regardless of the aggressive and often refractory course of PEG, medical treatment options, including prostaglandin analogs, β-blockers, selective $\alpha_2$ agonists and topical and systemic carbonic anhydrase inhibitors, as well as combinations thereof, are usually used as first-line therapy. When reviewing the literature, initial medical management is generally effective to reduce IOP in cases with PEG with most agents used today.[44,79,80] Even if topical drugs yield a good response in the first period of medical treatment, PES is generally recalcitrant to glaucomatous medical treatment and patients with PEG usually need further treatment options.

## Laser management

Laser trabeculoplasty (LTP) is a commonly used procedure in the management of glaucoma, often used as an intermediate step between topical medications and surgery. It has been shown that laser therapy is especially effective in cases with PEG, possibly associated with higher uptake of laser energy from trabecular hyperpigmentation.[81] The two most common forms of LTP in use are argon LTP (ALT) and selective LTP (SLT). It is thought that ALT induces focal scarring in the trabecular meshwork through high-energy thermal beams, opening the conduit through intervening perforations.[82] SLT differs by specific cell targeting and using less energy to generate similar results without visible scarring.[83] A number of studies have shown that LTP (ALT or SLT) is effective in reducing IOP in patients with PEG.[84,85] However, the effect of LTP is not permanent[86,87] and the initial significant effect on IOP gradually declines, although it is hopeful that SLT might be more repeatable and tolerable than ALT for the treatment of glaucoma.[44]

## Surgical management

Eyes with PEG usually need surgical treatment, due to its progressive and serious clinical course.[77,78] Surgical management is usually undertaken when glaucomatous progression occurs or IOP is elevated to a level that progression is deemed likely, despite appropriate medical therapy or laser treatment.

The techniques that can be used in the surgical treatment of PEG include trabeculectomy, angle-based procedures, express implants, and glaucoma-drainage devices.

Trabeculectomy still represents the most frequent incisional procedure for the surgical management of PEG with advanced glaucomatous damage or when appropriate medical or laser management is unsuccessful in controlling IOP levels.[88] Antifibrotic agents, such as mitomycin C or 5-fluorouracil, are commonly used to increase the success rate of trabeculectomy.[88] Trabeculectomy may provide the low IOP level that is often required in PEG.[89] On the other hand, vitreous loss due to zonular damage, a more pronounced inflammatory reaction tendency, hyphema, synechia formation, clinically significant choroidal detachment, and choroidal hemorrhage and cataract formation can complicate trabeculectomy in eyes with PEG.[89,90] Combined trabeculectomy and cataract surgery can also be another option in cases with PEG. It has been shown that uneventful phacoemulsification combined with trabeculectomy resulted in significant long-term reduction in IOP and glaucoma-medication requirements in eyes with PEG.[91]

Angle-based procedures represent a group of techniques that attempt to recover the natural aqueous humor–outflow channels, minimizing complications occurring in filtering surgery, particularly bleb-related problems.[88,90] The most commonly used angle-based procedures are ab interno trabeculectomy and trabecular aspiration. In addition to reducing postoperative complications, these procedures have the advantage of preserving the conjunctiva, so that penetrating surgery or aqueous shunt–device implantation can be performed in future. Although these procedures are efficacious for decreasing IOP in the early course, the effect of trabecular aspiration appears to regress by time, owing to new accumulation of PXM.[92] Viscocanalostomy is considered another angle-based procedure that avoids the risks associated with filtering surgery. Although the results of viscocanalostomy are particularly encouraging in PEG, there is some reluctance about this technique, since the final IOP target achieved is still not sufficient for patients with advanced glaucoma.[93]

The ExPress implant procedure (Alcon Laboratories, Fort Worth, TX, USA) was introduced to improve the trabeculectomy technique. The Express implant and trabeculectomy are very similar, but with the ExPress implant it is possible to avoid iridectomy or sclerostomy, because this implant is placed into the anterior chamber.[94] The learning curve to place the ExPress implant is fast, but this implant technique is 3.5 times as expensive as trabeculectomy.[94,95]

Glaucoma-drainage devices or aqueous shunts are artificial filtering devices that lower IOP by draining aqueous humor to the external subconjunctival space. Glaucoma-drainage devices are indispensable tools for the management of glaucoma, especially in eyes with previously failed trabeculectomy and complicated glaucoma, such as uveitic glaucoma, neovascular glaucoma, and pediatric glaucoma.[96,97] Implantation of these devices appears to have similar efficacy to trabeculectomy in lowering IOP, but requires less intensive postoperative follow-up. The predictability of aqueous shunt surgery is still moderate at best, though probably greater than that after trabeculectomy.[96,97]

Minimally invasive glaucoma-surgery methods are generally safer and less invasive than conventional glaucoma surgeries and suitable for mild–moderate OAG cases like POAG, PEG, and pigmentary glaucoma, because of their lower efficacy. They can also easily be combined with cataract surgery.[98–100] Esfandiari et al[100] presented 5-year outcomes of combined phacoemulsification and trabectome surgery in their study on OAG cases and found higher success rates in PXM cases.

## Corneal involvement

A quantitatively reduced and morphologically altered corneal endothelium in eyes with PES might lead to a distinct type of keratopathy that diffusely involves the entire cornea.[101] However, not all eyes with PES demonstrate clinically significant PES-associated keratopathy. Possible explanations might be interindividual differences regarding the involvement of various tissues of the anterior segment in the PES process. PES can affect all corneal layers and properties. Clinical studies on eyes with PES have revealed decreased corneal sensitivity, thinning of central corneal thickness, and impaired tear-film stability.[102–104] Patients with PES were found to have decreased corneal stromal cell counts, basal corneal epithelial cell counts, and subbasal neural integrity, which have been correlated with the decreased corneal sensitivity seen in patients with PES.[105–107] Deposition of PXM on the cornea endothelium has also been shown.[1,15] PES-associated endotheliopathy, a slowly progressing disease of the corneal endothelium, is usually bilateral, but is often asymmetrical.[101] PES-associated corneal endotheliopathy has been proposed to be caused by one or a combination of hypoxic changes in the anterior chamber, accumulation of extracellular matrix, fibroblastic changes in the endothelium, and increased concentration of TGFβ.[1,7,10] Corneal endotheliopathy in eyes with PES results from a reduced density of corneal endothelium and morphologic alterations, including

the direct involvement of corneal endothelial cells in PES, which increases the risk of corneal edema and endothelial decompensation, even with only moderate rises in IOP or surgical manipulations.[1] Reduction in IOP often leads to clearing of the cornea.[108] However, in advanced stages of PES-associated kerato/endotheliopathy, the potential of reversing endothelial decompensation can be limited. It can lead to early corneal endothelial cell decompensation, which can then induce severe bullous keratopathy, a vision-threatening disorder. Awareness of the compromised corneal endothelium may help to minimize critical intraoperative trauma with endothelial cell loss and postoperative corneal failure.

## Systemic associations

The detection of PXM in visceral organs, such as lungs, liver, kidneys, and gallbladder, and cerebral meninges has led to the hypothesis that PES might be associated with systemic comorbidities or comortality.[109] While several studies have reported that cardiovascular and cerebrovascular diseases, aortic aneurysms, and dementia are strongly associated with PES,[109–112] others have not supported this association.[59,113] Until now, most studies addressing vascular dysfunction in PES have been limited by several weaknesses: studies were frequently isolated; retrospective investigations conducted with a variety of methods on small patient populations from different geographic areas. Furthermore, systemic diseases associated with PES are not specific to PES. Therefore, their increased frequency in PES might potentially be associated with certain systemic biochemical changes that contribute to their clinical manifestations.[114,115]

The underlying mechanisms between PES and cardiovascular/cerebrovascular diseases are not completely understood, but several possible biological mechanisms have been proposed. The accumulation of PXM in various tissues seen with aging is one of the suggested causal mechanisms.[116] Pericellular accumulation of PXM can disturb the normal structure of the basement membrane and lead to endothelial dysfunction.[105] Other possible mechanisms are overexpression of the bFGF, an imbalance in matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs, and increased serum antiphospholipid-antibody level.[117,118] Additionally, increased serum oxidative stress and elevated serum homocysteine levels may play a role in the development of systemic vascular diseases in cases with PES.[119,120] There is evidence that an excess level of homocysteine can induce neural cell death and degradation of the elastic structures in the arterial wall.[117,121] It has also been shown that the aqueous humor endothelin 1 concentrations of PES patients are significantly higher than that of age-matched controls.[122] This process might, in due course, result in weakened elasticity and contractility of vascular wall muscles and increased vascular resistance. However, the exact mechanisms of action and other potential causative biochemical changes require further investigations to elucidate potential pathways of the effects of PES on vascular disease. Such studies need to be population-based and need to address quantitative relationships among potential biochemical changes and the severity of the corresponding vascular disease or dysfunction. Without this information, it is not possible to give a recommendation for the timing and frequency of cardiovascular/cerebrovascular evaluation of patients with PES.

## Conclusion

PES is an age-related, complex systemic disease and characterized by the progressive accumulation of PXM in all ocular tissue, in addition to other parts of the body such as the heart, liver, kidneys, lungs, cerebral meninges, vessel walls, and skin. Multiple epidemiological, geographic, and environmental factors play roles in its pathogenesis. Also, an association between genetic polymorphisms in the LOX1 gene and the disease is known.

There are many clinical findings related to PES, such as PEG, cataract, zonular instability, phacodonesis, impaired blood–aqueous barrier, melanin dispersion, posterior synechiae, and keratopathy. Cataract surgery is more difficult in cases with PES, with higher risk of intraoperative and postoperative complications. PEG is known to be more progressive than POAG with higher IOP levels and greater diurnal fluctuations. Cases with PEG usually need more aggressive antiglaucoma treatment, and glaucoma surgeries are frequently performed for these patients. Close monitoring of cases is necessary for the most appropriate medical and surgical glaucoma treatment, and the risk of surgical complications should be kept in mind.

## Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article. The authors alone are responsible for the content and writing of the paper.

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