ON COMPLICATIONS TO CATARACT SURGERY

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To my beloved family and in memory of my parents.

ABSTRACT

Cataract surgery, meaning exchange of the opaque lens in the eye with an artificial lens, is nowadays one of the most successful surgical procedures ever known. It is also the most frequent surgery performed in the Western world. In Sweden alone, more than 100,000 cataract operations are performed annually. Severe complications are rare, occurring only in a few percent of the patients, but owing to the large number of surgeries even infrequent complications amount to a substantial number of patients.

The aim of this thesis was to study two different complications – retinal detachment (RD) and late artificial intraocular lens (IOL) dislocation – and to analyze inflammatory mediators in the vitreous of phakic (no previous cataract surgery) and pseudophakic (previous cataract surgery with IOL) eyes.

Methods: Paper I is a multicenter case-control study evaluating the incidence and outcome of RD in eyes experiencing a perioperative complication with rupture of the lens capsule. Paper II and III are studies on patients with late IOL dislocation with a retrospective and a prospective observational design respectively. In paper IV the levels of inflammatory immune mediators were measured in vitreous from phakic and pseudophakic patients.

Results: The risk of developing RD after cataract surgery with a capsular rupture increased more than ten fold during the three-year follow-up period. Multivariate analyzes showed an odds ratio (OR) of 14.8 for RD. Additional risk factors were male sex (OR = 8.5) and lens remnants in the vitreous (OR = 14.4). The majority (62%) of eyes experiencing RD had a poor visual outcome of 0.1 or less. In patients with late IOL dislocation the median time to repositioning surgery was 6.5 years. This interval was significantly shorter in older patients and in eyes with perioperative complications (3.2 years). Pseudoexfoliations (PXF) were present in 60% of the patients and 36% had glaucoma. The annual incidence of late IOL dislocation in the pseudophakic population was calculated to 0.05%. Repositioning of the dislocated IOL with scleral sutures and a high frequency of pars plana vitrectomy procedures resulted in few complications and 59% of the patients obtained a visual acuity of ≥0.5. In patients with IOL dislocation and glaucoma, improved intraocular pressure (IOP) control was observed. Vitreous samples revealed significantly higher and sustained levels of immune mediators in pseudophakic eyes compared to phakic eyes.

Conclusions: RD following capsule rupture results in profound visual loss in the majority of patients. Late IOL dislocation requiring reconstructive surgery occurs annually in 1/2000 pseudophakic patients. Risk factors are initially complicated cataract surgery, PXF and old age. The prognosis after repositioning surgery is good and IOP control in glaucoma patients is improved. Cataract surgery and pseudophakia induce elevated and sustained levels of inflammatory immune mediators in the vitreous.

Keywords*:* cataract surgery, pseudophakia, capsular rupture, retinal detachment, IOL dislocation, glaucoma, vitreous, immune mediators, immunoassay, cytokines.

LIST OP PAPERS

This thesis is based on the following original articles, referred to in the text by their Roman numerals.

I. Gunnar Jakobsson, Per Montan, Madeleine Zetterberg, Ulf Stenevi, Anders Behndig, Mats Lundström. **Capsule complication during cataract surgery: Retinal detachment after cataract surgery with capsule complication: Swedish Capsule Rupture Study Group report 4.**
Journal of Cataract and Refractive Surgery 2009 Oct; 35(10): 1699-705.

II. Gunnar Jakobsson, Madeleine Zetterberg, Mats Lundström, Ulf Stenevi, Richard Grenmark, Karin Sundelin. **Late dislocation of in-the-bag and out-of-the-bag intraocular lenses: Ocular and surgical characteristics and time to lens repositioning.**
Journal of Cataract and Refractive Surgery 2010 Oct; 36(10): 1637-44.

III. Gunnar Jakobsson, Madeleine Zetterberg, Karin Sundelin, Ulf Stenevi. **Surgical repositioning of intraocular lenses after late dislocation: Complications, effect on intraocular pressure, and visual outcomes.**
Journal of Cataract and Refractive Surgery 2013 Dec; 39(12): 1879-85.

IV. Gunnar Jakobsson, Karin Sundelin, Henrik Zetterberg, Madeleine Zetterberg. **Increased levels of inflammatory immune mediators in vitreous from pseudophakic eyes.**
Submitted manuscript 2015.

CONTENTS

ABBREVIATIONS

AL	axial length
CDVA	corrected distance visual acuity
CI	confidence interval
CME	cystoid macular edema
CRVO	central retinal vein occlusion
CTR	capsular tension ring
DRP	diabetic retinopathy
ERM	epiretinal membrane
IL	interleukin
IOL	intraocular lens (artificial)
IOP	intraocular pressure
Log-MAR	logarithm of the minimum angle of resolution
MCP	monocyte chemotactic protein
MH	macular hole
NCR	national cataract register
Nd:YAG	neodymium-yttrium-aluminium-garnet
NSAID	non-steroid anti-inflammatory drug
OAG	open angle glaucoma
OCT	optical coherence tomography
OR	odds ratio
OVD	ophthalmic viscosurgical device
PC-IOL	posterior chamber intraocular lens
PCME	pseudophakic macular edema
PCO	posterior capsule opacification
PPV	pars plana vitrectomy
PVD	posterior vitreous detachment
PXF	pseudoexfoliations
RD	retinal detachment
SD	standard deviation
TASS	toxic anterior segment syndrome
VA	visual acuity
VEGF	vascular endothelial growth factor
VF	vitreous floaters
VMT	vitreo-macular traction

INTRODUCTION

Modern cataract surgery is one of the most successful surgical procedures ever known. Serious complications, either during surgery or in the postoperative period, are exceptional. The patient satisfaction rate is high [1]. The number of cataract operations performed annually worldwide can be counted in millions of people [2]. Progress made in cataract surgical technique has resulted in not only cataract patients being offered surgery, but also people with refractive errors like myopia or presbyopia. Global inequity is evident also in this field of medicine, with untreated bilateral cataracts still being the leading cause of blindness in many developing countries [3].

The Swedish National Cataract Register (NCR) has recorded a two-fold increase in the rate of cataract surgeries the last twenty years [4]. In Sweden more than 100,000 cataract operations were performed in 2014, making it the most common surgical procedure performed related to all diagnosis. In addition to this there were at least 10,000 cataract operations where the main indication was refractive error and not lens opacities [5].

Although cataract surgery is accomplished with a low complication rate, at just a few percent, considering the vast amount of people operated, a considerable number of patients will be affected by adverse events from their cataract operation, either during the surgical procedure or in the close postoperative period or even several years after surgery. Therefore these complications have a considerable public health impact. Often the conditions are treatable through additional surgical interventions or supplementary pharmaceutical attendance, but the final visual outcome is far from always satisfactory to the patient and in rare cases the complications will lead to severe visual loss and even blindness.

Background

The lens is positioned in the anterior segment of the eye along the optic axis (Figure 1). It refracts the light – together with the anterior surface of the cornea – and thereby provides a sharp image to the center of the retina. The lens is centered behind the pupil and iris by a suspending mechanism of collagen tissue – the zonular fibers – connecting the lens equator to the ciliary body. The lens capsule – a thin, transparent, elastic membrane – constitutes the outermost layer of the lens volume, containing the lens epithelium and the lens fibers. The lens fibers inside the lens are transparent to light due to precise geometric cellular

arrangement and the lack of cell nuclei and organelles, which are degraded during differentiation. Development of cataract in the lens leads to slow reduction of this transparency to light, which impairs the quality of the image projected on the retina. The absolute most common cause of cataract is natural aging processes.

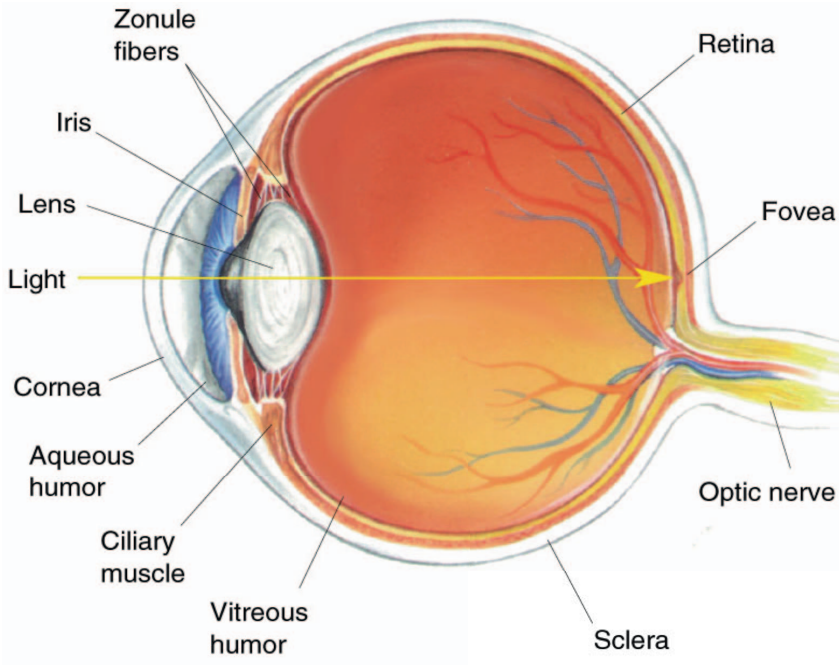

Figure 1. Anatomy of the eye.

The vitreous is a transparent gel consisting of hyaluronic acid, water and some collagen fibers. It forms more than 80% of the eye volume, and acts as a supporting tissue and also maintains the intraocular volume, especially in the growing eye. Like the lens it is surrounded by a very thin membrane, which also is lightly connected to the inner surface of the retina. The vitreous has no refractive qualities. Over time the biochemical structures in the vitreous is altered and it becomes more liquefied. This vitreous collapse leads to a separation of the surrounding vitreous membrane from the inner retinal surface and during this process there is a risk of retinal ruptures.

The retina is the most important tissue in the eye. It consists of several layers of light sensitive cells (photoreceptors) and a variety of neurosensory cells, all arranged in a complex pattern. When light is exposed on the retinal surface, the energy from the photons is transformed to neurosensory signals, which are processed in the different cell-layers in the retina. The formation of a sharp image in the optical system of the eye is essential for the ability of the retina to transmit a correct and real image to the brain. This sharp image is projected on the macula in the center of the retina, and unimpaired function in this structure – in conjunction with the optical system – is crucial to obtain good visual acuity. Since the retina covers the entire inner surface of the posterior segment of the eye, it also provides information to the brain concerning the visual field.

Cataract surgery performed with modern technique and in topical anesthesia is normally a quick outpatient procedure. The surgery begins with constructing of a main self-sealing tunnel incision in the limbal region and one or two additional side incisions. The anterior chamber is filled with a ophthalmic viscosurgical device (OVD) and a round opening or rhexis is performed in the anterior lens capsule. The lens is hydrodissected in order to separate the lens capsule from the lens contents. The lens nucleus is broken up by ultrasonic vibrations (phacoemulsification) and aspirated together with the lens cortex. Additional OVD is injected and a foldable, artificial intraocular lens (IOL) is implanted in the lens capsule bag. The OVD is evacuated and the wound is controlled to be watertight. The surgery is terminated with an injection of antibiotics in the anterior chamber.

The IOL is designed with two different segments. The central, optic part of the IOL with its refractive properties, and the haptics, which acts as support to the lens and provide the optic part to be in the center of the capsular bag. The IOL is often made of a soft acrylic material, allowing it to be folded and inserted through a small incision, but other transparent non-toxic materials are also used. The refractive power of the IOL must be calculated in advance for each individual eye.

Perioperative complications

During all surgical procedures, uneventful incidents can occur. Some are more or less predictable while others arise without prior warning. A perioperative complication must be handled with the utmost care, requiring both surgical

experience and an ability to improvise altered surgical steps in order to restrict further complications and successfully complete the operation. A major complication has an obvious risk of resulting in impaired visual function, but also minor perioperative complications – initially without any alarming signs – can result in progressive to severe complications later in the postoperative period.

Wound construction failure

An entrance to the anterior chamber is of course necessary in order to have access to the lens. The wound is performed in the limbal region as a short self-sealing tunnel incision about 2.0–2.5 mm wide, sometimes even less. The incision can be made in clear cornea or slightly involve the scleral tissue. If the tunnel is too short, there is a risk of a perioperative leakage, which restricts the capability of having optimal fluid control and maintaining a normal and content depth of the anterior chamber. It also promotes prolapse of the iris and this in turn can cause persisting iris damage, with an increased risk of postoperative glare symptoms.

A leaking wound must be sutured at the end of the operation. This can cause astigmatism and a less favorable refractive outcome than previously calculated. There is also an increased risk of endophthalmitis if a surgical wound is leaking postoperatively.

Even if the wound is adequately performed, there is a small risk of having a stripping of the corneal endothelium emerging from the inner entrance of the wound. If discovered in due time and handled with the use of OVD and application of an air-tamponade at the end of surgery if needed, this condition has a relatively low risk of postoperative complications.

Capsule complications

In modern cataract surgery the integrity of the lens capsule during surgery is crucial, due to the need of the capsule to support the implanted artificial IOL when the lens opacities are removed from the capsular bag. The posterior part of the lens capsule, together with the zonular fibers, is located directly in front of the vitreous body and thereby also acts as an important barrier between the anterior and posterior segment of the eye. Therefore, the preservation of an intact posterior lens capsule is essential in preventing several vision-threatening complications [6, 7].

A crucial moment in the cataract surgery is to perform a capsulorhexis, which is the tearing of a round opening in the anterior capsule. If this circle-

round opening has the right size – ideally 5.0 mm in diameter – the evacuation of lens contents can safely be accomplished and the remaining lens capsule with an intact capsulorhexis provides an excellent support to the IOL. During the tearing procedure there is a risk of making the opening to large thereby engaging the posterior capsule, which makes the further surgical procedure hazardous. There is also a risk of making the diameter of the rhexis opening to small, which aggravates the aspiration of the lens contents with a significant risk of damaging the posterior lens capsule. Furthermore, a small capsulorhexis present a greater risk of postoperative phimosis to the capsular opening with an increased risk of late IOL dislocation.

When damage to the posterior lens capsule occurs during the surgical procedure, the barrier between the anterior chamber and the vitreoretinal compartment is disrupted and a communication to the vitreous is established [6]. This often leads to a vitreous prolapse into the anterior chamber. This is a serious complication. The vitreous may incarcerate into the surgical wounds, affecting the corneal endothelium leading to corneal edema, give rise to vitreoretinal traction leading to retinal tears and retinal detachment and significantly increase the risk of developing bacterial endophthalmitis or cystoid macular edema. Furthermore, a capsule complication will make it difficult or even impossible to implant an IOL in the capsular bag. A vitreous prolapse also requires extended surgery including anterior vitrectomy and adjusted procedures for IOL implantation.

Risk factors to this complication include high age, dense cataract, ocular comorbidity like glaucoma or diabetic retinopathy, and surgical experience [7]. The prevalence of posterior capsule rupture is about 1-2% and the annual incidence according to statistics from NCR, indicates further reduction in the number of capsule complications reported [8].

Retained lens fragments and dropped nucleus

A specific type of perioperative complication that is a direct result of a posterior capsular rupture is when part of the lens material or the entire lens nucleus dislocates into the vitreoretinal cavity – the later is sometimes called "dropped nucleus" [9]. When this occurs an anterior vitrectomy often is necessary. If there are enough supporting capsular remnants, an IOL can be implanted between the iris and anterior lens capsule, i.e. implantation in the ciliary sulcus. Post-operatively there is usually anterior segment inflammation that is combined with elevated intraocular pressure and corneal edema. A pars plana vitrectomy and complete removal of retained lens fragments should be accomplished within

one or two weeks [10-12]. If the eye was left aphakic at the primary surgery, an IOL implantation is also performed.

Suprachoroidal expulsive hemorrhage

Bleeding from the choriodal artery vessels during the cataract operation or in the early postoperative period is one of the most feared complications due to the risk of extrusion of intraocular contents through the wound incision with major risks of devastating postoperative complications. The bleeding develops when the intraocular pressure drops during surgery and venous fluid effusion causes the sclera to separate from the choroid, which can cause the ciliary arteries to stretch and rupture leading to a massive intraocular hemorrhage. The intraocular pressure rapidly increases and the anterior chamber is shallowed. This complication was much more common when a larger incision was used to evacuate the lens [13], but since the development of modern small incision phacoemulsification surgery, the incidence has decreased to less than 0.1% [14]. Furthermore, if suprachoroidal bleeding occurs in case of small incision surgery, the extent of both the hemorrhage and the prolapse of intraocular tissue can be limited, due to the ability of immediate closure of the self-sealing incision. Nevertheless, although rare due to modern small incision surgery, a suprachoroidal hemorrhage still has the potential of causing severe vision-threatening complications [15].

Perioperative intraocular pressure rise

Another type of pronounced and immediate elevation of the intraocular pressure combined with shallowing of the anterior chamber is when irrigating fluid penetrates the zonular fibers and enters the narrow space behind the lens or directly into the vitreous. This condition is sometimes called “acute aqueous misdirection syndrome” [16] or “acute intraoperative rock hard eye syndrome” [17]. It can easily be confused with an expulsive hemorrhage, but no choroidal bleeding is involved. Continuing of surgery can be difficult, but if choroidal hemorrhage is excluded by ophthalmoscopy, the intraocular pressure can be normalized through careful evacuation of fluid from the vitreous cavity, allowing for completion of the operation including IOL implantation.

Postoperative complications

Complications in the postoperative period can be divided into early complications, occurring within 1-2 months postoperatively or late complications, which can occur even after many years from the cataract operation. Some complications, like IOL dislocation or retinal detachment, may occur either in the early or late postoperative period.

Aphakia

If an IOL for various reasons cannot be implanted during the primary cataract operation due to damage in the posterior capsule, there are different options for fixation of an IOL at a second surgery session. As long as there is no lens in the eye, the visual acuity is very low.

An anterior-chamber-IOL can be placed on the iris surface in front of the pupil and fixated by its haptics in the anterior chamber angle. The benefit of this type of IOL is relatively easy implantation and good fixation with no risk of dislocation to the posterior segment. However; there is a substantial risk of developing damage to the corneal endothelial cells and subsequent chronical corneal edema, which leads to severe visual loss. Although corneal transplant surgery is a later option in such cases, the visual prognosis is often impaired.

Iris-fixation-IOL offers less risk of affecting the corneal endothelial cells. The IOL can be fixated either on the anterior or the posterior surface of the iris. The surgery can be more challenging and there is a risk of dislocation of the IOL to the vitreous compartment if the fixation is on the posterior surface of the iris. Sometimes the iris-fixated IOL can compromise future observation of the peripheral retina due to restricted pupil dilation.

Implantation of an IOL in the posterior chamber with haptic fixation in the ciliary sulcus is an option most similar to IOL fixation "in the bag" which is the normal fixation in cataract surgery without complications. Sometimes there are enough capsular remnants allowing an IOL to be placed in front of the anterior capsule but behind the iris. In the absence of sufficient capsular support, the haptics of the IOL must be fixated to the scleral wall using either sutures or intrascleral tunnels. These procedures for secondary IOL-implantation in cases of aphakia are technically more challenging but offer the most correct optical and anatomical position of the IOL comparable to an IOL fixated in the capsular bag, which is the natural position for the lens in the eye. When an IOL is fixated with scleral sutures it can later dislocate due to hydrolysis of the sutures. This typically occurs about ten years after IOL fixation

surgery and requires an additional surgical procedure. Future improvement of suturing material will likely overcome this complication. When using the scleral tunnel technique for IOL fixation, there is an increased risk for IOL dislocation in the early postoperative period, whereas the long-term fixation seems to be safe [18].

Endophthalmitis

Postoperative bacterial intraocular infection is a devastating complication typically occurring within six weeks of surgery. The origin of the infection is often entrance of bacteria into the eye during the surgical procedure, although there is also a possibility for bacteria to penetrate the eye in the postoperative period through insufficiently sealed surgical wounds [19].

Acute endophthalmitis is an ophthalmic emergency. The patient typically presents with severe visual loss, eye pain and a severe inflammation with hypopyon in the anterior chamber and vitreous opacities. Prompt treatment, including sampling of bacteria and intravitreal injection of antibiotics and sometimes also surgical intervention with pars plana vitrectomy, is vital in order to save visual function and integrity of the eye. The prognosis is determined by the status of the eye at presentation, appropriate treatment without delay and the type of bacteria. An infection from coagulase-negative staphylococcus has a fairly good prognosis whereas an infection caused by species of streptococci, Haemophilus, Pseudomonas or various other bacteria, has a considerably worse prognosis with severe visual loss or blindness and in some cases even a necessity to remove the eye.

One important prophylactic move in order to reduce the risk of endophthalmitis, in addition to aseptic preparation and sterile surgical technique, has proven to be the use of intracameral antibiotics injected at the completion of surgery. In Sweden - where this method was first routinely introduced – the incidence of endophthalmitis has been reduced by more than 50% due to the use of intracameral antibiotics [5]. This prophylactic use of low-dose single injection of antibiotics in order to reduce postoperative infection has been introduced in several other countries, but there is still a certain amount of resistance to achieve consensus regarding this regime [20-24].

The incidence of endophthalmitis is less than 0,1%, which is considered very low, compared to other surgical procedures. Endophthalmitis is registered in the NCR and the incidence in Sweden is calculated to be about 0,02% in recent years, probably due to the consistent use of prophylactic intracameral antibiotics [5, 22].

Chronic low-grade endophthalmitis

Chronic low-grade endophthalmitis is a condition characterized by a prolonged postoperative intraocular inflammation, sometimes with late onset and without the more dramatic clinical signs of acute endophthalmitis. Otherwise harmless bacteria, like Propionibacterium acnes, with low pathogenicity and a slow growth rate, can survive on the IOL surface or within the capsular bag and cause prolonged inflammation. Often, the eye is initially treated with an increased amount of topical steroids and also responds to this treatment, but recurrent inflammation will follow. Injection of intraocular antibiotics is often not enough, but instead additional surgical intervention with removal of the capsular tissue, anterior vitrectomy and even removal of the IOL may be necessary in order to eradicate the infection. The prognosis following adequate treatment is often good [25-28].

Toxic anterior segment syndrome (TASS)

TASS often develops within the first 24 hours after surgery and clinically mimic endophthalmitis. The condition is characterized by an intense inflammatory reaction in the anterior segment of the eye with typical diffuse widespread corneal edema and fibrin reaction in the anterior chamber, sometimes with hypopyon. The vitreous is not engaged which is an important difference to acute endophthalmitis. The etiology of TASS is a sterile, toxic inflammatory reaction to some substance introduced during the surgical procedure. Often it is difficult to identify the origin of the substance causing TASS in the individual patient. Various unidentified toxic agents in solutions, medications or residual debris on surgical instrument due to inadequate cleaning can cause a toxic reaction despite correct sterilization. Prompt and intensive treatment with topical steroids is often effective, although some patients may experience prolonged corneal edema. Although the onset of TASS is earlier than endophthalmitis, there are reports of aggressive bacterial endophthalmitis presenting within 12 hours of surgery. Therefore, TASS often initially has to be managed as a suspected endophthalmitis [29-32].

Pseudophakic cystoid macular edema (PCME)

PCME – or Irvine-Gass syndrome – is an extracellular accumulation of fluid in the fovea in the center of the retina. The condition is driven by a postoperative inflammatory reaction and the exact pathophysiological mechanisms for the development of the edema are not known in detail [33]. The risk of PCME is increased if there are predisposing conditions in the eye like diabetes

retinopathy or uveitis or if there are perioperative surgical complications. Typically, PCME develops within a few weeks or months of surgery. PCME is the most common course of unexpected postoperative visual reduction in patients who experienced an otherwise uncomplicated cataract operation with initially excellent visual results. The symptoms of PCME are various degrees of visual acuity reduction and in some cases distorted vision or metamorphosis. The diagnosis was previously often established by using fluorescein angiography but is now simplified since optical coherence tomography (OCT) offers a noninvasive and fast method for correct and early detection of PCME. Clinically significant PCME is supposed to occur in less than 2% of the patients [34]. However, 11-40% are reported to have some degree of, often subclinical, PCME in the early postoperative period. The difference in reported incidence in different studies is probably due to an ambiguous definition of the early stages of PCME and variation in patient characteristics [35-42].

The natural course of PCME is spontaneous resolution in the majority of patients with clinical symptoms [43], and the first-line treatment is topical steroids and non-steroid anti-inflammatory drugs (NSAID). In eyes refractive to topical treatment and progressing to chronic PCME, treatment is a challenge. Periocular or intraocular injection of steroids or anti-vascular endothelial growth factors (anti-VEGF) is reported to reduce PCME and improve visual acuity [44, 45], although there are disappointing studies as well. Intravitreal steroid implants with sustained drug release is a relatively new option, which might serve as an alternative to repeated intraocular injections [46, 47]. Oral treatment with carbonic anhydrase inhibitors has been tried with varying results, but the systemic side-effects restrict this treatment to few patients [48]. Pars plana vitrectomy may be considered, especially in the presence of vitreoretinal traction or an epiretinal macular membrane, and is sometimes tried as a last option if all other medical treatment has failed [34].

The variety of treatment modalities reflects the difficulty in providing efficient treatment to patients with chronic PCME. There are as yet no convincing randomized clinical trials, and those studies with encouraging results are uncontrolled. However, prophylactic treatment with NSAID, with or without additional steroids, is effective in preventing PCME according to several randomized trials [42, 49]. Topical treatment with NSAID can block inflammatory mediators emerging from the surgical procedure to initiate capillary leakage in the macular region in the posterior pole of the eye.

Combined with improvements in both technical equipment and surgical experience resulting in diminishing surgical trauma, prophylactic anti-

inflammatory treatment is likely to further reduce the incidence of PCME. However, in predisposed eyes susceptible to macular edema, such as diabetic retinopathy or uveitis, PCME will continue to be an important postoperative complication.

Prolonged postoperative inflammation

Uneventful cataract surgery in eyes with no ocular comorbidity normally induces only mild and transient postoperative inflammation [50]. In contrast, patients with previous or chronic uveitis, eyes with perioperative complications or otherwise susceptible to inflammation, prolonged and even intense postoperative inflammation is not unusual. However, in some cases there is a persistent intraocular inflammation without any predisposing factors. The prevalence has been estimated to approximately 0.2 %. Although these eyes often recover from prolonged uveitis, the visual outcome can be less favorable owing to the risk of developing CME, vitreous opacities and secondary glaucoma [51].

Persistent corneal edema

During the cataract surgical procedure – like any other intraocular surgery engaging the anterior chamber of the eye – the inner endothelial cell layer of the cornea will be affected. Preservation of the endothelium is crucial in order to maintain water balance and transparency to the cornea. Any mechanical injury to the thin monolayer cell surface, by direct touch from surgical instruments, other ocular tissues or irrigating fluids, can cause loss of endothelial cells, which may progress to corneal edema [52, 53].

There are several other etiological factors that contribute to postoperative corneal edema [54]. Elevated intraocular pressure, hyphema, complicated surgery with capsule rupture [55], intraocular inflammation due to retained lens material, endophthalmitis or toxic reactions (TASS) can all be the primary condition causing secondary corneal edema. Patients having known corneal diseases, like Fuch's endothelial dystrophy or otherwise low endothelial cell density, are particularly vulnerable to develop corneal edema.

When the edema persists, the eye will develop pseudophakic bullous keratopathy. The symptoms are severe visual loss and occasionally a painful eye. Treatment consists of corneal transplantation, either with penetrating keratoplasty or transplantation of the endothelial cell layer. Although the patient often experiences improved visual acuity and reduced ocular discomfort, the result is not strictly comparable to what is achieved in otherwise uncomplicated

cataract surgery. Moreover, there is a considerable recurrence rate following corneal transplantation [56], which in turn may require additional transplants.

Posterior capsule opacification (PCO)

The most common postoperative complication from cataract surgery is opacification of the posterior lens capsule. The cause of PCO is residual lens epithelium cells proliferating and migrating to the posterior capsule resulting in opacification of the capsule. When the opacification engages the optic zone the patient experiences symptoms similar to cataract as before surgery. The prevalence of PCO has decreased due to improved surgical techniques, hydrophobic IOL material[57-59] and IOLs designed with a sharp posterior edge [60-62]. In a recent study the prevalence of PCO was estimated at 12% in a pseudophakic population five years after surgery [58]. However, the prevalence of PCO continues to increase and is estimated to be more than one-third at ten years after cataract surgery [63, 64]. Opacification of the anterior capsule outside the optical zone is common, but often without any clinical significance. However, if the rhexis opening is to narrow, fibrosis of the edges of the rhexis opening will cause a constriction or phimosis, which can lead to visual symptoms or even dislocation of the IOL.

Treatment of PCO is a relatively easy and quick procedure. The posterior opacified capsule is opened with a neodymium yttrium - aluminium - garnet (Nd:YAG) laser capsulotomy technique. An opening the size of the optic zone is made in the posterior capsule behind the IOL. Additional complications after Nd:YAG-laser capsulotomy consist mainly of an assumed increased risk of developing retinal detachment. There are divergent reports in the literature, but the risk increase for retinal detachment is probably very low or insignificant [65-69]. There is also a reported increased risk of developing cystoid macular edema after laser capsulotomy, but data here is also contradictory [70-72].

IOL-dislocation

A dislocation of the IOL implies that the lens is not positioned in its optimum central position within the optic zone. If the dislocation is diagnosed directly after surgery or within the first month, it is classified as an early IOL-dislocation, which almost always is due to a perioperative capsular complication. Late IOL dislocation occurs when the initially properly placed IOL, later – often after several years – dislocates, either inferiorly or laterally behind the iris (figure 2) or posteriorly into the vitreous (figure 3). Late IOL dislocation occurs when

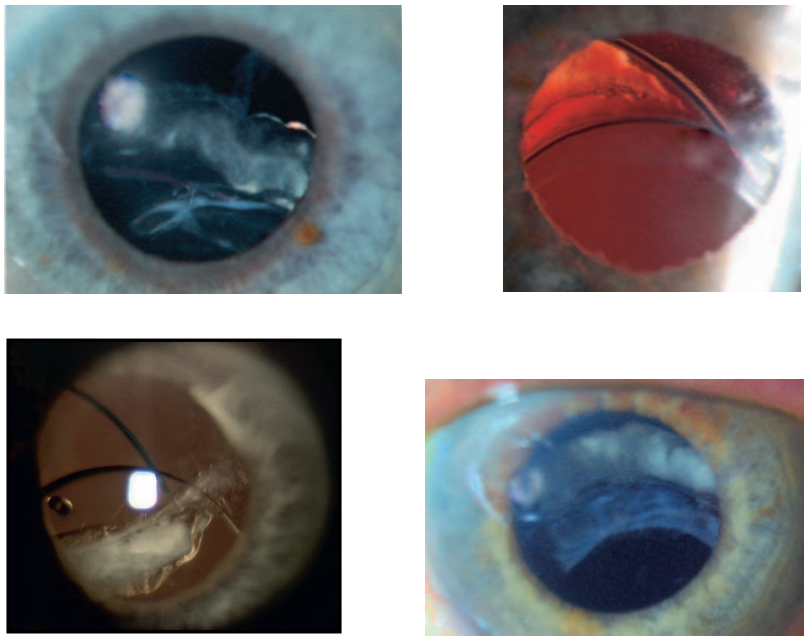

Figure 2. IOL dislocations both "in-the-bag" and "out-of-the-bag". ©Author

the support to the IOL becomes insufficient owing to progressive zonular weakness and shrinkage of the capsular bag, which can be facilitated by a narrow rhexis opening causing capsule phimosis. Often the IOL dislocates together with rest of the capsular bag, which is called "in-the-bag" IOL-dislocation, but in some cases the IOL dislocate separately or "out-of-the-bag". A minor dislocation does not necessarily cause any visual symptoms but as soon as the optic part of the IOL is outside the optic axis of the eye, visual acuity drops dramatically.

Main risk factors to late IOL-dislocation are the presence of pseudo-exfoliations, old age or previously complicated cataract surgery [73-76]. Other risk factors are high myopia, retinitis pigmentosa, uveitis, previous vitrectomy surgery and collagen tissue disorders like Marfan's syndrome [77-79].

Late IOL dislocation typically occurs 5-8 years from the cataract surgery [80]. The condition is relatively rare, with an estimated accumulated prevalence of 0,5-1% after ten years in pseudophakic Scandinavian populations [81, 82]. Owing to an increasing pseudophakic community, patients with late IOL-dislocations are more numerous [74] [83]. If there also is an increased

relative incidence has been questioned [84], but recent studies support this hypothesis [74, 82].

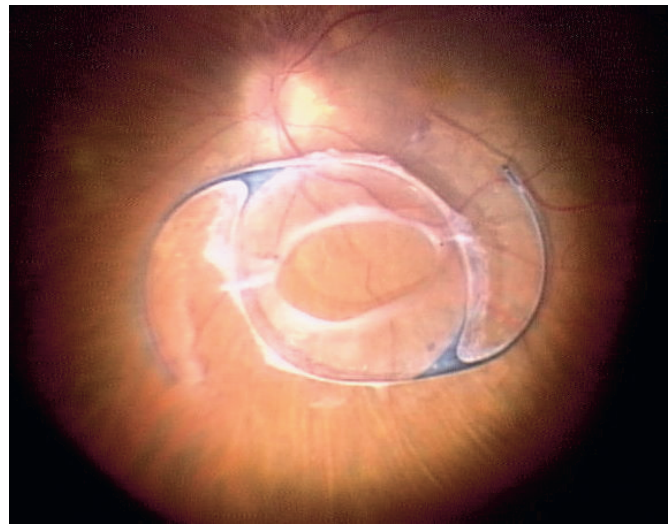

Figure 3. IOL "in-the-bag" dislocation into the vitreous. ©Author

Surgical options to treat a patient with a dislocated IOL consist of either repositioning with scleral fixation or replacement of a new IOL. The approach is mainly depending on how the IOL is dislocated and the type of IOL. A variety of surgical strategies are used and there is as yet no consensus of what exact surgical reconstructive alternatives provide the best results [77, 85-90].

Retinal detachment (RD)

Retinal detachment (RD) is the most common sight threatening complication following cataract surgery. Moreover, RD is an emergency case, requiring the patient to be referred to a vitreoretinal eye clinic without delay (figure 4).

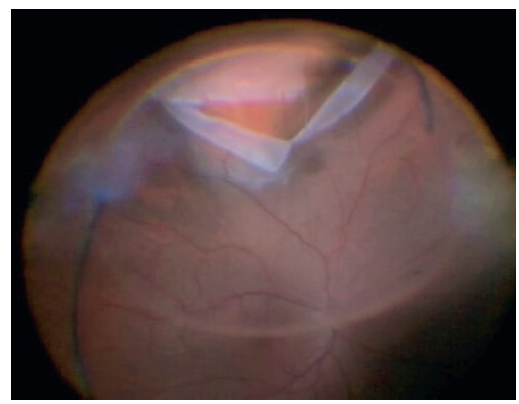

Figure 4. Superior retinal detachment with a large retinal tear. IOL visible in front. ©Lothar Schneider

The overall incidence of RD following cataract surgery is estimated to 0.5-2.0% [91]. The mean time from cataract surgery to RD is about three years [92], but the cumulative rate continues to increase even 10-20 years postoperatively [93]. RD is not a unique complication to cataract surgery, but the increased risk is

fourfold [94], showing a large variety in different subgroups. About one third of all RD cases are pseudophakic [95].

Main risk factors for RD are myopia, male sex, younger age at cataract surgery, absence of posterior vitreous detachment (PVD) and complicated cataract surgery [65, 96]. The risk increase can be multiplied if several risk factors are present. Complicated cataract surgery with capsular rupture leads to a pronounced risk increase in RD [75, 97]. RD surgery today often consists of pars plana vitrectomy, endolaser treatment of all retinal tears and a gas tamponade with duration of 2-3 weeks. The prognosis of visual recovery is dependent on the pre-operative extent of the RD.

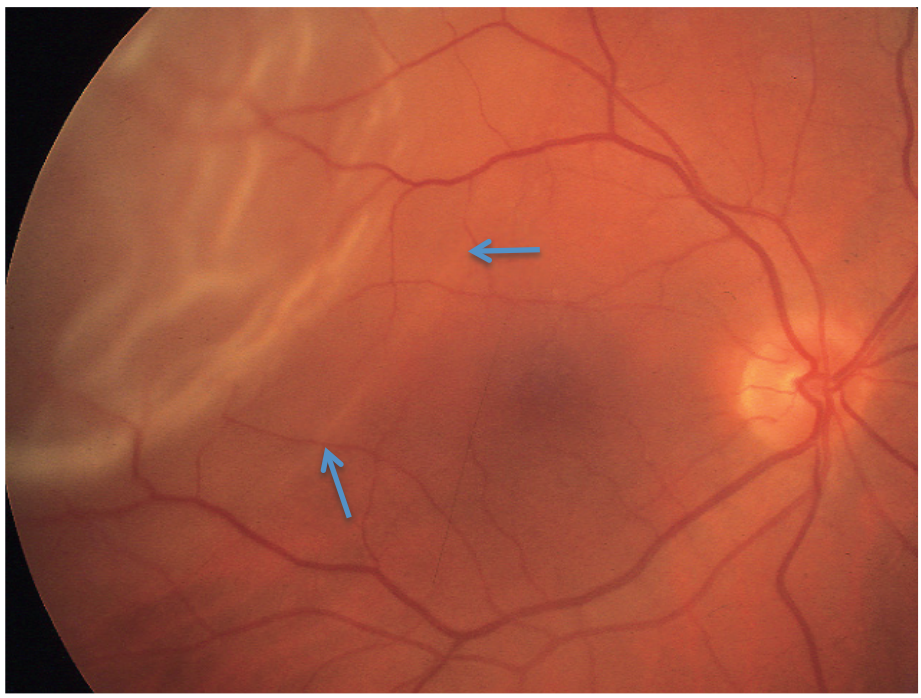

Figure 5. Retinal detachment progressing into the macula. Arrows indicate posterior border of RD. Distance to fovea < 2mm. ©Tommy Andersson

When the detachment involves the macula in the center of the retina – which occurs in 50% of RD cases – the visual acuity almost always remains considerably reduced, in spite of otherwise restored anatomical conditions (figure 5). There is also a risk of re-detachment, which occurs in 5-10 % of RD-patients. This necessitates additional and often more advanced surgical

procedures with further loss of retinal function and sustained visual morbidity [98].

The pathophysiological mechanisms leading to RD following cataract surgery, are not fully elucidated [99]. It is well known that PVD with formation of retinal breaks precedes RD, and several studies confirm that cataract surgery provoke a premature PVD [100-102], probably by inducing alterations in the vitreous gel as a result of the surgical trauma and removal of the crystalline lens [91, 103]. The importance of vitreous integrity is further confirmed by the fact that capsular rupture and vitreous loss during cataract surgery or lack of PVD – as in younger patients – are main risk factors for RD.

In summary, this exposé of complications to cataract surgery illustrates the potential of undesirable outcomes from a surgical procedure whit a high success rate and also optimistic expectations from the patient to regain improved or even excellent visual acuity.

Excluded from this review are comorbidity conditions that can aggravate and challenge the surgery; corneal haze, shallow anterior chamber, iris rubeosis, restricted pupil dilation, floppy iris, donesis of the lens, hyper mature cataract, previous glaucoma surgery or vitreous surgery, extreme anterior chamber depth or vitreous hemorrhage.

Minor postoperative complications are neither included; corneal epithelial erosions, temporary corneal edema, chemosis or hemorrhage in the conjunctiva, iris-prolapse, vitreous incarceration, hyphema or elevated intraocular pressure.

Pediatric cataract surgery and eyes with previous severe ocular trauma involve additional challenges, requiring both need for access to extended surgical equipment and robust clinical experience.

Finally, not only those patients who suffer from postoperative complications are disappointed of the outcome of their surgery. Some patients – in spite of uneventful cataract surgery – do not experience any visual improvement or have other new symptoms like glare or haloes [104-106]. An objective and correct preoperative information to each patient, including risks and explanation of what reasonable visual outcome can be expected, is fundamental in order to aware each patient of unpredicted outcome.

Modern cataract surgery still is the most successful surgical procedure ever performed on the human body.

AIMS OF THE THESIS

The general aim of this thesis is to identify characteristics, causation and clinical prognosis for some specific complications to cataract surgery and to evaluate if there are sustained biomedical alterations in the pseudophakic eye.

Specific aims

Paper I

- To evaluate incidence, patient characteristics and outcome of retinal detachment in patients with lens capsule complication after cataract surgery.

Paper II

- To characterize late intraocular lens (IOL) dislocation with regard to incidence, to describe risk factors and surgical management and determine the time interval between cataract surgery and IOL dislocation.

Paper III

- To study the outcome in patients having surgery for late IOL dislocation and evaluate different surgical techniques, to describe postoperative complications and analyze the impact of repositioning surgery on intraocular pressure.

Paper IV

- To detect and measure different inflammatory immune mediators in the vitreous and compare the levels of these bioactive molecules in pseudophakic and phakic eyes.

PATIENTS AND METHODS

Paper I

In this retrospective case-control multi-center study emanating from NCR in Sweden, data was extracted from cataract operations with a capsule complication during 2003. Capsule complication includes any communication between the anterior segment and the vitreous body during surgery, like zonulolysis, posterior capsule rupture, vitreous loss and lens remnants into the vitreous. Ten cataract clinics participated, representing 23,285 cataract procedures, or 29.7% of all cataract extractions reported to NCR that year. About 30 cases with a capsule complication were consecutively selected from each of the ten clinics, beginning from January 2003. Each control case was selected as the first uneventful case following a case with a capsule complication. A total of 324 patients with a capsule complication (study group) and 331 patients without a capsule complication (control group) were enrolled in the study. The medical records of patients in the study group and in the control group were analyzed for up to three years after cataract extraction. A standardized form was used and was completed by the participating ophthalmologists at each clinic.

The form addressed – among other clinical data – the retinal detachment (RD) and its relation to surgical events during cataract extraction, a general description of the detachment, its management, and the final functional outcomes. Additional data collected included demographics, preexisting eye conditions and axial length.

Paper I is the fourth report from the Swedish Capsule Rupture Study Group – a case-control multi-center study evaluating capsule complications during cataract surgery [6, 7, 55].

Paper II

All patients with a diagnosis of late IOL dislocation who had surgery with secondary IOL fixation during a three-year period were included in this retrospective case-observational study. Late IOL dislocation was defined as any case requiring IOL repositioning surgery that occurred after primary cataract surgery in which the initial postoperative IOL position had been noted as properly placed, thus excluding dislocations occurring during cataract surgery or detected at the first postoperative visit. Indications for repositioning surgery

were IOL dislocation causing visual symptoms or rapid and distinct dislocation. Cases of IOL dislocation from ocular trauma were excluded.

Medical records of the patients were analyzed using a standardized case report form designed for the study. Data on age, sex, coexisting eye disease, type of cataract, and presence of phacodonesis or pseudoexfoliations (PXF) prior to cataract surgery and date of cataract surgery were collected. Other data included type of cataract surgery, preoperative complications (e.g. capsule rupture or zonular dehiscence), use of mechanical pupil dilation or a capsular tension ring (CTR), type of IOL, and whether the IOL was placed in the capsular bag or in the ciliary sulcus. Data collected after cataract surgery included complications – e.g. high intraocular pressure (IOP) – and additional surgeries, including Nd:YAG laser treatment for posterior capsule opacification. Finally, the time between the cataract surgery and IOL repositioning surgery and the techniques used for repositioning were noted. Snellen visual acuity was measured between 2 and 12 months postoperatively.

The incidence of late IOL dislocation was calculated based on the estimated number of pseudophakic eyes during each year between 2004 and 2006 in western Sweden and the number of surgeries for late IOL dislocation during the same years. The pseudophakic prevalence was calculated using data from NCR, and statistics from population records.

Paper III

This prospective nonrandomized observational cohort study followed up the results and complications in all consecutive patients having surgery for late IOL dislocation during a 2-year period from January 2007 to December 2008. The definition of late IOL dislocation was malpositioning of the IOL occurring after conventional cataract surgery with initially normal IOL positioning at the end of surgery or at the first appointments postoperatively. The patients were scheduled for repositioning surgery if they had visual symptoms that could be ascribed to the dislocated IOL or if there was obvious progression of the dislocation.

The medical records of all patients were analyzed using a standardized form designed for the study. Data on age, sex, ocular comorbidity, type of cataract and presence of PXF, characteristics of the cataract surgery (including IOL placement) were collected. Data after cataract surgery included complications such as high IOP and additional surgeries. The time from cataract surgery to the diagnosis of IOL dislocation was recorded, as was the IOP at this

examination. Data were also collected from the examination performed just before the repositioning surgery, including the corrected distance visual acuity (CDVA) using the optimum refraction, IOP, position of the IOL, presence of PXF, ocular comorbidity and type of surgery. Details on the surgical technique used for repositioning the IOL were also registered.

The surgical techniques were either an anterior approach with repositioning of the IOL using scleral sutures and limbal incisions or a posterior approach with pars plana vitrectomy (PPV) and IOL repositioning using scleral sutures of the haptics. The choice of surgical technique was based on the extent of IOL dislocation and suspected vitreous involvement, but also the surgeons preference.

Follow-up parameters were CDVA, IOP, corneal pathology, IOL positioning, fundus abnormalities, current local treatment of the eye, and additional surgical procedures after the IOL dislocation surgery. The goal was a follow-up of 12 months or more; however, an interval of at least 1 month was accepted if no further controls were possible.

Paper IV

A number of 73 patients were consecutively enrolled in this prospective observational cohort study. All patients were subjected to elective pars plana vitrectomy (PPV) because of macular hole (MH), epiretinal membrane (ERM), vitreous macular traction (VMT) or idiopathic vitreous floaters (VF). The patients were divided into two groups – phakic (n=33) or pseudophakic (n=40) – and the pseudophakic group was in turn divided into early pseudophakic (n=17) where cataract surgery was performed within six months prior to PPV, and late pseudophakic (n=23) with cataract surgery performed six months or more prior to PPV. Exclusion criteria were previous complicated cataract surgery, previous intraocular surgery including intravitreal injections, history of uveitis, current vitreous hemorrhage, any degree of diabetic retinopathy (DRP), ongoing treatment with topical steroids or NSAID eye drops and age below 30 years.

Vitreous samples were collected during the period from November 2013 to June 2014. All surgeries were performed using small-size non-sutured valve incisions and undiluted vitreous (0.2-0.3 ml) was obtained by a vitreous cutter from the central vitreous compartment.

Altogether, 29 different inflammatory mediators were analyzed for each vitreous sample using a multiplex immunoassay system. Cryopreserved vitreous

Table 1. Studied inflammatory immune mediators.

Immune mediators included in analysis (n=14)	
Eotaxin	Eosinophil chemotactic protein
IP-10	Interferon-γ-induced protein - 10
MCP-1	Monocyte chemotactic protein - 1
MDC	Macrophage derived chemokine
MIP-1-α	Macrophage inflammatory protein-1-α
MIP-1-β	Macrophage inflammatory protein-1-β
TARC	Thymus activation regulated chemokine
IL-12p40	Interleukin-12p40
IL-15	Interleukin-15
IL-16	Interleukin-16
IL-7	Interleukin-7
VEGF	Vascular endothelial growth factor
IL-6	Interleukin 6
IL-8	Interleukin 8
Immune mediators excluded from analysis (n=15)	
Eotaxin 3	Eosinophil chemotactic protein -3
MCP-4	Monocyte chemotactic protein – 4
TNF-α	Tumor necrosing factor-α
IL-17	Interleukin-17
IL-1-α	Interleukin-1-α
IL-5	Interleukin-5
TNF-β	Tumor necrosing factor-β
IFN-γ	Interferon-γ
IL-10	Interleukin-10
IL-12p70	Interleukin-12p70
IL-13	Interleukin-13
IL-1-β	Interleukin-1-β
IL-2	Interleukin 2
IL-4	Interleukin 4
GM-CSF	Granulocyte-macrophage colony-stimulating factor

samples as well as all kit components were brought to room temperature before analysis. Reverse pipetting was applied in all pipetting steps to avoid bubbles. Samples were spun at 2,000 x g for 20 min to remove cell debris and aggregates and diluted 2-fold in sample diluent. Duplicates of diluted calibrator and samples were loaded on each plate. After washing, labeled detection antibodies were pipetted in the wells. All measurements were performed using one batch of reagents by board-certified laboratory technicians who were blinded to clinical data. Only inflammatory mediators for which at least 90% of the duplicate samples were in detection range were included in the statistical evaluation. A total of 14 out of 29 analyzed factors fulfilled this criterion. A list of the inflammatory immune mediators that were in detection range and those that were not is presented in table 1.

METHODOLOGICAL CONSIDERATIONS

All papers in this thesis include retrospective analysis of clinical records, which always yields some error owing to missing or inaccurate data. Paper I is a case-control multicenter study where the aim was to analyze cases with RD following a capsule complication. The total number of patients in both study groups was 655. Since RD is a relatively rare complication, and there is limited sensitivity in a cohort-study, a larger number of cases would have been more accurate in order to more precisely evaluate the incidence of RD following capsule rupture. Also the follow-up time (three years) is a bit too short, since other studies have detected a continuing increase in the rate of RD several years later.

In papers II and III; although the patients all had late IOL dislocation, there was a significant heterogeneity in the initial cataract surgery regarding to IOL design, surgical experience, comorbidity and time interval to IOL repositioning surgery.

Paper III is a prospective study of eyes undergoing repositioning surgery of late IOL dislocations with follow-up data of VA, IOP, additional surgery and complications. However, no pre- or postoperative optical coherence tomography (OCT) was performed, which had been useful when analyzing reasons to unexpected postoperative VA loss. Perimetry was not consistently used in glaucoma patients, neither before surgery nor during follow-up to evaluate any impact on visual field owing to repositioning surgery. The decision of whether to perform an anterior or posterior approach to reposition a dislocated IOL should be based on the degree of vitreous engagement, but this was not standardized and therefore the surgeons preference was the main basis for the decision of chosen method.

Paper IV is a case-control study comparing cytokine levels in vitreous of phakic and pseudophakic eyes. The selection of patients was not randomized and the controls were not selected immediately adjacent to the study patients. The samples were collected in accordance with established clinical routines, but four different vitreoretinal surgeons were involved in the case series, which might have resulted in differences in sample collection technique. There was no information among the pseudophakic eyes on previous Nd:YAG capsulotomy or type of IOL. Both groups of patients had vitreoretinal disorders – like ERM or MH – which theoretically can give rise to elevated levels of some immune mediators, but sample collection of vitreous from healthy human eyes is of course not possible. Since the most interesting finding was the sustained levels of immune mediators following cataract surgery, it would have been even more

interesting if cases with longer duration of pseudophakia before vitrectomy had been included. This will hopefully be subject to an additional study.

STATISTICS

Several statistical methods were applied in order to evaluate all data in the different studies. For continuous parameters (e.g. age, IOP) mean and standard deviation (SD) or median values and interquartile range (IQR) were used to describe the data. For the statistical analyses, Student's t-test (for normally distributed data) or Mann-Whitney U-test (for non-normal distributions) were used. For categorical data, Fisher's exact test was used and in paper II it was also used to compare the incidences of late IOL dislocation between 2004 and 2006. In paper III visual outcomes after surgery were analyzed using Student's paired-sample t-test after conversion of visual acuity from Snellen notation to logMAR notation and the effects of IOL repositioning surgery on IOP were evaluated using the Wilcoxon signed-rank test. In paper IV, Bonferroni correction for multiple comparisons was used when comparing three subgroups of IOL duration or phakia and levels of immune mediators. Binary logistic regression was used in paper I to analyze risk factors for RD after capsule complication and in paper III to analyze factors associated with decreased postoperative visual acuity. Spearman's rank correlation test was used in paper IV to evaluate the association between duration of pseudophakia and vitreous level for each substance. Multiple linear regression analysis was used in paper IV to correlate levels of immune mediators with different patient parameters.

All statistical analysis was performed using SAS (version 9.2) and SPSS (version 16–22) for Macintosh software and a p-value ≤ 0.05 was considered statistically significant.

RESULTS

Paper I

Thirteen patients out of 324 in the study group were identified as having RD related to cataract extraction. In the control group (331 patients) one patient developed RD. The 3-year incidence of RD after cataract surgery with a capsule complication was 4.0%. In the control group, one patient (0.3%) had RD during the follow-up period. The difference in RD frequency between the control group and the study group was statistically significant using single factor analysis (odds ratio [OR], 13.8; 95% confidence interval [CI], 1.8-106; $p<0.001$) and at a multivariate level including age and sex in the analysis (OR, 14.8; 95% CI, 1.9-114; $p=0.01$).

Variables that were significantly associated with RD in single-factor analyses without adjustment for confounding factors were male sex, longer axial length (AL), lens remnants in the vitreous, and IOL implanted in the ciliary sulcus outside the capsular bag. In the multiple logistic regression, however, only male sex (OR, 8.5; 95% CI, 1.7-43.8; $p=0.001$) and lens remnants (OR, 14.4; 95% CI, 2.6-78.8; $p=0.002$) remained as significant risk factors for RD.

Nine of the 13 patients with RD had no previous diagnosis of ocular disease except cataract. No patient had a confirmed history of ocular trauma. On preoperative examination, four patients had miosis or phacodonesis. The fundus could be visualized in all patients prior to cataract surgery. All patients except one had cataract surgery by an experienced cataract surgeon. Anterior vitrectomy was performed using a vitrector in nine cases. Only sponges and scissors were used in two cases, and no vitrectomy was performed in two eyes. Two cases were converted to the traditional extracapsular technique because of a large zonular dehiscence. Seven patients had an IOL placed in the ciliary sulcus, and three patients had an anterior chamber IOL. The remaining three patients were left aphakic.

The median period between cataract surgery and RD was three months (range 1 day to 29 months). The RD occurred within three weeks in a relatively high proportion of patients (38%). Eight patients had macula-off RD at presentation. Nine patients had RD surgery, all except one with primary PPV. Four patients were not operated on because the surgery was considered to be of no benefit (two cases) or was declined by the patient (two cases). Six of the nine patients required one surgical session for RD surgery; three patients required two or three procedures. In three cases, silicone oil was used as an internal tamponade and gas tamponade was used in six cases. The median follow-up

time was 28 months (range 11 to 39 months). A majority of the patients had low visual function at the end of the follow-up period; eight eyes (62%) had a visual acuity worse than 0.1 and six eyes of 0.02 or worse. One eye developed phthisis, and one eye was enucleated because of secondary glaucoma. Three eyes achieved a visual acuity of 0.5 or better.

Paper II

Eighty-four patients fulfilled the criteria of late dislocated IOL and were enrolled in the study. Coexisting eye disease was diagnosed in 47 patients at the time of IOL repositioning surgery, with the most prevalent being primary open-angle glaucoma. A significant number of patients with glaucoma had PXF and were thus classified as having pseudoexfoliative glaucoma.

The overall median time between cataract surgery and IOL dislocation surgery was 6.5 years (range 1 month to 26 years), (figure 6). Eight patients (10%) had IOL dislocation surgery within one year of cataract surgery; the interval between the two surgical procedures was ten years or more in 24 cases (29%). The time between cataract surgery and IOL dislocation surgery was significantly shorter in the "out-of-the-bag" group (median 38 months) than in the "in-the-bag" group (median 80 months, p=0.029).

The time to IOL repositioning showed a significant negative correlation with patient age; that is, the younger the patient, the longer the interval. There

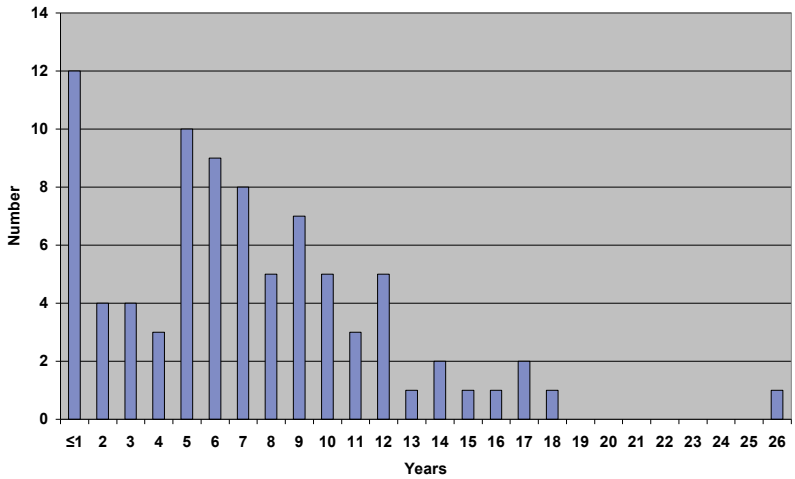

Figure 6. Interval between cataract surgery and IOL dislocation repositioning. Median time interval from the cataract operation to IOL repositioning surgery was 6.5 years.

was a strong association in the "in-the-bag" group between zonular dehiscence at cataract surgery and a shorter time to repositioning surgery (p=0.009).

The surgical technique consisted of either a posterior approach with PPV, which was used in 50 cases (60%), or an anterior approach with or without anterior vitrectomy in 34 cases (41%). In almost half the cases managed by the posterior approach, the IOL was repositioned with scleral sutures of the haptics under triangular scleral flaps just peripheral to the corneal limbus.

CDVA was measured in 75 eyes (89%) after the IOL repositioning. CDVA was ≥ 0.5 in 51% and ≥ 0.1 in 86 % of eyes.

The estimated prevalence of pseudophakic patients in 2005 was 58,300 (3.8%) out of 1.53 million inhabitants in western Sweden; 57.7% of these patients had bilateral surgery. Thus, the incidence of surgery for late dislocated IOL in 2005 was 0.050% (29 of 58,300 patients), or 0.032% when considering the total number of operated eyes. In 2004 and 2006, the incidence of surgery for late dislocated IOL in the pseudophakic population in the region was 0.042% and 0.052%, respectively, corresponding to 0.027% in 2004 and 0.033% in 2006 in relation to the number of pseudophakic eyes. The slight increase in the incidence from 2004 to 2006 was not statistically significant (p=0.588).

Paper III

Eighty-nine patients (91 eyes) were included and participated in the follow-up examinations. The median follow-up was 17 months. Seventy-eight cases (85.7%) had a follow-up of at least six months, and 68 cases (74.7%) had a follow-up of at least 12 months. The main reasons for patients lost to follow-up were serious illness or death.

Eighty eyes (87.9%) had "in-the-bag" dislocation and 11 eyes, "out-of-the-bag" dislocation. The median time between the cataract surgery and diagnosis of IOL dislocation was 7.8 years (range 0.2 to 22.3 years).

In 86 cases (94.5%), the IOL was repositioned with scleral sutures. In three patients, the IOL was exchanged. Additional surgical interventions after IOL repositioning surgery were required in 13 eyes (14.3%). Of the 89 patients enrolled in the study, 16 (18%) had dislocation of the IOL in the fellow eye. Ten of these patients had IOL repositioning surgery in both eyes, two of them in the present study.

The mean CDVA preoperatively was 0.59 logMAR; the corresponding Snellen visual acuity (ie, geometric mean) was 0.26. The mean CDVA at the last follow-up was 0.46 logMAR; the corresponding Snellen visual acuity was 0.37.

Visual function was significantly improved, when comparing preoperative and postoperative CDVAs for each patient; the mean change was 0.13 logMAR (p=0.014).

Twenty-one eyes (23%) had worse CDVA after IOL repositioning surgery than before repositioning. Five of these cases had severe visual loss, with a CDVA less than Snellen 0.05. In three eyes, this was due to new pathology with two cases of RD and one of central retinal vein occlusion (CRVO). Two additional cases were attributable to worsening of preoperative ocular morbidity, macular degeneration, and optic nerve atrophy, respectively.

Pseudoexfoliation-syndrome was identified in 52 eyes (57%) during the time from cataract surgery to the last follow-up. The glaucoma group included 28 cases with glaucoma or suspected glaucoma; the majority (n = 23) were cases of secondary glaucoma associated with PXF. No case of closed-angle glaucoma was identified. Six cases of glaucoma were diagnosed at the same time as the IOL dislocations were detected. Three additional cases had temporary IOP-lowering treatment between diagnosis of IOL dislocation and the last follow-up without developing glaucoma. One patient developed rubeotic glaucoma during the follow-up period as a result of CRVO.

The majority of OAG patients had a diagnosis of glaucoma at the time of cataract surgery or before the diagnosis of IOL dislocation. Fifteen eyes (53.6%) in the glaucoma group had well-regulated IOP during the follow-up, with the same amount of anti-glaucoma medication therapy as before surgery. In the glaucoma group, the mean IOP was significantly lower (6.7 mm Hg) at the preoperative examination before IOL repositioning surgery than at the time of IOL dislocation diagnosis (p=0.001). The mean IOP was also significantly lower (3.0 mm Hg) at the last follow-up compared to preoperatively (p=0.028), excluding one case requiring trabeculectomy and one case requiring additional PPV due to vitreous hemorrhage. In the non-glaucoma group, the mean IOP was 16.5 mm Hg before and after surgery. The mean IOP for the entire study group (n=91) at the time of IOL dislocation surgery and at the last follow-up was 17.4 and 15.9 mm Hg, respectively.

Paper IV

Demographic analysis showed no difference in age or sex between pseudophakic and phakic patients. Pseudophakic eyes exhibited significantly higher levels of immune mediators in the vitreous except for VEGF. The median level of different immune mediators varied from less then 2 pg/ml to more then 700 pg/ml. The highest levels were discovered for MCP-1, IL-10 and

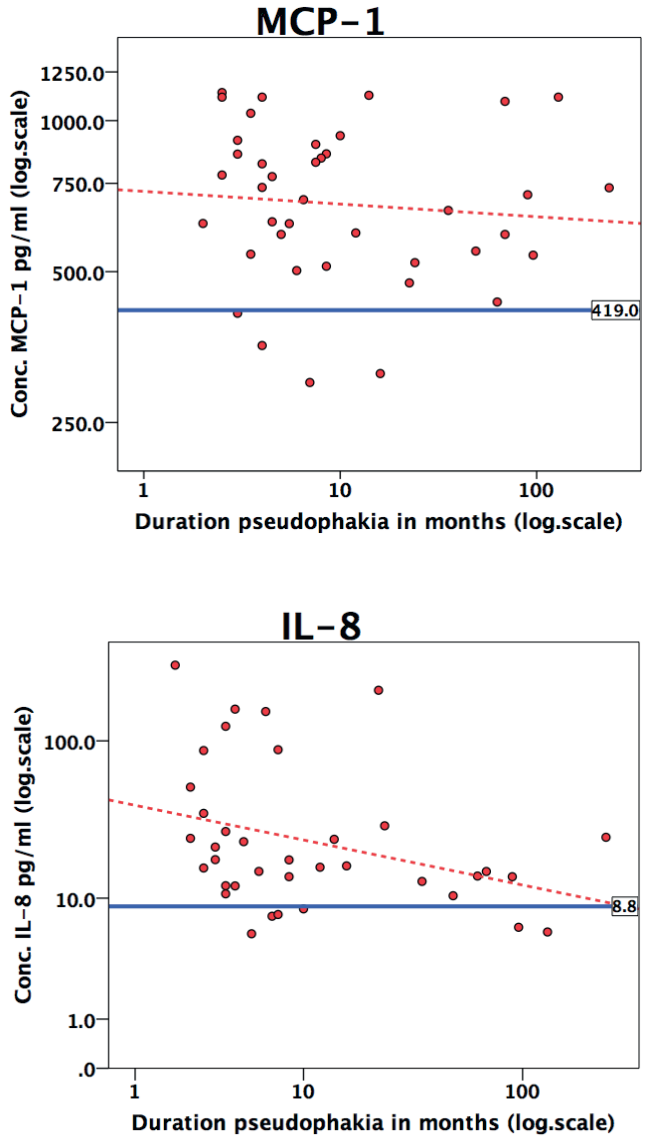

Figure 7: **Correlation of vitreous levels (MCP-1 and IL-8) and duration of pseudophakia.** Two representative immune mediators with varying levels over time are shown in the figure. Each dot represents a single pseudophakic eye. X-axis: Duration of pseudophakia in months, log.scale. Y-axis: pg*/ml, log.scale. Horizontal line: Median level (pg/ml) for all phakic cases. Dashed line: Linear relation between declining level of the detected immune mediator and increasing duration of pseudophakia. [* picogram (10^{-12} g)]

MDC. These variations were similar with a parallel distribution in both groups. The increase in median vitreous levels between phakic and pseudophakic eyes ranged from 20% to 165%, median value 39% (VEGF excluded).

For the vast majority of immune mediators, no significant correlation was found with age, neither for the whole study group nor when analyzing phakic and pseudophakic eyes separately.

Vitreous levels of immune mediators in pseudophakic patients with short IOL-duration (< 6 months) compared to longer duration (≥ 6 months) did not differ significantly, whereas both pseudophakic subgroups had significantly higher levels compared with phakic eyes. The duration of pseudophakia and the vitreous level for each substance was analyzed. Four immune mediators had a statistically significant trend of decreasing concentration over time; IL-6, IL-8, IL-15 and IL-16. The other inflammatory immune mediators, showed no statistically significant equalization over time to the levels of phakic eyes, although the correlation coefficient was negative in all cases, indicating a declining trend. The increased levels of immune mediators in pseudophakic eyes compared to phakic eyes were maintained for a long period and two examples (MCP-1 and IL-8) are shown in figure 7.

Using multiple linear regression analysis with age, sex, phakia/pseudophakia and diagnosis (only patients with ERM or MH were included) as covariates, the increased level of immune mediators in pseudophakic eyes was confirmed. All immune mediators, except VEGF, were significantly elevated in the vitreous of pseudophakic as opposed to phakic eyes. In the majority of immune mediators, pseudophakia was the only covariate that showed significant correlation with concentration. However, for MCP-1 and IL-7 there were significant correlations with age (lower and higher age respectively) and for IL-16, IL-7, IL-6 and IL-8 higher concentrations of immune mediators were significantly associated with diagnosis of ERM as compared to MH.

DISCUSSION

Paper I

In this multicenter case-control study, patients with RD after complicated cataract surgery were identified according to registration of communication with the vitreous in the Swedish NCR. It was found that in the study group a capsule complication during surgery caused a more than ten-fold increase in the risk of RD after cataract surgery. The 3-year incidence of RD after capsule complication was 4.0% compared with 0.3% in the control group (no capsule complication), yielding an OR of 14.8. Other studies report an OR ranging from 5.7 to 19.9 for the enhanced risk of subsequent RD after a capsule complication [65, 67, 107-109]. A posterior capsule tear has the highest impact on risk increase for pseudophakic RD, although most cases of RD after cataract surgery occur in patients with other preexisting risk factors [65].

Previously described major risk factors for pseudophakic RD are myopia (or increased AL of the eye), younger age and complicated cataract surgery [65, 67, 91, 93, 110-112]. Less is known about factors that cause RD after cataract surgery with a capsule complication

There was a highly significant association between male sex and RD after a capsule complication in paper I. Several other studies indicate male sex as a risk factor for pseudophakic RD [65, 113, 114] whereas others do not [111, 115, 116]. One might suspect that ocular trauma, which is reported to be much more common in men, [117, 118] could explain the sex-specific increased incidence of RD. However, no RD patient in this series had a history of ocular trauma.

The difference in AL between patients with RD after capsule complication and patients with a capsule complication only, showed that the RD patients were slightly more myopic. Myopia is a well-known risk factor for RD even preoperatively without ocular surgery. In paper I however, the difference in AL between cases with a capsule complication with RD and cases with a capsule complication without RD was significant at a single-factor level only and not in the subsequent multiple-factor analysis.

Lens fragments in the vitreous appear to predispose to RD following a capsule rupture [115]. However, only three of ten patients with lens remnants required specific surgery with pars plana vitrectomy (PPV), which was performed within eight days. In the other seven cases, minor lens remnants were absorbed without additional surgery. Several studies indicate that if surgery for nuclear fragments lost in the vitreous is urgently planned and performed

with a PPV approach, the rate of complications, such as RD, can be further reduced [119-121]. The high rate of RD patients with lens remnants in paper I may reflect the severity of the capsule rupture rather than the actual presence of lens fragments in the vitreous. Another variable that was associated with RD in patients with a capsule complication was the type of IOL. No patient with RD had a PC-IOL in the capsular bag; in contrast, 23.9% of patients with a capsule complication without RD had a PC-IOL in the capsular bag. This probably reflects the more severe capsule ruptures in the patients with RD.

All but one patient with RD in the study had cataract surgery by an experienced cataract surgeon. Although it is known that capsule complications are more common with less experienced cataract surgeons [7, 108], this factor did not lead to a higher incidence of postoperative RD, which was also noted in another study [122]. The reason for this is not obvious. Some patients with risk factors for RD may be directed to more experienced surgeons. In addition, a less experienced surgeon faced with an unexpected capsule complication would be prone to ask for immediate assistance from a more experienced colleague. It should also be noted that 74% of all patients with a capsule complication had cataract surgery by an experienced surgeon [7].

The visual results in the study group were poor. Only three eyes (23%) attained a visual acuity of 0.5 or better, and six eyes (46%) had visual acuity of worse than 0.02; four of these eyes did not have RD surgery. In Sweden, approximately 74,000 cataract procedures were performed in 2003, and the incidence of "communication with vitreous" reported to the NCR was 2.6%, or roughly 1900 cases. If our results were extrapolated, the 4% RD incidence associated with a capsule complication would translate into 75 eyes. Of these, nearly 50 eyes could be expected to obtain a visual acuity worse than 0.1. As a comparison, the incidence of postoperative bacterial endophthalmitis in Sweden reported to the NCR between 2002 and 2004 was 0.048%, corresponding to 36 eyes yearly [24]. It is thus clear that a capsule complication, if complicated by RD, poses a far greater risk of very poor visual outcome than the feared complication of endophthalmitis.

There is no answer in the literature as to whether RD after cataract surgery with a capsule complication is more severe than pseudophakic RD without a capsule complication. However, vitreoretinal surgeons have observed that RD associated with a capsule complication can be very challenging [123]. The cases in paper I confirm this. Out of the nine patients who had RD surgery, four had silicone oil tamponade, indicating advanced and complicated detachment. In two cases, the patients were not subject to surgery because the

RDs were considered to be incurable. Of the nine patients operated on for RD, five had a final visual acuity of 0.1 or better; thus, the overall poor outcomes of RD after a capsule complication might be because some patients did not have RD surgery. In addition, the majority of the patients with RD in the study group had a macula-off detachment. It is well established that the visual prognosis after RD is dependent on the status of the macula before RD surgery [91, 124, 125]. It is therefore important that all patients with a capsule complication during cataract surgery, which by itself leads to a substantial increase in the risk for RD, are informed of the early symptoms of RD. This information should also be given to cataract surgery candidates with other known risk factors for pseudophakic RD, like myopia or young age [126].

There is a risk that patients with advanced RD following cataract surgery and who are not subject to surgery, will not be registered as having an RD. These cases would not be detected in a retrospective surgical registration if only actual postoperative RD surgeries were identified.

Most cases of pseudophakic RD occur in patients with risk factors identified before cataract surgery [65]. However, if a capsule complication occurs during cataract surgery, the patient is exposed to a new and highly increased risk for RD. Thus, every effort to minimize the risk for a capsule complication during cataract surgery should be made. If a capsule complication does occur, appropriate surgical intervention is crucial. More frequent postoperative reviews will probably not detect an early RD because the presence of an RD without symptoms is unlikely. In addition, RD is an emergency condition that develops rapidly and is less likely to be discovered at scheduled reviews. On the other hand, the patient must be given accurate and detailed information about the increased risk for RD and should be encouraged to seek immediate ophthalmologic consultation if early symptoms of RD appear.

Paper II

Paper II comprised 84 patients, where the majority or 75% had "in-the-bag" IOL dislocations. The possible factors predisposing to late IOL dislocation were assessed.

According to NCR data, the prevalence of glaucoma in cataract patients in Sweden was 8.6% in 2005, which is much lower then the frequency (35.7%) of patients with late IOL dislocation in this study. Most cases of glaucoma were here classified as associated with PXF; therefore, the presence of PXF rather

than other glaucoma-related factors may be the main risk factor for IOL dislocation.

All previous studies on late IOL dislocation, especially "in-the-bag" dislocations, conclude that PXF is a significant risk factor [77, 127, 128]. Paper II supported this because the frequency of PXF was substantially higher (60%) than the reported prevalence in average Scandinavian populations, which ranges between 11% and 40% in comparable age groups [81, 129-133].

Additional potential risk factors for IOL dislocation reported in other studies [8,9] are previous ocular trauma and myopia. A history of ocular trauma was reported in three cases and denied in five cases. Previous surgical trauma, for example pars plana vitrectomy, was reported in seven cases. Myopia was reported in 14 cases. Hence, as is the case with many retrospective studies, reliable data could not be obtained for all parameters; for example, the prevalence of previous ocular trauma or the axial length could not accurately be estimated.

The median time interval for "in-the-bag" dislocations was 6.7 years. This is similar to reports in previous studies of late IOL dislocation (6.8 years [128], 6.9 years [127] and 8.0 years [82]). It is reasonable to assume that the presence of risk factors might induce a dislocation earlier. To assess the possible risk factors for IOL dislocation, several variables were analyzed in the "in-the-bag" group to determine whether there was an association with the time from cataract surgery to IOL repositioning. Older age at cataract surgery and zonular dehiscence were significantly associated with shorter intervals. However, the presence of PXF did not cause IOL dislocation earlier than the absence of PXF, even though the high prevalence of PXF in the study indicates it might be a risk factor for IOL dislocation. In paper II the time interval was 7.0 years for PEX-patients with late "in-the-bag" dislocations, and in another recent studies [74, 79] with late "in-the-bag" dislocations associated with PEX, the mean time from the initial operation to surgical correction was 8.5 years in both studies. This is somewhat surprising because one would expect an eye with an additional risk factor for zonular weakness, such as PXF, to develop IOL dislocation sooner. The true importance of PXF as a primary cause of weakening of the zonular apparatus may become more clear through studies of late IOL dislocation in populations in which PXF is rare [134].

The time between cataract surgery and IOL repositioning was considerably shorter in the "out-of-the-bag" dislocation group than in the "in-the-bag" dislocation group. Thus, zonular dehiscence and primary placement of the IOL in the sulcus induced IOL dislocation sooner than in uncomplicated

cataract surgery cases. This is also reflected in the high proportion of patients (38%) with zonular dehiscence at cataract surgery in the "in-the-bag" dislocation group. Because cataract surgery complications occur in only a small percentage of cataract extractions, zonular dehiscence seems to be a greater additional risk factor for late IOL dislocations than PXF alone [6].

Capsular tension rings (CTR) are often used when there is phacodonesis or zonular dehiscence at the cataract surgery. It has been proposed that a CTR should be used when there are existing risk factors for IOL dislocation, such as PXF [77], even if the cataract surgery is otherwise uncomplicated. Considering the high prevalence of PXF, especially in the Scandinavian countries (between 11% and 40%) this proposal would involve implanting a CTR in a substantial proportion of patients having cataract surgery [80] most of whom will never develop IOL dislocation. In paper II, 21 eyes (27%) with IOL dislocation had a CTR in place [76]. In 19 eyes, the indication for the CTR was zonular dehiscence, which indicates that CTR implantation was performed for the correct indication. There are several reports of dislocated CTR–IOL complexes [135-138]. Evaluation of the role of CTRs in preventing IOL dislocation is not yet complete. However, the presence of a CTR with an IOL–capsular bag complex often facilitates IOL fixation and repositioning, [139, 140]. This procedure requires less surgical intervention, and even complicated IOL subluxations can be handled with small-incision surgical intervention.

Many types of posterior chamber IOLs were used in the study, and no correlation was found between the type of IOL and an increased risk for dislocation. A Nd:YAG capsulotomy does not seem to create an additional risk for IOL dislocation [80]. This is supported by paper II, in which only 17% of patients required a Nd:YAG capsulotomy.

The need for IOL repositioning surgery is evident if the patient has visual symptoms caused by the dislocation or if the progression is obvious and rapid. However, some eyes with minor IOL dislocation have no visual symptoms and do not require surgical intervention if the dislocation does not progress during short-term follow-up examinations.

Several surgical techniques are used to reposition a dislocated IOL. The choice of technique often depends on the surgeon's preferences. There is no consensus on what technique to use and several surgical procedures are reported to give good results. Management of the IOL with different suturing techniques and whether the IOL is preserved or exchanged can differ [77]. Some prefer replacing the posterior chamber IOL with an anterior chamber

IOL [127]. The preferred strategy in paper II and also in paper III was anterior approach with scleral sutures of one or both haptics if the IOL is dislocated along the iris plane only and some of the optic is visible in the pupil. An anterior vitrectomy is performed when there is prolapsed vitreous gel in front of or around the IOL. However, if the IOL is dislocated posteriorly into the vitreous cavity or laterally from the posterior chamber into the vitreous base, a PPV is performed and the haptics are sutured to the scleral wall into the ciliary sulcus. A posterior vitrectomy facilitates removal of vitreous strands from the haptics and capsule remnants, thereby reducing the risk for peripheral retinal breaks and subsequent retinal detachment [141].

Often it is desirable to preserve and reposition the existing IOL if possible [139-141]. Although there might be a slight hyperopic spherical shift when the present IOL is repositioned to the ciliary sulcus, the surgical trauma is less when no corneal wound is created to exchange the IOL [142] thereby avoiding a postoperative increase in refractive astigmatism [143].

Today, cases of late IOL dislocation are not rare because of the large and growing pseudophakic population. One objective of paper II was to compare the incidence of late IOL dislocation between different years to determine whether it had changed over time. Therefore, the yearly incidence of surgery for late IOL dislocation was correlated with an estimation of the number of pseudophakic people in the Västra Götaland region using NCR data and official statistics on the Swedish population. There are two additional Swedish studies estimating the incidence of late IOL dislocation. The first from 2009 involves a cohort of 810 cataract patients followed for 10 years after surgery with examinations assessing IOL dislocation. Five patients had been subject repositioning surgery for a dislocated IOL during this time, resulting in a 10-year incidence of 0.6% and an estimated cumulative incidence of 1.0% [81]. The second recent study [82] evaluated the 10-year cumulative risk for late "in-the-bag" IOL-dislocation to 0.55%. Moreover, this later study found an increasing relative incidence of IOL-dislocations over a time-period of 20 years. This is in contrast to data in paper II, which however only included IOL-dislocations during a three-year period.

It is not clear whether the increased incidence of late IOL dislocations is only due to the growing pseudophakic community or whether the cataract surgery technique also plays a role. The only case-control study of late "in-the-bag" IOL dislocations performed to date [82], found significantly increased phacoemulsification time in the dislocation group compared to the control group. The increase in the number of patients with late IOL dislocation who

require repositioning surgery has been [80] reported as "a dramatic increase in the spontaneously dislocated IOLs." This increase in late IOL dislocations is also observed by other authors [73, 77, 128, 144, 145].

Paper III

In paper III a series of 91 eyes with late IOL dislocations are described with follow-up results, including visual acuity, IOP alterations, and complications. The surgical approach in most cases (94.5%) was repositioning of the preexisting IOL with scleral sutures. The goal of attaining a follow-up of at least 12 months was achieved in 74.7% of cases, which is a reasonable proportion taking into account that the median age was 81 years in the entire group and 88 years in the superior quartile; thus, it was difficult for some patients to attend repeated postoperative examinations. The median follow-up time was 17 months, which is sufficient for visual function and IOP to stabilize and to detect most postoperative complications. In a long-term study of 16 eyes followed for 10 years [146], it was found that most postoperative complications occurred within two years after IOL repositioning surgery.

There is a well-known association between PXF and progressive zonular dehiscence [77] explaining the higher rate of late IOL dislocation in patients with PXF.

A recent study [79] concluded improved IOP control in PXF associated OAG after reconstructing surgery in late IOL dislocations. In paper III this was the predominant type of glaucoma. It was found that IOP was better controlled after IOL repositioning surgery and that there was a significant decrease (3.0 mm Hg) in the mean IOP in glaucoma cases. Furthermore, three cases required IOP-lowering treatment before surgery that was terminated postoperatively without glaucoma development. Another six cases had suspected or manifest glaucoma at the time of the IOL dislocation diagnosis, requiring anti-glaucoma medication. These newly detected cases of high IOP explain the decrease in the mean IOP (6.7 mm Hg) between the IOL dislocation diagnosis and the preoperative examination. These circumstances indicate that IOL dislocation might in itself cause increased IOP, at least in patients with susceptibility to glaucoma. The reason for improved IOP control could be the result of alterations in the anatomy of the anterior segment caused by the dislocated IOL, including prolapse of the anterior vitreous surface. This may cause disturbed aqueous flow, leading to increased IOP, which then normalizes after IOL dislocation surgery, especially if it is combined with a vitrectomy procedure.

This was the predominant technique in our series; however, this is merely theoretical and further studies are needed to verify whether IOL dislocation surgery in glaucoma patients reduces IOP and enhances glaucoma control.

Because PXF is often a bilateral condition as well as a main risk factor for late IOL dislocation, some patients will inevitably have IOL dislocation in both eyes. A recent study [147] examining IOL position six to seven years after uneventful cataract surgery found that eyes with PXF had more downward IOL decentration than control eyes, although often without disturbing visual symptoms. In our study, bilateral dislocation was confirmed in 16 of 89 patients, ten of whom had IOL repositioning surgery in both eyes during the three-year observation period.

One important complication not evaluated in this study because it requires a longer follow-up is recurrent dislocation occurring five to ten years after IOL dislocation surgery. The main argument against repositioning with scleral sutures is the risk for suture degeneration attributable to hydrolysis and subsequent re-dislocation of the IOL [148]. Two cases in the present series required early additional surgery for inadequate IOL positioning after the first repositioning procedure. This was also noted in four other cases; however, if the patient did not have visual complaints or if the visual potential was low, some degree of IOL tilting or minor dislocation were accepted.

Because of the high mean age of most patients having IOL repositioning surgery, a technique with scleral sutures that last for up to ten years is often sufficient. However, some patients should have their IOL fixated for a longer time. In these cases, repositioning with other types of suturing material, such as 8-0 polytetrafluoroethylene (Gore-Tex®) [149] might be an option. However, there are no studies confirming the long-term results of this technique. Other options are IOL exchange and replacement with an IOL fixated to the iris without sutures [150, 151] or an open-loop anterior chamber IOL [89]. However, this often requires a more extended surgical procedure, including IOL exchange, than IOL repositioning alone. Although there are studies showing that 10-0 polypropylene sutures eventually degrade and break both in children [152] and adults [148], clinical experience also indicates that after the haptics are fixated in the sulcus with scleral sutures, formation of subsequent supporting scar tissue might develop [153] allowing the IOL to remain in position despite diminishing suture support [154, 155]. This could explain why late recurrent IOL dislocation after repositioning surgery with scleral sutures is rarely seen, even in patients who had the procedure performed more than ten years previously.

Several authors [74, 77, 80, 128, 156] have stated that there is an increasing trend of late IOL dislocations with need for repositioning surgery. Because of wider indications for cataract surgery and a longer life expectancy, the growing proportion of pseudophakic persons in the population will undoubtedly lead to more IOL dislocations and more IOL repositioning surgery. In addition, the increasing use of premium IOLs (i.e., toric and multi-focal models) will likely cause visual symptoms with minor dislocations, which will result in extended indications for additional surgery and a demand for more accurate surgical techniques that ensure precise IOL positioning.

Repositioning with scleral sutures or IOL exchange with iris-supported secondary IOL implantation, which are the predominant techniques today, may not be sufficient for restoring the level of visual capacity patients with toric and multifocal IOLs demand. Moreover, many new IOLs are designed for intracapsular support only and are not always suitable for repositioning with scleral sutures. However, a new technique [88] with scleral fixation of the haptics into intrascleral tunnels provided excellent IOL centering and long-term safe ciliary sulcus fixation [18]. Another technique [149] also seems to ensure accurate IOL positioning of a secondary multi-focal or toric IOL. When these techniques are used it might require IOL exchange; however, this may be the best way to achieve sustained optical qualities. Thus, there will be a need for enhanced surgical procedures to provide optimum positioning and long-term IOL fixation to a growing pseudophakic population with individually calculated premium IOLs who want to maintain excellent optical qualities even after reconstructive surgery for IOL-dislocation.

Paper IV

The development of ultra sensitive techniques with multiplex bead immunoassays [157] has enabled detection of a substantial number of immune mediators and several studies have revealed a substantial amount of bioactive molecules present in fluid of eyes with various ocular disorders [158-161].

Uncomplicated pseudophakia is usually not considered a pathological condition. However, in a study from 2005, Neal et al compared the vitreous humor proteome and viscosity in phakic and pseudophakic donor eyes [162] and found that the protein composition was altered in the pseudophakic eyes.

Pseudophakia has been shown [163] to induce an increased level of cytokine MCP-1 in the aqueous humor of glaucomatous pseudophakic eyes compared to phakic glaucoma eyes. The elevated cytokine level that was

revealed was sustained, and the suspected clinical implication was a lower success rate of IOP regulation in pseudophakic eyes following filtering surgery due to increased risk of tissue fibrosis. Findings revealed a low but significant inflammatory activity in the anterior segment of glaucomatous pseudophakic eyes.

During cataract surgery with phacoemulsification, the barrier between the anterior and posterior segment is affected by intraocular pressure fluctuations and immense fluid perfusion through the anterior chamber. This can cause cortical debris to leak into the vitreous even without capsular damage, which together with mechanical forces strong enough to arouse ocular globe deformation may lead to vitreous destabilization and inflammatory reactions in the vitreoretinal tissues [164]. Paper IV demonstrates a significant increase in various immune mediators in the vitreous, which was maintained for an extensive period of time. These bioactive molecules may be primarily due to the surgical trauma, but because the vitreous is capable of eliminating potentially damaging substances through a protein turnover mechanism [165], sustained levels of cytokines are probably the result of continuous production by immunoactive cells in the eye itself. The vitreoretinal compartment is an immune privileged environment, separated by the blood-retina-barrier from circulating blood cells, hence the retinal conditions in the studied population may themselves be preceded by inflammatory mechanisms such as formation of epiretinal membranes (ERM) [166]. Nonetheless the difference in cytokine levels remained when other diagnoses like macular hole (MH) or vitreomacular traction (VMT) were excluded. Multiple regression analysis revealed that pseudophakia was the strongest predictor for increased vitreous levels for all immune mediators except VEGF, while diagnosis (ERM vs. MH) was a predictor in only four out of fourteen increased immune mediator levels. The levels of VEGF were equally low in phakic and pseudophakic eyes, precluding angiogenesis or increased vascular permeability as an explanation of the increased vitreous levels of other cytokines [167]. Another study also concluded that soluble factors detected in vitreous are mainly recruited from ocular tissues [161].

In a recent study [159] MCP-1, IP-10 and MDC were detected in the vitreous of both study patients and controls when analyzing cytokines in the vitreous of patients with proliferative diabetic retinopathy. In our study these three immune mediators – MCP-1, IP-10 and MDC – showed the same pattern with relatively high vitreous levels. MCP-1 is expressed by endothelial and inflammatory cells and is upregulated after tissue injury leading to recruitment

of inflammatory cells. IP-10 has both anti-angiogenic and anti-inflammatory properties [168] and MDC exert chemotactic activity. However, cytokines, chemokines and pro-inflammatory factors often have a variety of properties. How the interactive mechanisms are mediated in the immune response in the eye is poorly understood.

In aqueous humor from pseudophakic glaucoma eyes, the elevated levels of MCP-1 and IL-8 compared to phakic glaucoma eyes were found in cases with a mean duration of pseudophakia of over seven years [163]. In paper IV, some cytokine levels eventually decreased to the same levels as in phakic eyes. However, for the majority of inflammatory immune mediators, no significant equalization to the levels of phakic eyes could be detected. This implies that the sustained elevated level of immune mediators is related to the pseudophakic status itself, and not only as residuals of an inflammatory reaction induced by the previous cataract surgical procedure.

Most patients in the study were subjected to PPV due to ERM, and this condition can theoretically cause higher vitreous levels of immune molecules due to the presence of posterior vitreous detachment and increased mobility of fluids in the vitreoretinal compartment compared to for example MH, where the vitreous is often still attached. Using multiple linear regression analysis, the cytokine concentrations of IL-16, IL-7, IL-6 and IL-8 were significantly higher in vitreous samples from patients with ERM compared to MH. Another study found no correlation between cytokine levels in vitreous samples from ERM and MH respectively [159].

Limitations of this study are the lack of data concerning the type of IOL implanted and also the lack of information relating to previous Nd:YAG laser capsulotomy. However, we believe that the majority of the pseudophakic eyes had sharp-edged hydrophobic acrylic IOLs, which are the most common type of IOL used in Sweden. Moreover, the cataract surgery was performed less than 24 months prior to PPV in the majority (75%) of cases, which suggests a low PCO prevalence [58].

The clinical relevance for sustained elevated vitreous levels of inflammatory immune mediators in pseudophakia is yet unclear. In the majority of pseudophakic eyes it probably has no clinical implication. However, for those patients who develop complications from cataract surgery, e.g. CME, postoperative chronic uveitis, PCO, progression of DRP, pseudophakic RD or late spontaneous IOL dislocation, a low but sustained increase in immunological activity due to cataract surgery and pseudophakia, may play a crucial role in the patho-physiological processes leading to these conditions. Inflammatory

reactions are the main cause of both CME and postoperative uveitis and also for postoperative progression of DRP [159]. Pseudophakic RD develops due to vitreous collapse with formation of retinal tears [99] and it has been suggested that cytokines are involved in the pathogenesis [169]. Late IOL dislocation can occur when the zonular fibers are gradually weakened. Both these later conditions are preceded by normal aging processes, which can be accelerated by altered immunological vitreous activity. A low grade of increased inflammatory reaction can be described as para-inflammation and might contribute to age-related pathological alterations in the eye [170, 171].

CME is mediated by an inflammatory postoperative reaction following cataract surgery. It is clinically evident only in 2% of patients experiencing impaired visual acuity. If the diagnosis of CME is based on other methods like fluorescein angiography, the prevalence of CME can be established in up to 20% of cases [40, 41], implying a more frequent postoperative intraocular inflammation also extended to the posterior segment. In a recent systematic review of clinical trials for treatment of pseudophakic CME, the authors concluded that treatment with topical NSAID is effective in preventing inflammation and reducing the incidence of CME [42]. Data in paper IV can support the need for effective and perhaps prolonged treatment with local anti-inflammatory topical drugs in order to control postoperative intraocular inflammation.

Paper IV demonstrates increased levels of inflammatory immune mediators in the vitreous of pseudophakic eyes. Even if this does not imply a clinical, chronic intraocular inflammation, it indicates an amplified immunological response sustained for an extended time with a potential to influence pathophysiological processes involved in postoperative complications following cataract surgery. Although several studies indicate the central importance of inflammatory components, the significance of increased levels of immune mediators is not known in detail. However, in view of these findings, the belief that the difference between a phakic and a pseudophakic eye is merely an exchange of the lens properties must be dismissed as a myth.

CONCLUSIONS

The occurrence of capsule rupture during cataract surgery and risk of subsequent retinal detachment has been observed in other studies, but the poor outcome with profound visual loss highlights just how severe this complication can be.

Late spontaneous IOL-dislocation requiring reconstructive eye surgery occurs annually in every two thousand pseudophakic patient. Risk factors are initially complicated cataract surgery, PXF and old age.

In patients with late IOL dislocation, repositioning surgery with scleral sutures and a high frequency of pars plana vitrectomy result in improved vision and a low rate of complications in most patients. In eyes with elevated IOP or glaucoma, repositioning surgery seems to improve IOP control.

Increased and sustained levels of inflammatory immune mediators were detected in the vitreous of pseudophakic eyes. These observations cannot unconditionally be translated to a clinical application, but the results indicate that inflammation may be involved in processes leading to complications related to cataract surgery.

FUTURE PERSPECTIVES

Is it possible to reduce the amount of cataract surgery complications?

The development and improvement in cataract surgical technique and experience will continue. There is already an evident reduction in the incidence of perioperative lens capsular ruptures, which is feared because of its potential of resulting in subsequent severe complications. The introduction of femtosecond laser cataract surgery demonstrate the ability of reducing surgically induced trauma, especially in vulnerable eyes, for example with low endothelial cell density or zonular weakness. A consistent use of prophylactic intracameral antibiotics can reduce bacterial endophthalmitis to the minimal level present in those countries and clinics where this policy is already introduced.

It is reasonable to believe that the pseudophakic population will increase owing to expanded indications for cataract surgery and a longer lifespan. Aligned with this there will be more patients having late complications, primarily IOL-dislocations, requiring reconstructive surgery. In addition, there is a growing use of premium IOLs (toric and multifocal) and as a result this will increase the need for developing surgical technique and IOL designs suitable for fixation aside from intracapsular support, if the patients shall retain the optical capacity present in the eye before dislocation. The extent of late IOL dislocations is difficult to predict but the increasing trend already observed, prognosticate a significant individual and public health burden of this condition, although the visual function often can be restored.

The incidence of pseudophakic retinal detachment (RD) can also be expected to increase. In spite of the improvements in cataract surgical technique the last decades, RD still is the most important late complication to cataract surgery. Half of the patients present with a macula-off detachment, which inevitable will cause a lifelong reduction in visual acuity. Considering that RD occurs more often among the younger part of the pseudophakic population, this complication is even more important in consideration of the total number of years with decreased vision. All pseudophakic patients, and especially those with risk factors for RD, should have accurate information on the early symptoms of RD in order to immediately seek ophthalmological care before a macula-off RD has developed.

Risk factors for RD, like increased axial length of the eye or younger age, are well documented but the pathophysiological mechanisms of how these risk factors in some patients are translated to RD are not completely understood. The presence of a posterior vitreous detachment (PVD) – which is

a normal aging process in the eye – prior to cataract surgery, is probably essential in reducing the risk of postoperative RD. Prospective cohort studies of pseudophakic patients with or without preoperative PVD, would have the potential of giving answer to whether the presence of PVD reduces the risk of RD. Large register-based studies of cataract surgeries and pseudophakic RD could also elucidate risk factors more precisely, which would be beneficial when predicting the risk of postoperative RD.

How does an uneventful cataract surgery and pseudophakia influence the intraocular environment? Regularly there will be some corneal endothelial cell loss, some extra stress to the zonular apparatus and some alterations in the vitreous compartment, which may cause a preterm PVD. If pseudophakia also cause an enhanced inflammatory activity sustained for a longer period of time, this might be part of an explanation why some complications occur. Further research is necessary to understand the intricate network of immune mediators involved in the control and activation of different inflammatory responses in the eye.

As the mean age of cataract or lens exchange surgery is decreasing, late complications – predominantly IOL dislocations and RD – will increase to an unknown quantity. However, there are also advantages of performing cataract surgery earlier. People can benefit from optimal and renewed optical qualities in their eyes during longer time of their life. The cataract surgical procedure might be less traumatic compared to at older age, which then will reduce the level of both peri- and postoperative complications. The public health costs may also be reduced if people have their surgery done earlier.

Hopefully, future research will result in more precise epidemiological data together with fundamental understanding on how specific complications evolve, and thereby provide each individual patient with information needed for evaluating risks and benefits before a decision to have cataract surgery is made.

SVENSK SAMMANFATTNING / SUMMARY IN SWEDISH

Operation av katarakt – eller grå starr – är numera en mycket vanlig och framgångsrik metod för att byta ut en grumlad ögonlins mot en syntetisk linsprotes med likvärdiga optiska egenskaper som i det friska ögat. Den årliga volymen av kataraktoperationer i Sverige är mer än 100 000 och gör det därmed till ett av de vanligaste kirurgiska ingreppen överhuvudtaget. Dessutom utförs cirka 10 000 operationer per år där anledningen inte är katarakt utan istället görs ett utbyte av ögats lins till en konstgjord lins för att ändra ögats optiska egenskaper och därigenom slippa glasögon eller kontaktlinser.

Även om komplikationer endast uppträder hos en minoritet av patienterna, så medför de stora patientvolymerna att även ovanliga komplikationer kan drabba ett stort antal individer. Vissa komplikationer kan uppträda hos flera procentenheter av patientpopulationen. En del komplikationer inträffar redan under eller direkt efter operationen medan andra kan dröja till många år senare. Flera av de svårare komplikationerna, som näthinneavlossning eller att den inopererade konstgjorda linsen lossnar från sitt läge, kan ge kraftig synnedsättning och det krävs oftast avancerade ögonkirurgiska ingrepp för att om möjligt återställa hela eller delar av ögats synförmåga.

Frågeställningen för avhandlingen är att beskriva omfattning och konsekvenser av en del av dessa komplikationer samt att försöka hitta biokemiska förändringar i ögon med inopererad linsprotes för att öka förståelsen för mekanismerna bakom hur en del komplikationer uppstår.

Artikel 1 är en del av en större studie som omfattar tio ögonkliniker i Sverige och där mer än 300 patienter som opererades för grå starr och fick skada på linskapseln under operationen, jämfördes med lika många som opererades utan denna komplikation. Syftet är att studera skillnader i komplikationer under en tre-års period efter operationen och artikeln analyserar särskilt de patienter som får näthinneavlossning. Resultatet visar en mer än tio gånger så stor ökning av näthinneavlossning om det inträffar en tydlig skada på linskapseln under operationen, samt en mycket dålig synprognos för majoriteten av dessa ögon med näthinneavlossning.

Artikel 2 är en undersökning av drygt 80 patienter som drabbats av lossning – dislokation – av sin linsprotes, och opererats på ögonkliniken vid Sahlgrenska Universitetssjukhuset i Mölndal. Denna komplikation kommer ofta flera år efter en kataraktoperation och är tidigare relativt lite studerad. Syftet är

att beskriva patientpopulationen, utvärdera riskfaktorer, definiera tidsintervall och uppskatta hur vanlig denna komplikation är. Resultatet visar att komplikationer under det första kataraktingreppet, glaukom (grön starr) samt hög ålder är riskfaktorer för senare lins-dislokation, men att en del patienter även får denna komplikation helt spontant. Tidsintervallet är i medeltal 6,5 år räknat från grå starr operationen. Den årliga risken beräknades till 0,05 % vilket innebär att var 200:e patient som haft en linsprotes i 10 år drabbas av att linsen lossnar och ögat måste opereras igen.

Artikel 3 är en studie med syfte att utvärdera resultaten efter kirurgi för sena linsdislokationer. Undersökningen omfattar drygt 90 ögon som också opererats på ögonkliniken vid Sahlgrenska Universitetssjukhuset i Mölndal. Resultatet visar att om den lossade linsprotesen sys på plats igen, blir resultatet oftast återställd syn med få nya komplikationer hos patienten. Dessutom visar det sig att de patienter som också har glaukom får en bättre kontroll av ögontrycket efter operationen.

Artikel 4 är en jämförande studie av inflammatoriska biomolekyler, s.k. cytokiner i ögat. Proven utgörs av en liten mängd glaskropp från drygt 70 patienter som opererat bort glaskroppen (s.k. vitrektomi) för olika sjukliga förändringar i ögats bakre delar. Knappt hälften av patienterna var tidigare opererade för katarakt och hade en inopererad linsprotes och den andra hälften hade kvar sin naturliga lins. Sammanlagt 14 olika cytokiner kunde påvisas i ögats glaskropp hos dessa patienter och det visar sig att gruppen med tidigare inopererad ny lins hade signifikant högre värden av cytokiner än de ögon som inte opererats tidigare. Dessutom kvarstod förhöjningen under lång tid på flera månader och t.o.m. år för vissa substanser. Detta kan tolkas som att en kataraktoperation med implantation av ny linsprotes ger en utdragen låggradig inflammatorisk reaktion som i vissa fall skulle kunna orsaka påverkan på ögats inre vävnader, vilket i sin tur kan ge upphov till efterföljande komplikationer. Mer forskning krävs dock för att kunna bekräfta detta samband.

Slutsats: Operation av grå starr är en säker operation som oftast ger mycket bra resultat för patienten med förbättrad syn. Komplikationer är relativt sällsynta men inträffar hos några procent av patienterna. Eftersom ingreppet är så pass vanligt, så innebär det dock att antalet patienter som får någon form av komplikation inte bara är ett fåtal. Även om komplikationerna i många fall kan behandlas med bra resultat, så kan inte alltid synen återställas hos alla patienter. En kataraktoperation medför en långdragen ökning av inflammatorisk aktivitet i ögat, vilket kan ha betydelse för utvecklingen av vissa komplikationer.

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