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Quality and complications after cataract surgery

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QUALITY AND COMPLICATIONS AFTER CATARACT SURGERY

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ABSTRACT

Research about IOL parameters` influence on posterior capsule opacification (PCO) and lens glistenings may be rapidly applied in clinical practice and may help the industry to manufacture intraocular lenses (IOLs) with higher quality, which will be of benefit to the patients.

In **paper I** we compared the influence on PCO of 3 different IOLs; a sharp-edged hydrophobic acrylic, a round-edged silicone and a round-edged heparin-surface-modified polymethylmethacrylate (HSM-PMMA) IOL in a 5 year randomized prospective study with 180 patients. The PCO fraction and severity did not differ significantly between the hydrophobic acrylic and the silicone IOL 5 years after surgery. The capsulotomy rate was significantly higher in the silicone (29%) than in the acrylic IOL group (8%). The HSM-PMMA IOL had significantly higher PCO fraction and severity and capsulotomy rate (54 %) than the arylic and the silicone IOLs.

In **paper 2** PCO and anterior capsule opacification (ACO) were assessed 12 years after surgery in the same patients as in paper I. The PCO fraction and severity did not differ between the hydrophobic acrylic and the silicone IOL 12 years after surgery. The PCO fraction was significantly higher in the HSM-PMMA IOL than in the silicone IOL, but not higher than in the acrylic IOL. The PCO severity did not differ between the HSM-PMMA and the hydrophobic acrylic and the silicone IOLs. There was no significant difference in overall survival without capsulotomy between the acrylic and the silicone or the silicone and the HSM-PMMA IOLs. The acrylic had significantly better overall capsulotomy free survival than the HSM- PMMA IOL. The median capsulotomy free survival time was higher in the silicone IOL (>150 months) than the acrylic (108 months) and the HSM-PMMA (53 months) IOLs.

In **paper III** we compared lens glistenings in the same 3 IOLs as in paper I in 46 eyes; and investigated the influence of dioptric power on lens glistenings 12 years after cataract surgery. There was significantly more glistenings in the hydrophobic acrylic than in the silicone and the HSM-PMMA IOL, and significantly more glistenings in the silicone than in the HSM-PMMA IOL. The IOL dioptric power did not influence the amount of lens glistenings in the acrylic IOL. The other two IOLs had too little glistenings to be evaluated for this purpose.

In **paper IV** we studied factors influencing patient-reported visual function after cataract surgery in 14 817 patients, using data from the Swedish National Cataract Register. We found that the improvement in subjective visual function, the postoperative visual function and the satisfaction with vision were influenced by age, preoperative and postoperative corrected visual acuity, ocular comorbidity, a first- or second-eye surgery, gender, and achieved postoperative refraction.

LIST OF PUBLICATIONS

I. Rönbeck M, Zetterström C, Wejde G, Kugelberg M.

Comparison of posterior capsule opacification development with 3 intraocular lens types: five-year prospective study. Journal of Cataract and Refractive Surgery 2009 Nov;35(11):1935-40.

II. Rønbeck M, Kugelberg M.

Posterior capsule opacification with 3 intraocular lenses: 12-year prospective study. Journal of Cataract and Refractive Surgery 2014 Jan;40(1):70-6.

III. Rønbeck M, Behndig A, Taube M, Koivula A, Kugelberg M.

Comparison of glistenings in intraocular lenses with three different materials: 12 year follow up. Acta Ophthalmologica Scandinavica 2013 Feb;91(1):66-70.

IV. Rönbeck M, Lundström M, Kugelberg M.

Study of possible predictors associated with self-assessed visual function after cataract surgery. Ophthalmology 2011 Sep;118(9):1732-8.

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LIST OF ABBREVIATIONS

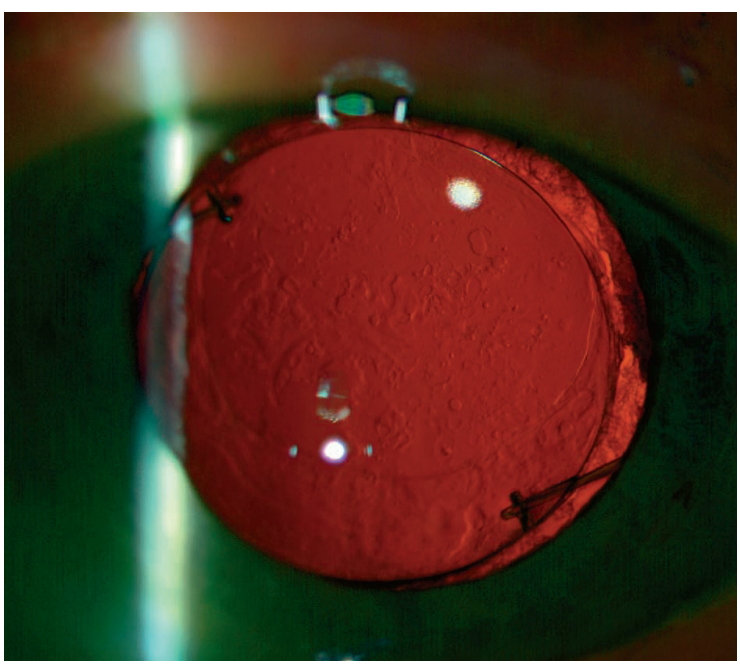
AQUA	Automated Quantification of After-Cataract
ACO	Anterior capsule opacification
°C	Celsius degrees
CCT	Classical test theory
CDVA	Corrected distance visual acuity
ECCE	Extracapsular cataract extraction
EPCO	Evaluation of Posterior Capsular Opacification
EU	European Union
FDA	Food and drug administration
HSM	Heparin surface modified
IOL	Intraocular lens
LEC	Lens epithelial cell
logMAR	Logarithm of the minimum angle of resolution
MICS	Micro incision cataract surgery
NCR	National cataract register
Nd:YAG	Neodymium:Yttrium Aluminium Garnet
NIKE	Nationell Indikationsmodell för kataraktextraktion
OR	Odds ratio
PCO	Posterior capsule opacification
PMMA	Polymethyl methacrylate
POCO	Posterior capsule opacification software
USA	United Stated of America
VA	Visual acuity
VF-14	Visual Function Index 14
Tg	Glass transition temperature

1 POSTERIOR CAPSULE OPACIFICATION

1.1 INTRODUCTION

In modern phacoemulsification surgery with intraocular lens (IOL) implantation, the lens contents are removed leaving the posterior lens capsule intact. The IOL is implanted into the remaining capsular bag. The posterior capsule forms an anatomical barrier between the anterior and posterior segments of the eye, reducing the risk of posterior segment complications following surgery. To achieve good visual function after surgery, the posterior capsule should be clear. The posterior part of the capsular bag, i.e. the posterior capsule, can be opacified months to years after surgery, i.e. posterior capsule opacification (PCO) (Figure 1).

Figure 1. Posterior capsule opacification.



1.2 IMPLICATIONS OF PCO

There has been a substantial amount of research over the years to find safe and effective methods to reduce the amount of PCO, both in the short and long time run. The many implications of PCO, both clinical and financial, give investigators many reasons to continue this research.

PCO has been recognized since the origin of extra capsular cataract surgery (ECCE). Sir Harold Ridley noted PCO in his first IOL implantations in the 1950s. The incidence of PCO in the 1980s and early 1990s ranged between 25-50 %. [1, 2] Since then, considerable improvements in IOL design and surgical techniques have taken place, which has led to a reduction in PCO incidence to less than 10 % in some studies.[1, 2] Despite this, PCO remains the most common complication after cataract surgery.

It still is a major clinical problem, especially in pediatric cataract surgery, where the incidence is very high (>40%; sometimes 100%). Delayed diagnosis of PCO in children may lead to irreversible amblyopia.[3]

PCO leads to loss of visual acuity and contrast vision.[4, 5] The mechanism behind the vision loss is forward light scattering into the eye by the PCO or movement and decentration of the IOL. The observed amount of PCO does not always correlate to visual symptoms. Some patients may have significant symptoms with only mild haze in the posterior capsule while others are relatively asymptomatic with significant PCO on slit lamp examination.[6] The currently only available treatment for adults is Nd:YAG laser capsulotomy, which clears the visual axis by creating a central opening in the opacified posterior capsule. This treatment has many significant complications including transient intraocular pressure rise,[7, 8] laser IOL cracks, IOL dislocation, cystoid macular edema,[8] retinal detachment[9] or floaters

due to remaining posterior capsule pieces; it often does not improve visualization of the peripheral retina.[10] In highly myopic eyes it is especially important to avoid PCO, because a Nd: YAG capsulotomy will induce a greater risk for retinal breaks and retinal detachment.[11] It also leads to a major cost burden on the health care systems. In the USA Nd:YAG laser treatments of almost one million PCO patients per year cost up to $250 million annually around the millennium.[12] The YAG laser treatment is often not available in developing countries. Also in western countries, old patients may contribute further vision loss after cataract surgery to "old age", and will be delayed in seeking treatment.[13] Patients implanted with premium lenses are more vulnerable to PCO. In multifocal IOLs even small amounts of PCO may cause a substantial clinical impact.[14] Also, bag fibrosis is one of the reasons behind the difficulties producing a really accommodative IOL. These IOLs often rely on a dynamic process of presumed active accommodation, a mechanism that could be prevented by bag fibrosis or an Nd: YAG capsulotomy.

1.3 PATHOPHYSIOLOGY

The lens epithelial cells (LECs) in the normal crystalline lens are restricted to the region under the anterior lens capsule and to the equatorial lens bow. They consist of a single row of cuboidal cells, and can be divided into two different biological zones, each zone being the primary source of one of the two PCO types; fibrotic or regenerative.

The first biological zone is the LECs residing in the zone of the anterior lens capsule (A cells). They consist of a monolayer of flat cuboidal, epithelial cells with very low mitotic activity. After cataract surgery the anterior epithelial cells may proliferate and transdifferentiate into myofibroblast, which lay down collagen

(fibrous metaplasia). The anterior LECs are the major source of anterior capsule opacification (ACO)/fibrosis. ACO may hinder visualization of the peripheral retina and can cause decentration and tilting of the IOL. In the more extreme cases, they also may cause capsular phimosis (shrinking of the anterior capulorhexis).[15] They also may migrate posteriorly and cause wrinkles and fibrosis of the posterior capsule, i.e. fibrotic PCO.

The second biological zone is the LECs residing in the equator region (E cells). Cell mitosis, division and proliferation are quite active in this region. The LECs in this zone are important in the formation of regenerative PCO. After surgery with IOL implantation the residual equatorial LECs try to produce new lens fibers to build up a new lens. This process is called lens fiber regeneration. The E-cells tend to form large balloon like bladder cells (Wedl cells). Clinically regenerative PCO is visible as pearls (Elschnig pearls). The morphology of Elschnig pearls has been shown to change within time intervals of only 24 hours. This dynamic behavior of PCO is illustrated by the appearance and disappearance of pearls as well as progression and regression of pearls within this short time intervals.[16] Equatorial cells (E-cells) also form Soemmering's ring, using cortical remnants as a substrate. The Soemmering's ring, which is a donut shaped lesion surrounding the IOL optic in the peripehery of the capsular bag, is a direct precursor to regenerative (pearl) PCO. The equatorial LEC can also contribute to the fibrous form of opacification, but the most likely type of growth is in the direction of regenerative PCO. Regenerative PCO is much more common than fibrotic PCO, and is the main cause of a decrease in visual function after cataract surgery.

1.4 FACTORS INFLUENCING PCO

Factors influencing PCO may be patient, surgery or IOL related. The patient factor age influences PCO the most,[3, 17] but also concomitant intraocular or systemic disease may contribute.[18] The influence of diabetes mellitus on PCO is still controversial. [19] [20, 21]

In the last decades surgical techniques and IOL design in cataract surgery were improved, which has resulted in reduced incidence of PCO. The evolution of cataract surgery techniques and IOL design is a good example of the improvement of medicine with the active cooperation of science and industry. The reciprocal evolution of cataract surgery techniques, IOL implantation and the management of PCO have gone hand in hand.

The main surgery related factors in phacoemulsification that reduce PCO include hydrodissection-enhanced cortical cleanup, in-the-bag (capsular) fixation of the IOL[22] and position of the anterior capsulorhexis. With hydrodissection-enhanced cortical cleanup the capsule is efficiently separated from the cortex by a flow of fluid. This facilitates cortical and cellular cleanup in the capsular bag. With in-the-bag (capsular) fixation of the IOL the optic stays fully in the bag and is in direct contact with the posterior capsule and the IOL optic barrier effect is maximized. If one or both haptics are not placed in the bag, cells may grow posteriorly toward the visual axis in a potential created space.[22] The anterior capsulorhexis should be completely centered on the optic, i.e. the capsulorhexis should be in complete contact with the IOL optic 360 degrees around to induce less PCO development.[23, 24] A capsulorhexis that is partly on and off the IOL optic

leads to capsular bag shrinkage exerting an asymmetrical force down on the IOL, causing the IOL to tilt away from the posterior capsule. The LECs tend to penetrate under the IOL where the capsulorhexis is off the IOL surface.[24 A capsulorhexis completely centered on the IOL optics is easier to achieve surgically when the optic is larger.

IOL design has improved considerably the last decades, and this has further contributed to the reduction in PCO. The AcrySof IOL was introduced by Alcon Laboratories in 1993, and in the early clinical trials the German surgeon Echkard Medhorn observed that this IOL had remarkable clear posterior capsules.[13] Originally researchers misattributed the PCO preventing property of the AcrySof IOLs to be caused by the hydrophobic acrylic material. In the late nineties animal studies by Nishi et al showed that PCO inhibition may be dependent on IOL design, i.e. the sharp edge, and not material.[25, 26] Later on several clinical studies also showed that it was the sharp posterior edge and not the hydrophobic acrylic material that was causing less PCO. Currently the main IOL related factor known to reduce PCO development is a sharp optic edge.[27-29]

The advantage of the posterior edge is mainly showed in studies of 1-3 years, and is only shown after 5 years in the silicone IOL.[29] The sharp-edged design creates a bending of the posterior capsule, and the fibrosis occurring in the bag after IOL implantation causes the posterior capsule to be pulled against the anterior capsule in in a shrink-wrap fashion, leading to the fusing-together of the anterior and posterior capsules. [30] The IOL and the sharp edge are thereby pushed against the posterior capsule creating a mechanical barrier against proliferating lens epithelial cells (LECs) behind the IOL. One study created a mathematical model of the forces between an IOL and the capsule.[31]

Even though the sharp posterior edge is considered the most important PCO inhibiting factor, it is still not clear weather different optic materials also may offer advantages over one another in terms of PCO inhibition. In the publications of a series of histological and immune histochemical studies of explanted IOLs, Linnola et al launched the "Linnola sandwich theory" in year 2000 as an explanation of why the hydrophobic acrylic IOLs may have less PCO than the PMMA and silicone IOLs. This theory suggests that the bio adhesive forces between the hydrophobic acrylic IOL material and the capsular bag are stronger than between other IOL materials and the capsular bag. They suggested that fibronectin is the major extracellular protein responsible for this stronger attachment, because of its stronger binding to the hydrophobic acrylic material than to other IOL materials.[32, 33]

Several clinical studies with duration of 1-3 years studies have shown that hydrophobic acrylic IOLs were associated with less PCO than silicone IOLs, but most of these studies compared acrylic IOLs with sharp edges to silicone IOLs with round edges.[34, 35] Other clinical studies have shown non-significant trends of silicon IOLs having less PCO than hydrophobic acrylic IOLs.[36] [37]

There was no significant differences in PCO prevention between different IOL optic materials (hydrophobic acrylic, hydrophilic acrylic, PMMA, silicone) in a meta-analysis (Cochrane review), although the silicone material induced less PCO in several studies.[38] Several of the studies in the meta-analysis compared acrylic IOLs with sharp edges with silicone IOLs with round edges, which complicates the data.

Some studies have shown less PCO development with the hydrophobic acrylic material than with the hydrophilic acrylic material.[39] This is explained by the quality and sharpness of the sharp edge profile rather than the material.

Hydrophobic acrylic and silicone IOLs have in electron microscopy studies been shown to have sharper posterior optic square edge than most hydrophilic acrylic IOLs.[40] This is likely because of the posterior edge profile of hydrophilic materials are damaged in the manufacturing process in which they are lathe cut in a dehydrated state, then rehydrated and then dried and polished to remove processing burr. Different hydrophobic acrylic IOLs also differ in edge profiles, and the sharper the edge, the better the PCO prevention.[41] The limit the material puts on the manufacturing process seems to determine the sharpness of the edge profile. However, currently Bausch&Lomb launches a hydrophilic micro incision IOL (INCISE), which they claim have one of the sharpest edges on the market.

To inhibit PCO the best, the optic edge should be sharp 360 degrees around and not interrupted in the optic-haptic junction. An interrupted sharp edge in the optic-haptic junctions will lead to centripetal LEC migration behind the IOL optic in the area of the junction.[42]

Posterior convex and biconvex IOLs have been shown to induce less PCO. [43] Retro angulation of the IOL haptics or anterior capsule fibrosis (ACO) can potentially increase the retropulsive effect of the pressure barrier created by the sharp edge.[13] Increasing hydrophobicity of the IOL material (eg, silicone>hydrophobic acrylic> PMMA>hydrophilic materials) seems to increase the amount of ACO. More ACO may increase the retropulsive force pushing the IOL against the posterior capsule, resulting in better PCO prevention. The drawback is that ACO may hinder visualization of the peripheral retina and can cause decentration and tilting of the IOL.

1.5 METHODS USED TO ASSESS PCO

Several retroillumination image analysis systems have in the last decades been used to quantify PCO, and they are known by various acronyms such as the semiobjective system POCOman, the subjective system EPCO and the objective systems POCO and AQUA. They have been used in a vast number of studies and have relative advantages and disadvantages.[44] [45, 46] Scheimpflug images have also been used to assess PCO.[47]

In addition Nd: YAG capsulotomy rates have been used for many years to assess the amount of PCO development.

1.6 PCO IN THE LONG TIME RUN

The follow-up times for most PCO studies are 1- 3 years. Only a few studies have follow-up times of 5 year or more. Many patients will live more than 5 years after cataract surgery. The average life expectancy has increased by 10 years during the last 50 years in the European Union (EU) countries, Japan, and the USA. In the EU the expected lifespan for men is about 76 years and for women 82 years.[48]. The life expectancy at age 65 years in the EU, i.e., the mean number of years still to be lived by a man or a woman who has reached age 65, is about 21 years for women and 17 years for men. The life expectancy in Sweden has increased by 2 years for men and 1.5 years for women in the last 10 years. In 2010, the life expectancies for women and men were 83.5 and 79.5 years, respectively.[49] Of the cataract surgeries reported to the Swedish National Cataract register in 2010, 29% of the operated patients were younger than 70 years. The average age of Swedish patients undergoing phacoemulsification was 74.2 years in 2010.[50]

In addition, refractive lens exchange is performed in patients much younger, and IOL implantation also is performed in children. This indicates that many patients will live more than 10 years after phacoemulsification surgery, and that sustained PCO inhibition over time is important. Evaluation of PCO development over the long term after surgery is therefore of high interest.

The few PCO studies with duration of 5 years or more have reported reduced PCO preventing effect of the sharp posterior edge in the long time run, which emphasize the need for longtime studies of PCO.[51, 52]

2 LENS GLISTENINGS

2.1 DEFINITION

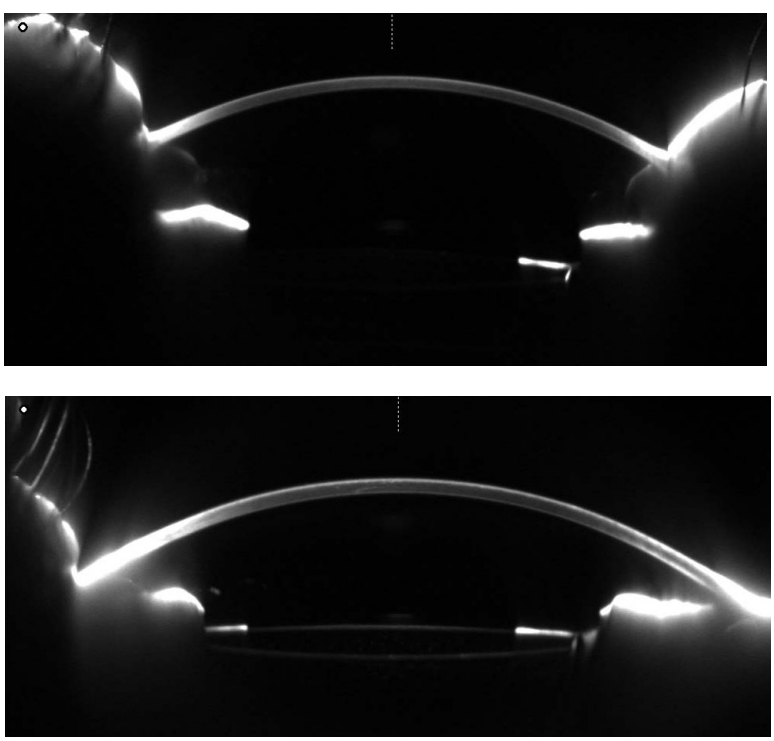
Glistenings are fluid-filled micro vacuoles that form within the matrix of the intraocular lens (IOL) when immersed in an aqueous environment. The hydrophobic acrylic IOL is the IOL that has received most of the attention in association with lens glistenings in the literature. Only a few studies have described the phenomenon in other IOL materials. Although the hydrophobic acrylic IOL has the greater degree of glistenings, this phenomenon have been observed in all IOL materials, including hydrophilic acrylic, silicone and PPMA materials. [53-55]

There has been some confusion in the literature around the terms lens glistening and surface light scattering. Both phenomena depend upon water phase separation and the formation of micro vacuoles containing water in the optic, although the sizes of the vacuoles is much smaller with surface light scattering than with glistenings.[56-60] The trace water molecules forming in the subsurface region causing surface scattering is not clinically seen as micro vacuoles. Glistenings observed clinically are mostly up to 10 μm in diameter, and larger glistenings up to 20 μm may be seen when using temperature fluctuations in in vitro studies.[61, 62] The glistenings have been shown to be distributed throughout the entire lens.[63] However, glistenings, represented by light scattering in Scheimpflug images, have been found to be most prominent near the anterior and posterior IOL surfaces.[64]

2.2 METHODS USED TO ASSESS GLISTENINGS

Common methods used to assess glistenings are subjective/semiquantitative grading of glistening density in the slit lamp,[53, 63] slit lamp photography of the IOL at high magnification with manual grading of the size and number of glistenings[55] and digital image analysis.[65] Scheimpflug photography is also used to quantify glistenings, and this method was first suggested by Klos.[66] With the Scheimpflug method light scattering both inside the optic and at the surface, can be used to assess the degree of glistenings (Figure 2).[67]

Figure 2. Scheimpflug images showing no glistenings in the superior image (the optic is hardly visible), compared to glistenings at the anterior and posterior IOL surface in the inferior image.



The light scattering is measured as computer compatible tape (CCT). This is a measure of reflected light from 0 (black) to 255 (white). Behndig and Mönestam evaluated the Scheimpflug method in a 10 year study and found a strong correlation between postoperative time and light scattering, interpreted as glistenings. The authors found a higher density of glistenings near the surfaces, with the anterior surface having the highest degree of glistenings.[64] In a letter to the editor Mackool and Colin[68] expressed their doubt in using the Scheimpflug method to quantify glistenings. In their opinion the Scheimpflug technique could not differentiate between light scattering due to glistenings and light scattering due to other parameters, such as biological biomaterials, PCO or aqueous-optic interface. Another study refuted this theory.[69]

2.3 MECHANISM OF FORMATION

Polymers with various architectural structures are used in the manufacturing of IOLs. Micro voids can be found within the network of the polymers. When immersed in an aqueous environment for an extended time, the polymers generally absorb water. The amount of water absorbed in relation to IOL weight (water absorption rate) varies in different IOL materials. The currently available hydrophobic IOLs generally have a water absorption rate of less than 1 %.[70] The water is present in the form of vapor within the polymer network and is therefore not visible. However, a visible water drop may form if water vapor detaches from its surrounding matter and gathers into a void within the polymer. The micro vacuoles have a sparkling appearance because there is a significant difference between the refractive index of water and the IOL

polymer (eg. 1.555 for AcrySof IOLs), leading to refraction of light at the water-polymer interfaces. The term glistening is therefore suitable.

The water absorption rate of IOL polymers changes with various temperature.[70] The glass transition temperature (Tg) marks the transition temperature from where the polymer exhibits rigid properties (lower temperatures) to where it is flexible (higher temperatures). When the temperature is below the glass transition temperature, water absorption is minimal for hydrophobic acrylic IOLs. However, water absorption increases when the polymer start to soften at temperatures above Tg. The currently used hydrophobic acrylic polymers normally have Tgs close to room temperature.

If the IOL is placed in warm water, the polymer becomes oversaturated. The excess of water gathers inside the voids within the polymer network. If the temperature is then lowered, the water will be visible as glistenings because of phase-separation. It is likely that small fluctuations in temperature in aqueous humor may lead to IOL glistenings in vivo. [57] Glistening formation is not observed when the IOL is placed in water below the Tg of the IOL material, e.g. at 15 degrees C, as shown in Japanese studies.[58]

The U.S. Food and Drug Administration (FDA) has recently suggested a different mechanism for glistening formation.[71] They propose that hydrophilic impurities are generated during polymerization in the manufacturing process of IOLs. The impurities are believed to segregate into polymer voids, leading to an osmotic pressure difference between the cavity and the aqueous humor. The influx of water into the cavity is thought to deform the surrounding polymer until it cracks or tears. This process would continue until equilibrium is achieved.

2.4 FACTORS INFLUENCING GLISTENING FORMATION

Several factors, such as IOL optic material, manufacturing technique, IOL packaging,[72] IOL dioptric power, [73] changes in temperature,[57] glaucoma, [74] breakdown of the blood–aqueous barrier,[75] and the use of anti-inflammatory eye drops containing a surfactant[67, 76] and antiglaucoma eye drops [74, 77] may influence glistening formation. Some studies indicate that the IOL dioptric power influence the glistening formation,[78] while others have not found any association.[79]

Hydrophobic acrylic IOLs are manufactured with 2 different processes: cast molding and lathe cutting. In the cast-molding process a monomeric mixture is polymerized in a casting mold and thereafter detached from the mold. This method is suitable for large-scale production. The disadvantage may be heterogeneous parts containing unreacted monomers. In the lathe cutting process a monomeric mixture is polymerized into acrylic sheets, and subsequently each IOL is lathe-cut for polishing to remove heterogeneous parts. This process may have a higher cost because of more processing steps. Studies have shown significantly more glistening with the cast molding process.[80]

The first reports of glistenings in the AcrySof IOLs were related to IOLs packaged in the AcryPak system, which was not used in the clinical trials before FDA approval. The AcryPac, which contained both the IOL and a folder, underwent terminal sterilization within this plastic case. Some authors believed the terminal sterilization facilitated lens glistening by changing the microenvironment.[72] The AcryPak was voluntarily withdrawn by Alcon.

Studies show that glistening also occur with the currently Wagon Wheel–packaged AcrySof IOLs, even though the earlier used AcryPac- packaged IOLs demonstrated significantly more glistening formation.[72] The core studies of this IOL used the Wagon Wheel- packaged IOLs.

2.5 INFLUENCE ON VISUAL FUNCTION

There is still not an agreement in the literature weather lens glistening influence visual function or not.

Several studies reported that the presence of glistenings does not affect visual function. One study found no correlation between lens glistenings and visual acuity, glare testing, wavefront analysis or contrast sensitivity, except there was a borderline correlation with contrast sensitivity in the high spatial resolution patch.[65] Another intrapatient study compared the same acrylic (AcrySof MA60BM) and silicone [SI40NB; Abbott Medical Optics (previously Allergan)] IOLs as in our study. Despite the finding of glistenings in 40% of the acrylic IOL, there was no significant difference in visual function between the 2 IOLs.[81] Hayashi et al found that visual function and optical aberrations were not significantly different for eyes implanted with a hydrophobic acrylic IOL compared with eyes implanted with silicone or PMMA IOLs more than 10 years after implantation, even though there was significantly more glistenings with the acrylic IOL.[82] Colin et al reported no statistically significant difference in VA, glare disability, and contrast sensitivity between groups with or without glistenings.[83]

Some clinical studies have reported an influence on visual function by lens glistenings. One study evaluated glistenings effect on visual function in 42 eyes

implanted with Wagon-Wheel packed AcrySof IOL 2.4 years postoperatively, and found significantly more glistenings in IOLs with 2+ or greater glistenings compared with IOLs with less than 2+ glistenings. There was no statistically significant difference in glare testing and contrast sensitivity between the same groups in this study.[81] Another study found that a higher degree of glistenings decreased contrast sensitivity.[63] One study found that glistenings influenced contrast sensitivity at the higher spatial frequency. However, there appear to be some discontinuities in this study, as earlier criticized.[70]

2.6 PROGRESSION OVER TIME

There is a controversy in the literature wether lens glistenings continue to increase over time or stabilize and stop developing after a period of initial increase.

A recent retrospective study with 260 eyes implanted with AcrySof reported no significant difference regarding glistenings incidence and severity in eyes with a follow-up shorter than 24 months compared to eyes with a longer follow-up.[74] Miyata et al. followed 129 eyes with AcrySof IOLs for 20 months in a prospective clinical study.[61] The glistenings became stable a few months after they first appeared. This was in concordance with an experimental study performed by the same authors, in which they immersed the IOLs in solution and decreased the temperature from 50°C to 35°C. No further changes in glistening formation was seen between 10 to 60 days after immersion.[61]

Other studies found that glistenings increase with postoperative time.[78] One study confirmed the increase in mean glistening density up to the last follow-up at 28 months.[84] Tognetto et al. evaluated glistenings in 7 different

foldable IOLs, including 2 silicone, 3 hydrophilic acrylic and 2 hydrophobic acrylic (AcrySof and Sensar) IOLs. All materials had different degrees of glistenings. In all groups, except the AcrySof, the percentage of eyes having glistenings increased up to 90 days, and then stabilized. The AcrySof IOL group increased continuously up to 720 days. The mean glistening grade increased in all groups up to 180 days, except for the AcrySof and the 911A (silicone) IOLs, which increased continuously.[53]

2.7 GLISTENINGS IN HYDROPHOBIC ACRYLIC LENSES

The currently used hydrophobic acrylic IOLs are manufactured from different materials and by different manufacturing processes. The 2 main manufacturing methods are mentioned earlier; direct cast molding and sheet casting and lathing.

Most studies in the literature have investigated glistening in the AcrySof material, and only a few studies have given attention to some, but not all, of the other hydrophobic acrylic IOLs on the market. Despite the scarce literature on other hydrophobic acrylic IOLs, it is likely that various hydrophobic acrylic IOLs exhibit different tendencies towards glistening formation.

An early study of the VA60CB (Acryfold) IOL (Hoya Corp., Japan), which is manufactured by lathe-cutting, showed that glistening was found in a much higher percentage in the Acryfold IOLs (62.1%) than in SA30AL (AcrySof) IOLs (35.3%). The same study also investigated the Sensar AR40e IOL (Abbott Medical Optics), which showed no glistening 6-18 months after implantation.[85] A team in Hoya Surgical Optics GmbH implemented improvements in the polymerization and cleaning processes. According to Hoya Corp. continued monitoring of the

manufacturing processes and customer complaints shows that these changes have been effective.[70] The early IOL

models of VA60CA and VA60CB were discontinued and never released outside Japan.

The XACT IOL is a 3-piece IOL launched in USA by Advanced Vision Science (USA), and is available in Japan with the trade name Eternity (Santen, Osaka, Japan). The material was later licensed to Bausch and Lomb, which has launched the same material as a 1-piece IOL (enVista). The XACT/enVista IOLs are the only hydrophobic acrylic IOLs packaged in solution. Clinical studies included in the FDA marketing application for the IOL showed no glistenings between 1 and 6 months in these IOL packaged in the currently used 0.9 % saline solution.[86]

A recent in vitro study reported that continuous manufacturing process improvements in AcrySof IOL materials have resulted in a significant reduction in glistening density (87% reduction in mean density) in AcrySof IOLs manufactured in 2012 compared to AcrySof IOLs manufactured in 2003.[87]

2.8 GLISTENINGS IN SILICONE LENSES

In an in vitro study Miyata et al. evaluated 2 silicone lenses; the SI40NB (Allergan, Inc.) and AQ110NV IOLs (Canon Staar). The IOLs were immersed in physiological saline at 50°C for 2 hours and then immersed in physiological saline at 35°C for 90 days. With slit lamp examination a granular opacity in the SI40NB IOLs and slight optic opacity in the AQ110NV IOLs were noted. These opacities decreased over time, but were still seen in a mild degree up to 90 days. Microvacuoles smaller than 5 μm

in diameter were seen when examining the IOLs under a light microscope. The opacities disappeared in both IOLs after drying.

The AcrySof IOL was shown to have a significantly higher mean vacuolar density than the silicone CeeOn Edge 911A IOL (Pharmacia) after 3 years in a clinical study with 25 patients in each IOL group.[88]

Two silicone IOLs (CeeOn Edge 911A IOL and SI40NB) were among the 7 different IOLs compared in the study by Tognetto et al.[53] Seven days after surgery 9% in the CeeOn Edge IOL group had glistenings, and 90 days after surgery 50% had glistening, with no further increase after that. There was a continuous increase in the mean grade of glistenings over time. In the SI40NB IOL group 47% had glistenings after 7 days and 50% after 30 days, remaining stable after that. The mean grade stabilized after 30 days and was lower than in the CeeOn Edge IOL.

The silicone iris-fixated phakic IOLs Artiflex have also been shown to have glistenings in a clinical study; four out of 20 IOLs were shown to have glistenings. The glistenings were not clinically significant and did not increase over time.[89]

In the early 1990s central haze and brown discoloration was observed in silicone IOLs. This was suggested to be caused by water vapor, which resulted from an anomaly in the curing process or incomplete extraction of large polymers. It was considered clinically insignificant. Improvements in the manufacturing process of silicone IOLs seemed to remove the discoloration.[90]

2.9 GLISTENINGS IN PMMA LENSES

The first observation of lens glistenings was in a PMMA IOL, and was reported in a letter by Ballin in 1984.[54] A 4 year prospective study of 73 eyes implanted with a PMMA IOL showed glistenings in 89% of the IOLs. No glistenings was observed before 3 years, and after 7 years all the IOLs had glistenings. The changes were first seen near the anterior and posterior surfaces and then became diffuse throughout the entire optic. There was no influence on the visual function.[55]

Glistenings must be differentiated from "snowflake degeneration" in PMMA IOLs. This may occur as long as 10 years after implantation and is a slow, progressive opacification of the PMMA IOL. The snowflake degeneration was observed in PMMA manufactured by injection molding and implanted in the early 1980s and mid1990s. It was suggested it resulted from UV exposure. It was found spherical lesions in explanted IOLs in the central and midperipheral parts of the optic, interpreted as degenerated PMMA material. The peripheral zone of the optic are free of "snowflakes", probably because it is protected by the iris.[91]

3 SUBJECTIVE VISUAL FUNCTION

3.1 INTRODUCTION

The goals of cataract surgery are improvement in visual function and quality of life. Visual acuity remains one of the most important clinical outcomes after cataract surgery for the surgeon. However, the perceived ability to perform everyday task is probably the most important outcome for the patient. The use of visual acuity neither estimates the full impact of cataract before surgery nor assesses the full benefit for the patient after surgery. Hence, visual acuity is a too blunt measure of clinical outcome after cataract surgery used alone. Information about how patients experience their visual function is important.

Assessment of patient-reported visual function has in the last decades increasingly been used to measure the impact of cataract surgery on visual disability.

3.2 QUESTIONNAIRES AND RASCH ANALYSIS

Many questionnaires have been developed for the purpose of measuring patient reported visual function.[92-96] Most of the questionnaires have been developed using classical test theory (CCT), which have several shortcomings.[97]

CCT has two main problems. Firstly CCT does not provide for interval-level measurement, and secondly it does not allow insight into the psychometric properties of the questionnaire. Likert scoring, used in traditional CCT, uses scores that are simple sums of ordinal values, like 1, 2, 3, 4 which are applied to response options (no difficulty, some difficulty, great difficulty, very great difficulty), and then the sum of these ordinal values is calculated across all questions. This scoring is built

on two wrong assumptions. It assumes that the quantitative difference between each response option is equal and that each item/question has the same value. However, neither assumption is valid, which make scoring non- linear.

These problems can be solved with Rasch analysis, which is a mathematical model based on probabilistic relationships between items (e.g., questions) and persons (e.g., patients). With the Rasch model the probability of a specified response is modeled as a function of person and item parameters. The probability of a response is modeled as a logistic function of the difference between the person and item parameter. The Rash model characterizes the ability of the patients and the difficulty of the items as locations on a continuous latent variable. Rasch analysis makes interval level measurement possible from raw questionnaire data, and therefore parametrical statistics can be used on the measurement data. This analysis also provides insights into psychometric properties of the questionnaires.

The advantages of improved psychometric assessment and interval-level scoring have led to the development of new questionnaires[98, 99] using Rasch analysis and to reengineering of existing questionnaires.[100-104] A study compared 16 Rasch-scaled cataract surgery questionnaires to find the most responsive to cataract surgery (ability to detect clinically important change). The study found that all the Rasch-scaled questionnaires tested are psychometrically robust and suitable for use, but the Catquest- 9SF[104] was the most responsive.

3.3 VARIABLES INFLUENCING SUBJECTIVE VISUAL FUNCTION

All county councils in Sweden agreed in 2003 to let patients select their health treatment providers, while allowing the money to follow the patients. Also, a political

founded national guarantee for a maximum waiting time for treatment of 3 months was implemented on November 2005 in Sweden. [105] These two health policy decisions made it more important to evaluate the at the time large variations in indications for cataract surgery. To ensure that the entire population in Sweden would receive health care on equal terms, an instrument, Nationell Indikationsmodell för kataraktextraktion (NIKE) was proposed by Lundström et al. in 2006.[106] The purpose was that this instrument should be used as a new clinical tool for establishing levels of indications for cataract surgery. A second version of NIKE is now widely used in Sweden.

With this background it became increasingly important to identify and assess potential predictors with influence on patient assessed visual function after surgery, because this may be helpful when setting indications for surgery. There may be many potential predictors influencing the subjective visual function after surgery, and it is important to keep this in mind when deciding the levels of indications and informing the patients before cataract surgery.

Many developed countries have waiting lists for cataract surgery, and this surgery is usually performed on a first-in, first-out basis. There is not always an apparent relationship between time spent on waiting lists and the urgency of cataract extraction.[107] Many studies have shown an increased incidence of falling with resulting fractures during the waiting time.[108]

Only a few published studies have tried to identify potential factors influencing the duration of waiting time. One study found that the presence of anisometropia shortens the waiting time.[109] Other studies have found that women wait longer than men,[110] older patients wait longer than younger patients, and a

lower socio-economic status increases the time on the waiting list.[111] Regarding the relation between subjective visual function and waiting time, one study showed that patients with a short waiting time of 1 month had a lower preoperative subjective visual function than patients waiting for surgery for 12 months.[108] Another study found no association between the preoperative Visual Functioning index score and the waiting time.[112]

There is scarce published evidence addressing the relation between patient-assessed visual function after cataract surgery and waiting time. One study showed that patients reporting general difficulties in daily living spent shorter time waiting for surgery, and that the waiting time did not significantly influence changes in VF-14 scores.[113]

Several studies have shown a higher preoperative visual function in men than in women,[114-116] indicating that men seek treatment for cataract at a lower level of perceived visual disability. One study found a higher subjective visual function in men also postoperatively.[116] The same study found no significant gender-related differences in CDVA (corrected distance visual acuity) of the operated eye before or after surgery.

One study showed that patients ≥85 years old had on average a good result regarding self-assessed visual function as measured by the Catquest questionnaire, although not as good as younger patients. Patients in the ≥85 years age group had a significantly higher no-benefit outcome than patients in the ≤84 group when no ocular comorbidity was present. However, when ocular comorbidity was present, there was no significant difference regarding no benefit.[117]

Earlier studies have had conflicting results regarding how the preoperative CDVA in the operated eye influences postoperative subjective visual function. Several studies reported that a low CDVA before surgery increases the subjective visual function after surgery.[118, 119] Other studies have shown that when adjusting for ocular comorbidity, the preoperative CDVA does not influence the level of postoperative subjective visual function.[120, 121] The vision of the better eye has been shown to influence the subjective visual function more than the vision of the worse eye.[114, 122].

Many studies have reported higher self-assessed visual function after second eye surgery compared to after first eye surgery.[123-125]

Ocular comorbidity has been shown to reduce subjective visual function after cataract surgery. [120, 126, 127]

4 GENERAL AIMS

Paper I: To compare PCO with 3 different IOLs 5 years after phacoemulsification cataract surgery and to evaluate if the centration of the anterior capsulorhexis influences PCO.

Paper II: To compare PCO and ACO with 3 different IOLs 12 years after phacoemulsification cataract surgery.

Paper III: To compare the amount of intraocular lens glistening in 3 different IOLs 12 years after surgery.

Paper IV: To evaluate the influence of preoperative predictive factors on subjective visual function after phacoemulsification cataract surgery.

5 MATERIAL AND METHODS

5.1 PAPER I - PCO AT 5 YEARS

5.1.1 Study design

This was a prospective randomized study. The study was performed during the years 1995-1998, and 180 patients who underwent cataract at St. Erik's Eye Hospital were randomized to implantation with 3 different IOLs: a HSM-PMMA IOL (809C, Pharmacia & Upjohn, Uppsala, Sweden) (n=61), a foldable silicone IOL (SI-40NB, Allergan, Irvine, CA) (n=60), or a foldable hydrophobic acrylic IOL (AcrySof MA60BM, Alcon, Fort Worth, TX) (n=59). The acrylic IOL had a sharp posterior edge and the silicone and the HSM-PMMA IOLs had round posterior edges. The optical diameter of the HSM-PMMA IOL was 5.0 mm. Both the acrylic and silicone IOLs had 6.0 mm optical diameters and loop haptics angulated by 10 degrees. The patients were between 60 and 83 years old (mean, 73 years) at the time of surgery.

5.1.2 Inclusion/exclusion criteria

Patients with corneal pathology, exfoliation syndrome, glaucoma, a history of uveitis or intraocular surgery, preoperative oral steroid therapy, and diabetes mellitus were excluded. The patients had no other ocular pathology except cataract. All the patients had a potential VA of 20/40. Patients with mild macular degeneration were included.

5.1.3 Surgery

Preoperatively the pupil was dilated and topical and subconjunctival anesthesia was administered. One cataract surgeon performed all the operations. A corneoscleral incision was made and the ophthalmic viscoelastic device Healon (Pharmacia, Uppsala) was used. Hydrodissection and hydrodelineation was performed with balanced saline solution (BSS). Phacoemulsification was performed in the capsular bag and irrigation/aspiration with BSS and adrenaline for intraocular infusion was used to remove cortical lens material. The incision was widened and the IOL was implanted in the bag. Topical dexamethasone was prescribed for 3 weeks in a tapered dose after surgery.

5.1.4 Experimental Design

At the 5-year follow-up visit, the corrected distance visual acuity (CDVA) was recorded, the pupil was dilated and a retroillumination digital photograph of the posterior capsule was taken using a slit lamp and photographic setup to evaluate the PCO. The POCOman computer-analysis system was used to analyze the images.[46] The POCOman measures the PCO fraction semi-quantitatively and the PCO severity qualitatively. In this program PCO fraction is defined as the PCO percentage of the total area of the posterior capsule inside the capsulorhexis. The POCOman exploits the concept that the human eye is good at recognizing PCO, but not at quantifying it. To evaluate the PCO with the POCOman program, the IOL optic rim was marked and the capsulorhexis was drawn interactively on the loaded image of the posterior capsule. The posterior capsule was divided into several small segments by an applied grid. All small segments with an area of PCO

exceeding 50% of the segment's total area were semi quantitatively marked by an interactive observer and qualitatively graded as mild, moderate or severe. The PCO fraction (in %) and PCO severity were then calculated by the POCO man program. One observer performed two measurements and the average was calculated.

The same retroillumination images were used to evaluate the position of the anterior capsulorhexis in relation to the anterior optic. The capsulorhexis position was graded as completely centered, i.e. the rhexis was overlapping the IOL optic 360 degrees around, partly decentered, or completely off relative to the anterior optic.

Nd:YAG capsulotomy rate before the 5-year follow-up visit was recorded. Patient-reported complaints and/or a decrease in VA attributable to PCO on the slit-lamp examination were criterion for the need to perform Nd: YAG capsulotomy.

5.1.5 Statistical analysis

Kruskal-Wallis analysis of variance with multiple comparisons was used to analyze the PCO fraction and severity and the CDVA. The PCO rates at various positions of the anterior capsulorhexis was analyzed with the Mann-Whitney U test. The chi-square test was used to compare the Nd: YAG capsulotomy rates between the groups.

5.2 PAPER II -PCO AT 12 YEARS

5.2.1 Study design

Prospective randomized study with 12 years of follow-up. The study was en extended follow-up of the study in paper I, the design was the same as described for paper I.

5.2.2 Inclusion/exclusion criteria

The inclusion/exclusion criteria were the same as in paper I.

5.2.3 Surgery

The surgery was performed as described for paper I.

5.2.4 Experimental design

Retroillumination digital photographs of the posterior capsule was taken and the POCOman computer-analysis system was used to analyze the images and calculate the PCO fraction and severity in a similar fashion as described in paper I.

Slit lamp digital photographs of the anterior capsule were taken to evaluate the ACO. ACO was graded subjectively both directly at the slit lamp and by evaluating the anterior capsule photographs. We combined one image taken at the nasal side and on image taken on the temporal side to produce one image of the entire anterior capsule. A subjective grading system previously described was used to grade the ACO. [128] We evaluated two subtypes of ACO: the ACO at the capsulorhexis edge and ACO of the entire anterior capsule that was in contact with the optic, i.e. diffuse ACO. Each subtype was divided into four severity grades:

none (clear/transparent anterior capsule), mild (mild whitening without capsular folding), moderate (moderate whitening, sometimes with areas of capsular folding), and severe (intense whitening, with areas of capsular folding).

The number and timing of Nd: YAG capsulotomies during the 12 year period from surgery to the end of the study were recorded. The median time and the overall survival without Nd: YAG capsulotomy were calculated. The median survival time is when 50% of the patients had undergone Nd: YAG capsulotomy. The overall survival was calculated using Kaplan Meier survival analysis, and the whole period from surgery to 12 years after surgery was taken into account. i.e. the survival is not calculated for the 12 year time end point, but for the whole period. Kaplan Meier survival analysis offers advantages in long time studies with many patients lost to follow-up, because it makes use of the information from these patients up to the date of last examination before they are lost to follow-up.

5.2.5 Statistical analysis

Kruskal-Wallis analysis of variance with multiple comparisons was used to analyze ACO and PCO fraction and severity. The survival rate without Nd:YAG capsulotomy was calculated with survival analysis with Cox regression. The Wilcoxon-Gehan exact test with pairwise comparisons was used to analyze the overall survival between the groups. Kaplan-Meier curves was used to illustrate the survival time without Nd:YAG capsulotomy for the three IOLs and for men and women.

5.3 PAPER III- LENS GLISTENINGS

5.3.1 Study design

Prospective randomized study with 12 years of follow-up, an extended follow-up of the study described in paper I. The study design was the same as described for paper I and II.

5.3.2 Inclusion/exclusion criteria

The inclusion/exclusion criteria were the same as in paper I and II.

5.3.3 Surgery

The surgery was performed as described for paper I.

5.3.4 Experimental design

Each eye was photographed with the Pentacam® HR Scheimpflug camera (Oculus Inc., Lynnwood, WA, USA). This noninvasive system uses the principle of Scheimpflug imaging to characterize the anterior ocular segment. Lens and image planes of a camera are normally parallel, and the plane of focus is parallel to the lens and image planes. If the subject is not parallel to the image plane only a small area is in focus with a normal camera. The main difference between the Scheimpflug imaging and conventional techniques is that the object plane, lens plane, and image plane are not parallel to each other, but intersect in a common straight line. The main advantage of the Scheimpflug technique is that it yields a wide depth of focus. This method to measure light scattering and glistening has been described previously.[64, 66, 67] The objectivity is higher with Scheimpflug imaging than subjective staging of glistenings at the slit lamp. This technique also provides information about the axial

location of the glistenings. Objective grading of glistenings with the Scheimpflug technique has been shown to correlate well with clinical grading.[129]

We used a superior and a temporal camera position when taking the Scheimpflug images. The ImageJ image analysis program was subsequently used to analyze the images. This program can be used to quantify the degree of light scattering within the full or part thickness of the IOL from the Scheimpflug images in a 1.5-mm zone at the visual axis. The light-scattering data was further processed in a macro written in Microsoft Excel. The peak light scattering sometimes seen on the posterior IOL, was interpreted as PCO and was therefore discarded by the macro. The degree of light scattering/glistenings was expressed in arbitrary units (AU).
The IOL optic is approximately 500 μm thick. The glistening was evaluated in the entire thickness, in the deep interior (the middle 350 μm) and the very deep interior (the middle 300 μm) of the IOL optic.

5.3.5 Statistical analysis

The lens glistenings among the three IOLs were compared using The Kruskal–Wallis analysis of variance with multiple comparisons. Regression analysis could be used to analyze the influence of IOL power on lens glistenings only in the hydrophobic acrylic group, because too small amount of glistenings appeared in the other groups.

5.4 PAPER IV - SUBJECTIVE VISUAL FUNCION

5.4.1 Study design

This prospective multicenter study included 14 817 patients with cataract who underwent surgery from 2000 to 2006. The data was extracted from the Swedish

National Cataract Register (NCR). Forty-two ophthalmology surgical units in Sweden participated in the study. During the month of March of each year during the study period the Catquest questionnaire was used for all patients who had undergone cataract surgery in the participating surgical units. The patients completed the Catquest questionnaire before and 6 months after surgery. The Catquest questionnaire, which is based on CTT and Likert scoring, was originally used by the Swedish NCR from 1995 for collecting data on subjective visual function after cataract surgery. This questionnaire comprises 17 items. The Rasch-scaled Catquest-9SF questionnaire was developed after assessing and optimizing the Catquest questionnaire using Rasch analysis. The resulting 9 questions in the revised Catquest-9SF were extracted from the Catquest for analysis. The Catquest-9SF questionnaire contains 7 questions about perceived difficulty in performing specific activities during daily life and 2 global questions about general difficulties in performing activities in daily life and about general satisfaction with vision. There are 4 response options to each question, which designates different levels of visual function.

In this study the relations between 10 different predictive factors and 3 response variables were assessed. The nonparametric grading of answers was re-coded by Rasch analysis, making it possible to perform parametric statistical analysis.[104] The first response variable was change in patient-reported visual function from before to 6 months after surgery. The other 2 response variables were both from 6 months after surgery. The second response variable was the average outcome of all the questions in the questionnaire 6 months after surgery, hereafter referred to as mean visual outcome. The third response variable was the question about general satisfaction with vision in the questionnaire 6 months after surgery. The question regarding general

satisfaction also had 4 response options, but in the analyzing process this variable was dichotomized into generally satisfied or generally dissatisfied.

The covariates analyzed in relation to the response variables were

-waiting time before surgery (months)

-gender

-patient age (years)

-corrected distance VA (CDVA) logarithm of the minimum angle of resolution (logMAR) before and after surgery

-a first- or second-eye cataract surgery

-ocular comorbidity (yes/no)

-achieved postoperative refraction (diopters [D])

-correct sign biometry prediction error (D)

- absolute biometry prediction error (D)

The CDVA was first measured in Snellen decimal VA and then converted to logMAR. Macular degeneration, glaucoma, diabetic retinopathy or other ocular diseases were the ocular comorbidities reported in the NCR. The achieved refraction was calculated as the spherical equivalent of the spherical and astigmatic corrections at the final follow-up. The spherical equivalent was categorized into 4 different levels: High myopia (<−2.0 D), myopia (−2 to 0 D), hyperopia (>0 to +2 D), and high hyperopia (>+2 D).

The correct sign biometry prediction error (refractive surprise) was the difference between targeted and actually received refraction, and was calculated in spherical equivalents. This covariate was also categorized into 4 levels:

Unexpectedly high minus (<−2 D), unexpected minus (−2 to 0 D), unexpected plus (>0 to +2 D), or unexpectedly high plus (>+2 D).

5.4.2 Statistical analysis

Parametric statistics could be used, because the questionnaire raw data was recoded using Rasch analysis. The logit unit, which is the natural log-odds of a participant being successful versus being unsuccessful at a task,[102] was used for the response variables change in subjective visual function and the mean subjective visual function.

In all analysis multivariate statistics were used. Multiple regression was used for the continuous response variables change in subjective visual function and mean visual outcome, with dummy variables when appropriate. The third response variable, the global question about satisfaction with vision, was dichotomized and logistic regression was used. For all statistical analysis we used STATA/IC 10.1 (Stata Corp., College Station, TX).

6 RESULTS AND DISCUSSION

6.1 PAPER I AND II – PCO AT 5 AND 12 YEARS

6.1.1 Patient data at 5 years

At the 5 year follow-up, 28 of the initial 180 patients were lost to follow-up. The statistical analysis included 152 patients.

6.1.2 CDVA and PCO at 5 years

There was no significant difference in CDVA in the 3 IOLs. The previously Nd: YAG treated patients were excluded in the analysis of CDVA.

The POCOman PCO calculations were performed both when the patients who had previously undergone an Nd: YAG capsulotomy were included, and when they were excluded. The patients that had undergone Nd: YAG capsulotomy before the 5 year control were given the highest rank in the statistical analysis of PCO and excluded from further image analysis.

In the calculation of POCOman PCO scores including the Nd: YAG treated patients the HSM-PMMA IOL group had a significantly higher fraction (%) of PCO than the silicone ($P = 0.00003$) and the acrylic ($P = 0.000001$) IOL groups, but there was no significant difference between the silicone and the acrylic ($P = 1.0$) IOL groups. The HSM-PMMA IOL group also had significantly higher PCO severity than the silicone ($P = 0.000082$) and acrylic ($P = 0.000001$) IOL groups, but there was no significant difference between the silicone and the acrylic ($P = 1.0$) IOL groups. When the Nd: YAG treated patients were excluded in the calculation, the same relationships in PCO fraction and PCO severity between the three IOL groups were also true (but with slightly different P values).

6.1.3 Nd: YAG capsulotomy rates at 5 years

At the 5 year control the HSM-PMMA IOL group had a significantly higher Nd:YAG rate than the than the silicone ($P = 0.012$) and acrylic ($P<0.0001$) IOL groups. The silicone group had a significantly ($P = 0.0068$) higher Nd:YAG rate than the acrylic group up to 5 years (Table 1). After the 5 year control (when the eyes evaluated to need Nd:YAG capsulotomy at the 5 year control were included) the Nd:YAG frequency in the HSM-PMMA IOL group still was significantly higher than in the silicone ($p = 0.0051$) and AcrySof ($p = 0.0001$) groups. However, it was no significant difference in Nd:YAG capsulotomy rate between the silicone and AcrySof ($p = 0.21$) IOL groups after the 5 year control. The Nd: YAG rates before and after the 5 year control are listed in table 1.

Table 1. Nd:YAG frequency before and after the 5-year follow-up.

Parameter	**HSM PMMA 809C**	**Silicone SI-40NB**	**AcrySof MA60BM**
	n= 54	n= 48	n= 50
Nd:YAG frequency(%) at the 5-year follow-up	54	29	8
Nd:YAG frequency(%) after the 5-year follow-up	61	33	22

6.1.4 Anterior capsulorhexis at 5 years

We found an anterior capsulorhexis with complete centration on the anterior optic 360 degrees around in 90 patients, and a partly decentred capsulorhexis in 53 patients.

In 4 patients the capsulorhexis was completely off the optic, and this group was excluded from the analysis since they were so few. Taking into account all the patients in the study, the PCO fraction (p= 0.0076) and severity (p=

0.0081) were significantly higher when the anterior capsulorhexis was partly off the IOL optic than when it was completely in contact with the IOL optic.

This was not true when comparing separately in each of the 3 IOL groups. There was no significant difference between eyes with centered and partly decentered capsulorhexis within each of the 3 IOL groups.

6.1.5 Patient data at 12 years

After the mean follow up time of 12.3 years (11.3 to 13.4 years) 74 patients were lost to follow-up and 106 patients were eligible for further analysis. The patients we knew had undergone Nd: YAG capsulotomy were not asked to come to the 12 year examination. 46 patients came to the 12 year follow-up and were photographed. The photographs were evaluated for ACO in 46 patients and for PCO in 36 patients. Nine patients who came to the 12 year follow-up had already had a

Nd: YAG capsulotomy elsewhere and 1 patient was excluded from the PCO analysis because of poor image quality.

6.1.6 PCO at 12 years

The HSM-PMMA IOL had significantly higher PCO fraction than the silicone IOL ($P < 0.05$), but between the HSM-PMMA and acrylic IOLs ($P = 0.45$) or the silicone and acrylic IOLs ($P = 1.0$) there was no significant difference.

There was no significant difference regarding PCO severity between the HSM-PPMA and silicone ($P = 0.052$), the HSM-PMMA and acrylic IOLs ($P = 0.47$) or the silicone and acrylic IOLs ($P = 1.0$).

6.1.7 Survival without Nd: YAG capsulotomy during 12 years

One-hundred-and- seventy-nine patients were included in the statistical analysis of the median and overall Nd: YAG free survival time. One patient in the silicone group was excluded because of intraoperative capsule rupture.

The median survival time without Nd:YAG capsulotomy was 53 months in the PMMA, exceeded 150 months in the silicone, and was 108 months in the acrylic IOL group. The acrylic IOL had a significantly higher overall survival without Nd: YAG than the PMMA IOL ($P < 0.001$). There was no significant difference in overall survival between the PMMA and silicone (P=0.073) or the acrylic and silicone (P = 0.17). Because the median time of Nd:YAG-free survival was highest in the silicone group, this result may seem contradictory. However, in the calculation of the overall survival the whole survival curve from surgery to 12.3 years after surgery is taken into consideration. Events in the start of the curve, when more patients were at risk, were more important than later.

The median survival time without an Nd:YAG capsulotomy in men exceeded 150 months and was 63 months in women. There was no significant difference in overall survival (P =0.173) between men and women.

6.1.8 ACO at 12 years

The silicone IOL had significantly more edge ACO than the acrylic IOL evaluated in photographs. ($P = 0.041$), but there was no significant difference between the

silicone and the PMMA IOLs (P = 1.0) and the acryl and the PMMA IOLs (P = 0.067).

Edge ACO evaluated clinically at the slit lamp (P =0.136), diffuse ACO evaluated at the slit lamp (P =0.246) or in photos (P = 0.479) did not differ significantly between the three lenses.

6.1.9 Discussion paper I and II - PCO at 5 and 12 years

It is important to inhibit PCO development in a long period after surgery, since many patients will live more than 10 years after phacoemulsification surgery.
The results from our studies indicate that even though a sharp-edged hydrophobic acrylic IOL may delay PCO development in the early years after surgery, the PCO protective effect of this IOL seems at the best, very low, at 5 years and almost lost at 12 years compared to a round-edged silicone IOL. Both the silicone IOL and the acrylic IOL could prevent PCO in comparison with the PMMA IOL after 5 years, but after 12 years this advantage was reduced or lost.

After 12 years all the three IOLs tended to induce about the same amount of PCO, even though the PMMA IOL still had a higher PCO fraction than the silicone IOL after 12 years. In the Kaplan Meier survival analysis there was a better overall Nd: YAG free survival in the acrylic IOL than in the PMMA IOL, i.e. when taking the whole period from surgery to 12 years after surgery for all the patients into consideration. Between the sharp-edged acrylic and the round edged silicone there was no difference in overall survival over the 12 years after surgery, even though the survival curve indicates that the acrylic IOL tend to inhibit PCO better in the early years and is surpassed by the round-edged silicone lens after about 6.5 years, which thereafter has a better Nd: YAG free survival.

There are not many studied in the literature with duration of 5 years or more, and many studies with shorter duration is complicated by the fact that they compare round edge IOLs with sharp edge IOLs. Two earlier studies indicate that a silicone IOL protects better against PCO than a hydrophobic acrylic IOL after 6 and 10 years.[51, 52] Another study showed that 10 years after surgery the Nd:YAG capsulotomy rates with silicone and hydrophobic acrylic IOLs were lower than those with PMMA IOLs, and there was no significant differences in Nd:YAG rates between a sharp-edged acrylic IOL and a round-edged silicone IOL.[82]

The reason behind why the acrylic IOL seems to lose the advantage regarding PCO inhibition it had in the earlier years after surgery, is probably loss of the barrier effect of the sharp edge. This delayed barrier failure is a result of late proliferation of LECs and creation of an emerging Soemmering ring in the peripheral capsular bag. The mechanical pressure from the Soemmering ring break the seal between the fused anterior and posterior capsule leaves. The barrier effect of the sharp edge is thereby lost and the LECs are free to migrate into the posterior capsule behind the optic.

The silicone IOL seems to offer effective protection against PCO in the long time run. This may reflect a specific material property. The silicone material is thought to have a higher adhesiveness to collagen and vitronectine and also to catalyze transdifferation of LECs into myofibroblasts, which lays down collagen. This creates a strong sealing `glue` at the sharp edge between the anterior and posterior capsule, which probably can withstand the mechanical pressure from the proliferating LECs for a longer time.

Previous clinical and autopsy studies have reported more ACO with silicone IOLs than with acrylic IOLs.[15, 130, 131] A high degree of ACO in silicone

lenses may create a greater backward pressure, which mechanically hinder LECS to migrate.

In conclusion, 5 to 12 years after surgery a sharp-edged acrylic IOL could not prevent PCO in comparison to a round-edged silicone IOL. According to the Nd:YAG free survival curve the acrylic IOL seemed to protect against PCO the best in the early years, but was surpassed by the silicone IOL after about 6.5 years. The total PCO protection benefit during the entire 12 year period, as reflected by the overall survival, seemed to be the same for both the acrylic and the silicone IOLs.

6.2 PAPER III – LENS GLISTENINGS

6.2.1 Patient data

Forty-six patients were available for evaluation of lens glistenings after a median follow-up time of 12.2 years (11.3 to 13.4 years). Eleven of the eyes were in the PMMA IOL group, 16 eyes were in the silicone IOL group and 19 eyes were in the hydrophobic acrylic IOL group.

6.2.2 Lens glistenings

All 3 IOL groups had glistenings. Considering the entire thickness of the optic, the median amounts of lens glistenings were 0 AU (range, 0–15.9) in the PMMA IOL, 256.1 AU (range, 0–967.7) in the silicone IOL and 662.0 AU (range, 74.6–1591.1) in the hydrophobic acrylic IOL. There was significantly more lens glistenings in the hydrophobic acrylic IOL than in the silicone ($p = 0.003$) and the PMMA ($p = 0.000$) IOLs. This relation was also true for the deep and the very deep interior glistenings, but with different p-values. The silicone IOL had significantly more lens glistenings

than the PMMA lens (p = 0.048) regarding glistenings in the entire thickness of the optic. There was no significant difference between the silicone and the PMMA IOLs considering the deep (P = 0.08) and the very deep glistenings (P = 0.10).

6.2.3 Influence of IOL dioptric power on lens glistenings

The degree of lens glistenings in the hydrophobic acrylic IOL group was not influenced by the IOL dioptric power (P = 0.64). Statistical analysis could not be performed in the other 2 IOL groups, because the degree of glistenings was too low.

6.2.4 Discussion paper III – lens glistenings

In this 12 year prospective study, the degree of lens glistenings was found to be significantly higher in the hydrophobic acrylic IOL than in the silicone and HSM-PMMA IOLs. The silicone IOL had very little glistenings, but it had significantly more than the PMMA, which had almost no glistenings.

Previously there has been very little research on glistenings in the silicone and PMMA IOLs, and to my knowledge no studies with such a long follow-up time as in our study. This study shows that even after a very long follow-up time of 12 years, these 2 IOLs still do not develop a substantial amount of glistenings. One study found no glistenings after 3 years in a PMMA IOL, but 7 years after surgery all the PMMA IOLs had some degree of glistenings.[55] Our result is not in concordance with this, showing almost no glistenings in the PMMA IOL after 12 years.

One study compared glistenings in 7 different IOLs, and included both the same silicone IOL as in our study as well as an AcrySof IOL. The AcrySof IOL was shown to have significantly more glistenings than the other IOLs both after 180 days, 360 days and at the last follow-up 2 years after surgery. The mean grade of glistenings in the SI-40NB IOL increased up to 180 days postoperatively and remained stable thereafter, and the percentage of SI-40NB IOLs with glistenings increased up to 90 days and then stabilized.[53]

The degree of glistenings in the silicone and PMMA IOLs in our study were too low to evaluate if the IOL dioptric power could have an impact on the glistenings in these 2 IOLs.

In the hydrophobic acrylic IOL there was a normal distribution of the degree of glistenings, and we found no impact of dioptric power on lens glistenings in this IOL. One study agreed and showed that the IOL power does correlate with the amount of glistenings[129]. Some other studies, with larger study population than in our study, found an association between IOL dioptric power and lens glistenings.[73, 74, 78] Our findings may be because of the small study group.

In conclusion, our study shows that even if the degree of glistenings in the AcrySof IOL is higher than in the silicone and PMMA IOLs, there is some glistenings even in the silicone IOL. The PMMA IOL has almost no glistenings after 12 years. The dioptric power did not influence lens glistenings in the hydrophobic acrylic AcrySof IOL after 12 years.

6.3 PAPER IV– SUBJECTIVE VISUAL FUNCTION

6.3.1 Patient -and demographic data

The study included 14817 patients. In 522 patients the targeted refraction was not recorded, and these patients were therefore excluded from the study. Nine patients completed only the preoperative questionnaire, and 15 patients completed only the postoperative questionnaire. It is not possible to calculate the change in subjective visual function in these patients, and they were therefore excluded from further analysis. When not all of the 9 questions were answered, the mean of the remaining questions were used. In total 14271 patients were included in the statistical analysis. The final number analyzed for the response variables change in visual function and mean visual outcome was 14151, because not all parameters were registered correctly in the NCR. Regarding the response variable satisfaction with vision, 13408 patients were included, because all the patients did not answer this global question.

The mean patient age was 75.9 years. There were 64.7% women and 35.3% men. The percentage of patients with ocular comorbidity was 31.1%. First eye surgery was performed in 60.8% and 39.2% had second eye surgery.

6.4.2 Waiting time

A shorter waiting time for surgery led to a higher change in subjective visual function from before to 6 months after surgery (P= 0.003), but it had no significant association with the 2 postoperative variables. The waiting time for surgery did not significantly influence the mean subjective visual outcome postoperatively (P= 0.53) and was not significantly associated with the OR of being generally satisfied (OR, 1.0; $P = 0.52$). This indicates that the patients with a shorter waiting time had lower perceived visual

function before surgery, but after surgery the waiting time did not influence their subjective visual function. The less content patients may have exerted extra pressure on the surgeon to have a prompt operation.

One study was in concordance with our result, and showed that a lower preoperative visual function was associated with a shorter waiting time (1 month compared to 12 months) waiting time.[108] Another study found that the waiting time did not significantly influence the preoperative patient-reported visual function.[112] There are few studies exploring the association between waiting time for surgery and postoperative subjective visual function. One study showed that waiting time did not significantly influence changes in Visual Functioning index score.[113]

6.4.3 Gender

Men had significantly higher mean visual function (P< 0.001) and OR of general satisfaction (OR, 1.27; P< 0.001) after surgery compared with women. However, women had significantly higher change in subjective visual function from before to after surgery compared to men (P 0.001). The reason for this is probably that women had a lower subjective visual function than men before surgery. The higher improvement in self-reported visual function from before to after surgery for women was not enough to make women more content than men postoperatively. Other studies also agree with our result regarding higher subjective visual function in men before surgery.[114-116] One of these studies also agreed with our result in that men had higher subjective visual function than women both before and after surgery.[116]

It is well-known that gender-related differences have been observed in objective and self-reported perceived health in general health care. Women have in

previous research been found to have a higher selective attention to their bodies.[132] The differences in health-related behavior between men and women have been explained with various models. Gender differences in biological makeup in terms of genes, hormones and physiology have been emphasized by some, and others have focused on life circumstances such as work, family and other socially determined factors that may increase the health risk.[133]

In the response variable change in subjective visual function in our study the patient was his or her own control, eliminating the effect of some category of patients, for example women or men, being more prone to be discontent with health.

6.4.4 Age

Younger patients had a significantly higher change in subjective visual function from before to after surgery (P< 0.001) and a significantly higher mean subjective visual function after surgery (P< 0.001) compared to older patients. Age was not associated with the OR of being generally satisfied (OR, 1.0, $P = 0.88$). This indicates that younger patients both have a higher improvement and a better subjective visual function after cataract surgery. One study using the Catquest questionnaire, found that patients ≥85 years old had not as good self-reported visual function as patients ≤84 years old, even though they on average had a good result.[117]

6.4.5 CDVA before and after surgery

A low CDVA before and a high CDVA after surgery were significantly associated with a higher change in subjective visual function (P<0.001) and higher postoperative

mean subjective visual function (P<0.001) and satisfaction with vision (OR preop CDVA, 1.13, P<0.001; OR postop CDVA, 0.37, P< 0.001). This indicates that patients with a low preoperative CDVA and a high postoperative CDVA in the operated eye both have a higher gain and higher postoperative content with vision.

Regarding the preoperative CDVA other studies had varying results. Some studies reported similar results as ours.[118, 119] Others reported that when adjusting for ocular comorbidities, the preoperative CDVA in the operated eye was not significantly associated with subjective visual function.[120, 121] Many studies agreed with our result regarding the postoperative CDVA.[118, 119, 134, 135] One study showed no correlation between postoperative CDVA and satisfaction with vision, which did not agree with our result.[135]

6.4.6 First- or second-eye cataract surgery

The 2 postoperative response variables mean subjective visual function (P<0 0.001) and satisfaction with vision (OR, 1.99, P< 0.001) were significantly higher in second eye surgery patients than in first eye surgery patients. However, first eye surgery patients had significantly higher change in subjective visual function from before to after surgery (P= 0.001). The explanation for this may be that the first eye surgery patients were more dissatisfied before surgery because they may have had bad vision in both eyes compared to second eye surgery patients who may have had good vision in the already operated eye. This is in agreement with other studies, which have shown that the self-reported visual function correlates best with the better eye.[96] In most cases the better eye was the eye which already had undergone cataract surgery. The second eye surgery patients probably had better self-assessed visual function

after surgery, because of good vision in both eyes after cataract surgery with better binocular vision and a lower degree of anisometropia as compared with first eye surgery patients after surgery. Many studies have had findings in agreement with our postoperative result regarding higher subjective visual function after cataract surgery in both eyes as compared to after surgery in only one eye.[123-125]

6.4.7 Ocular comorbidity

Absence of ocular comorbidity was associated with a higher change in subjective visual function (P<0.001), higher postoperative mean visual function (P<0.001) and satisfaction with vision (P<0.001) compared to when ocular comorbidity was present. Many studies, using Likert scoring, agreed with this.[114, 120, 126, 127]

6.4.8 Refractive parameters after surgery

Patients with achieved postoperative myopia (−2 to 0 D) had a significantly higher change in subjective visual function (P= 0.001) and a significantly higher postoperative mean subjective visual function (P= 0.012) compared to patients with achieved hyperopia (>0 to +2 D). In the comparisons of any other categories of this parameter, there were no significant differences in this 2 response variables of self-assessed visual function. Regarding satisfaction with vision the categories of achieved postoperative refraction did not differ from each other, with varying P values.

The reason patients with myopia (−2 to 0 D) had higher subjective visual function, may be that with myopia the patients may be independent of spectacles for near distance reading, whereas with hyperopia the patients need

correction for both near and distance vision. The explanation for the lack of significant differences between the other categories may be that there were large differences in group sizes.

We were surprised to find a higher change in the subjective visual function in patients with a correct sign biometry prediction error (refractive surprise) of unexpected plus (>0 to +2 D) compared to unexpected minus (−2 to 0 D) (P= 0.006). The categories of correct sign biometry prediction error did not have various effects on the postoperative subjective visual function or the odds of being generally satisfied, with varying P values. The actual mean spherical equivalents of the patients in the groups were −2.8, −0.63, +0.37, and +2.1 D, respectively. Some of the group sizes where very small (only 3 % in the (<−2 D) category and 0.8 % in the (>+2 D) group), which may explain the lack of significant differences. Also, in the categories with larger group sizes, the actual mean spherical equivalents of -0.63 in the group with unexpected minus (−2 to 0 D) and + 0.37 in the group with unexpected plus (>0 to +2 D) where very good refractive results and did not differ much from 0 D, which also may be a reason for the lack of significant differences between the categories.

It was also surprising to find that the absolute biometry prediction error did not have any significant association with the change variable (P= 0.70), the postoperative mean visual function (P= 0.70) or the satisfaction with vision variable (OR, 0.94; $P = 0.19$). Other questionnaires, like the Quality of Life Impact of Refractive Correction questionnaire, may be better at finding significant associations between subjective visual function and refractive result after surgery.

7 MAIN CONCLUSIONS

1. There was no difference in the evaluation of PCO between the sharp-edged hydrophobic IOL and the round-edged IOL 5 years after cataract surgery. The HSM-PMMA IOL had more PCO than the other 2 IOLs. The AcrySof IOL had lower Nd:YAG rate than the other two IOLs at the 5-year follow-up.
2. The sharp-edged hydrophobic acrylic and the round-edged silicone IOLs had similar PCO semiquantitive evaluation 12 years after surgery. The acrylic IOL had significantly better overall survival without Nd: YAG capsulotomy than the HSM-PMMA IOL, but between the silicone IOL and the 2 other IOLs there were no significant differences. The silicone IOL had the longest median Nd: YAG free survival time.
3. The hydrophobic acrylic IOL had significantly more lens glistenings than the silicone and the HSM-PMMA IOL 12 years after surgery. The HSM-PMMA IOL had almost no glistenings. The IOL dioptric power did not significantly influence the degree of lens glistenings in the hydrophobic acrylic IOL.
4. A higher change in subjective visual function from before to after surgery was significantly associated with a low preoperative CDVA, no ocular comorbidity, high postoperative CDVA, first-eye surgery, female gender, young age, postoperative myopia, and a correct sign biometry prediction error of plus in comparison with their counterparts. A higher postoperative subjective visual function was significantly associated with a low preoperative CDVA, no ocular comorbidity, a high postoperative CDVA, a second-eye surgery, male gender, young age, and postoperative myopia in comparison with their counterparts. A higher OR of being generally satisfied than dissatisfied was significantly associated with male gender, no ocular comorbidity, second-eye surgery, a low

preoperative CDVA, and a high postoperative CDVA in comparison with their counterparts. The subjective visual function after surgery was not significantly associated with the absolute biometry prediction error.

8 FUTURE PERSPECTIVES

We have been able to delay PCO with modern surgical techniques and sharp-edged IOLs, but not to eradicate it. A sharp-edged design has been shown to reduce PCO during the early years, while lens material may play a role in the long term. The prevention of PCO is unfortunately still the largest unmet need in modern cataract surgery. The struggle to inhibit PCO is difficult and a fight against nature, because LEC migration and transdifferentiation are nature's back-up strategies to the loss of lens tissue.

In the prevention of PCO there are other features related to capsule morphology after IOL insertion that likely play a role. Studies in eyes implanted with disc-shaped or dual-optic IOLs have shown that an open and expanded capsular bag retains transparency.[136-138] This may be due to the concept "no space - no cells" as well as other mechanisms. With no place, there will be no space to grow for the LECs. Also, the inner part of the capsular bag may be constantly irrigated by aqueous humor when the bag is left expanded and open. A capsular bag exposed to stretch or mechanical pressure may result in inhibition of LEC metaplasia, migration and proliferation. Such IOL designs may result in better PCO prevention in the future. Furthermore, these IOLs may, by restricting fibrosis, offer a more flexible capsular bag for an accommodating IOL.

Other research directions have been applied in clinical practice for many years now. Marie-José Tassignon, MD, from Belgium has used the "bag in the lens" IOL design and implantation technique. With this technique a specially designed lens permits the positioning of both the anterior and posterior capsulorhexis inside a fine groove surrounding the optic of the lens.[139] Others have developed a technique of

posterior capsulorhexis with posterior optic buttonholing. A 4.5-mm posterior capsulorhexis is made and a three-piece IOL is pushed behind it (buttonholing), leaving the haptics inside the bag.[140] According to the researches these alternative techniques should prevent LECs from gaining access to the retrolental space.

In the future it would also be interesting to investigate if cataract surgery with femtosecond laser will reduce PCO. The femtosecond lasers may produce a more predictable diameter and centration of the capsulorhexis, and future studies may show if this reduces PCO.

The manufacturers of IOLs are working hard to improve the manufacturing process of IOLs to reduce the amount of glistenings. A good example of this is that the AcrySof IOL, which has received most of the attention regarding lens glistenings, recently has been shown to develop much less glistenings after improvements of the manufacturing processes.[87] This offers hope for future reduction in the degree of lens glistenings.

The new Rasch revised questionnaires, evaluating the relation between cataract surgery and subjective visual function, offer promise for the future as they will produce more reliable results than the old questionnaires based on CTT with Likert scoring. Rasch revised questionnaires could also be used to evaluate the association between PCO and subjective visual function.[141] It is still controversial weather lens glistenings influence visual function. Maybe well-designed studies investigating the potential association between patient-reported visual function and lens glistenings could contribute to this debate?

Furthermore, it could be interesting to investigate how the choice of IOL influence the subjective visual function in relation to cataract surgery; and

whether for instance any of the new premium IOLs (multifocal, toric, accommodating) influence subjective visual function. May performing micro incision cataract surgery (MICS) or femtosecond laser cataract surgery influence subjective visual function?

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