Prevention of postoperative capsular bag opacification using intraocular lenses and endocapsular devices maintaining an open or expanded capsular bag

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Postoperative capsule opacification is a multifactorial physiological consequence of cataract surgery that remains the most common complication of this procedure. A literature review that included several intraocular lenses (IOLs) and endocapsular devices studied in our laboratory found that devices maintaining the capsular bag in an open or expanded state were associated with improved bag clarity. This observed effect likely occurs secondary to the complex interactions of myriad mechanisms, which include formation of a barrier to lens epithelial cell (LEC) migration, mechanical compression of residual LECs, mechanical stretch at the level of the capsule equator, maintenance of overall bag contour, and enhanced endocapsular circulation of aqueous humor. We review the designs of endocapsular devices and IOLs that minimize the degree of postoperative capsule opacification by preventing capsular bag collapse and discuss the underlying mechanisms that contribute to this phenomenon.

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Posterior capsule opacification (PCO) is a well-recognized complication of cataract surgery with intraocular lens (IOL) implantation. Although research has led to improvements in surgical techniques, IOL materials, and design-related factors that have reduced the incidence, PCO remains the most common long-term complication of cataract surgery. The opacifying material can have both cortical/pearl and/or fibrotic components that lead to decreased visual acuity. An effective treatment of this condition is neodymium:YAG (Nd:YAG) laser posterior capsulotomy, which places patients at increased risk for additional vision-related complications and represents a significant financial burden on the healthcare system.[1] Surgical methods currently used to eradicate PCO formation include performance of a primary posterior capsulorhexis combined with optic buttonholing and implantation of the bag-in-the-lens following creation of a primary posterior capsulorhexis equal in size to the anterior capsulorhexis.[2,3]

Anterior capsule opacification (ACO) is essentially a fibrotic entity. Histopathologic studies confirm that the basic ACO lesion consists of proliferated cellular and extracellular matrix components with fibrous metaplasia of anterior lens epithelial cells (LECs).[4–6] The advent of new multifocal and accommodating IOLs has been accompanied by increased concern about the development of ACO, which becomes

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clinically relevant when fibrotic contraction of the anterior capsule leads to anterior capsule shrinkage and constriction of the anterior capsulectomy opening.[7]

The development of IOLs and endocapsular devices that effectively prevent postoperative capsular bag opacification is the subject of ongoing research. It has been hypothesized that endocapsular devices and IOL designs maintaining an open or expanded capsular bag are associated with better bag clarity.[A] These devices and IOLs are the subject of this review. The interaction of myriad mechanisms likely contributes to this observed effect and will be discussed in detail later in this article.

POSTERIOR CAPSULE OPACIFICATION PATHOGENESIS

For a better understanding of the mechanisms of PCO prevention related to the devices and IOLs described in this review, a brief summary of the pathogenic mechanisms of capsular bag opacification is provided. The epithelium of the crystalline lens comprises a single cuboidal sheet of epithelium that consists of an anterior-central region of epithelial cells (A cells) in continuity with epithelium at the equatorial lens bow (E cells).[1] The E cells are characterized by proliferation and posterior migration along the posterior lens capsule, forming large balloon-like bladder cells known as cells of Wedl. These cells are mainly responsible for the Elschnig pearl variant of PCO. The E cells are also implicated in the formation of Soemmerring ring, with proliferative cortical material in the capsular bag fornix. Thus, factors that interfere with Soemmerring ring formation directly contribute to the primary prevention of PCO.[1] The extension of Soemmerring ring material between piggyback IOL optics in the capsular bag also results in interlenticular opacification (ILO).

The A cells are quiescent and have minimal mitotic potential. They tend to undergo transformation into fibrotic tissue in a process that Font and Brownstein termed *pseudofibrous metaplasia*.[8] The A cells are primarily implicated in the pathogenesis of ACO and the fibrotic form of PCO.[8] Anterior capsule fibrosis and opacification tend to occur in areas in which the posterior aspect of the anterior capsule comes in contact with the anterior surface of the IOL optic.[9] Plate-haptic silicone IOLs, which have large areas of contact between the plate and the anterior capsule, are especially predisposed to ACO.[7]

CAPSULAR RINGS AND DEVICES

Endocapsular Equator Ring

In 1991, Hara et al.[10] introduced the concept of an endocapsular equator ring. The equator ring was originally developed to maintain the circular contour of the postoperative capsular bag while remaining compatible with modern small-incision surgical techniques.[11] Called the E-ring, the original device was a closed flexible circle made of silicone; it measured 1.0 mm in width, 1.0 mm in thickness, and 9.0 mm in diameter. The design featured squared edges and a groove on the ring's inner aspect to facilitate IOL loop fixation (Figure 1).

The authors later postulated that the width, thickness, and squared edges of the ring might also prevent PCO through the mechanical inhibition of proliferating LECs at the capsule equator. Studies in rabbits, monkeys, and, more recently, humans have confirmed a PCO preventive effect. In a 1995 study in the rabbit model,[11] 70% of eyes with implanted equator rings maintained transparency of the posterior capsule at a mean postoperative time of 3.5 months. A 1998 study in monkeys showed that eyes with the equator ring in addition to an IOL showed significantly less PCO formation than eyes with an IOL alone.[12] In humans, a PCO preventive effect was first documented in 2007[13] following implantation of the equator ring in 1 eye of a 22-year-old man with atopic cataracts. In this case, clarity of the posterior capsule was maintained in the treated eye 2 years postoperatively.[13] In contrast, the eye that had received an IOL alone developed extensive PCO and Nd:YAG capsulotomy was indicated 2.5 years after surgery. In a much larger 2011 clinical study,[14] the equator ring was implanted in 51 eyes that were followed from 2 to 7 years. Early in the study, the device was optimized for the human capsular bag and its diameter was increased to 9.5 mm. The PCO was again significantly less in the equator ring group than in the control group (4.4 versus 11.4, $P = .005$, with PCO values expressed on a scale ranging from 0 [clear] to 255 [cloudy]).[14] Furthermore, the rate of Nd:YAG laser posterior capsulotomy was markedly different between the equator ring group and the control group; ie, 0% and 45%, respectively.

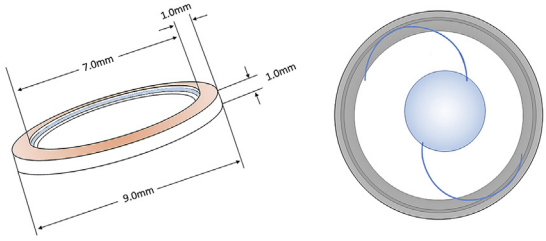

Figure 1. The endocapsular equator ring. *Left*: Overview. *Right*: Anterior view with a standard IOL positioned within the ring. Drawings modified from Hara et al.[13]

Postoperative Scheimpflug photography performed in the clinical studies clearly showed no contact between the IOL and the posterior capsule in the presence of the ring,[12,13] demonstrating that contact between the IOL optic and the posterior capsule may not be necessary for PCO prevention in this circumstance. The equator ring likely prevents postoperative PCO through several other mechanisms. The outward radial stretch that is imposed on the capsule at the equator is effective in maintaining the capsule's circular shape and preventing its collapse. When properly positioned at the capsule equator, there is ample space within the capsular bag and the anterior and posterior capsules are completely separated.[14] Expansion of the capsular bag contributes to the unimpeded circulation of aqueous humor, which contains inhibitory growth factors.[15–21] It is hypothesized that the ring's squared edge counteracts the development of PCO by mechanically disrupting the posterior migration of LECs at the capsule equator.

Capsular Bending Ring

The capsular bending ring is a specially designed capsular tension ring (CTR) that was developed by Nishi et al. in 1998.[22] Made from poly(methyl methacrylate) (PMMA) material, the capsular bending ring is an open band-shaped ring that measures 0.2 mm in thickness, 0.7 mm in width, and 11.0 mm in diameter with pretension and 13.0 mm in diameter when open (Figure 2).[22] Sharp rectangular edges enable the creation of a discontinuous capsular bend at the equator following implantation.

In a 2001 clinical study by Nishi et al.,[23] the ring was implanted in 60 human eyes that were followed for 2 years after phacoemulsification. Eyes with the ring had significantly less PCO, striae, and folds of the posterior capsule than eyes that did not receive the ring, with subjective PCO scores of 0.398 ± 0.248 (SD) and 1.111 ± 0.296, respectively ($P = .01$). Rates of Nd:YAG capsulotomy were also significantly less in the group with the ring. Posterior capsulotomy was indicated in 4 eyes with the ring and 17 eyes without the ring ($P \leq .01$) at a 2-year postoperative assessment. The ring was also effective in preventing ACO. Fibrosis of the anterior capsule was detected in 100% of eyes without the ring and in only 30% of eyes with the ring, which also showed markedly reduced rates of anterior capsule shrinkage.

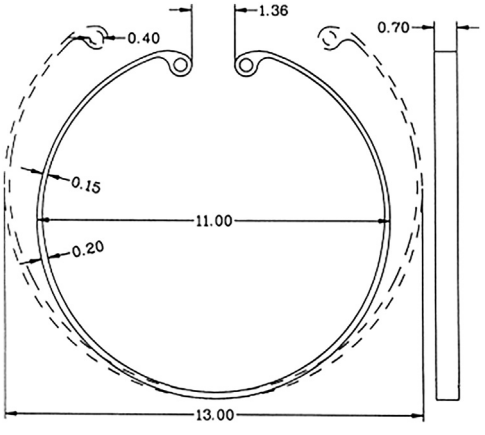

Figure 2. The capsular bending ring with associated dimensions. Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[24]

In a 2008 clinical study by Menapace et al.[24] assessing the capsular bending ring's long-term safety and efficacy in PCO prevention, the ring was implanted in 60 eyes that were followed for up to 3 years postoperatively. In the patients who completed all follow-up examinations through 3 years, the mean regeneratory PCO (pearl form of PCO) was 2.1 in the eyes that had the ring and 4.6 in the eyes that had the IOL alone ($P \leq .001$). The number of quadrants affected by PCO was also significantly reduced; ie, 1.8 and 3.8, respectively ($P \leq .001$). In the eyes assessed beyond 1 year postoperatively, haptic-induced stress folds were present in 0% of eyes with the ring and 42% of eyes in the control group ($P \leq .001$). In eyes with the ring, fibrosis of the anterior capsule leaf was observed only when a capsulorhexis opening smaller than the optic and a bulky high-diopter IOL allowed contact between the capsulorhexis rim and the optic surface. In contrast, anterior capsule fibrosis was widespread in eyes with the IOL alone.[24]

The capsular bending ring is effective in preventing PCO via several mechanisms that are similar to those of Hara et al.'s endocapsular equator ring.[13] As this is an open ring, close apposition of both eyelets is desirable to ensure circumferential capsule bending. Otherwise, the capsular bend will be discontinuous, providing a gateway for equatorial LEC migration. The inhibition of ACO is likely accomplished secondary to the ring's width and its stretching effect on the capsule, which function to maintain the capsulorhexis edge at a distance from the IOL optic.[23,24] Preventing contact between the anterior capsule and the IOL optic avoids the induction of fibrous pseudometaplasia, and subsequent anterior capsule fibrosis and opacification do not occur.[23]

Capsular Adhesion-Preventing Ring

The capsular adhesion-preventing ring was developed by Nagamoto et al. in 2009.[25] Made of PMMA, the ring measures 2.0 mm in height and has an inner diameter of 6.5 mm and an outer diameter of 8.5 mm. The design features 4 grooves that enable

IOL loop fixation and 4 holes that enhance the endocapsular circulation of aqueous humor (Figure 3).[25] As the name suggests, the capsular adhesion-preventing ring holds the anterior capsule away from the posterior capsule, which opens the capsular bag, preventing the formation of anteroposterior capsule adhesions and augmenting the flow of aqueous humor through the ring's holes. In a 2009 study in 5 rabbits,[25] histopathologic examination 8 weeks after surgery showed that eyes implanted with the ring in addition to an IOL had significantly less capsule adhesions, lens fiber regeneration, posterior capsule fibrosis, and posterior capsule wrinkles than eyes with the same IOL alone.

It remains unclear whether the enhanced endocapsular flow of aqueous humor by itself, with increased exposure to inhibitory growth factors, is sufficient to prevent PCO. Anteroposterior capsule separation may also be a critical component, and the combination of both mechanisms may be required for the PCO reduction that was observed. Isolating the effect of increased aqueous flow alone on the prevention of capsule opacification could be better assessed by directly comparing the incidence of PCO associated with capsular adhesion-preventing rings with perforations and the incidence associated with those without perforations.

Open-Capsule Device

In a 2014 study, the postoperative opacification in eyes with a new CTR-type device specifically developed to expand the capsular bag was evaluated.[26] Manufactured from both hydrophilic and hydrophobic materials, the open-capsule device is a closed circular-shaped ring with a square-edged design that measures 11.0 mm in total diameter and 1.5 mm in height. Notable design features include several windows that augment the endocapsular circulation of aqueous humor and an anterior surface "roof" that supports the anterior capsule away from the IOL, preventing contact between the posterior aspect of the anterior capsule and the anterior aspect of the optic (Figure 4).

In a preclinical study comprising 20 rabbits and 40 eyes, 4 permutations of hydrophilic and hydrophobic test devices with hydrophilic and hydrophobic IOLs were implanted in 26 study eyes.[26] The remaining 14 eyes received hydrophilic or hydrophobic IOLs alone and functioned as control eyes. The PCO score was significantly correlated with the presence or absence of the device, but not with the variability in materials of the rings or IOLs. Six weeks following implantation, 22 of the original 26 study eyes remained available for analysis. Evaluation by slitlamp examination, Miyake-Apple posterior view, and histopathology showed PCO reductions of 69% ($P = .001$), 77% ($P = .000$), and 75% ($P = .000$), respectively. Eyes with the study device also exhibited an 81% reduction in Soemmerring ring formation ($P = .000$) compared with eyes with control IOLs alone.

Several aspects of this device's design have been associated with the inhibition of PCO in the past. The sharp 360-degree squared edge is thought to prevent posterior migration of LECs at the capsule equator, similar to the design of the endocapsular equator ring and the capsular bending ring. In a manner similar to Nagamoto et al.'s capsular adhesion-preventing ring,[25] the special windows in the sidewalls of the open-capsule device enhance the delivery

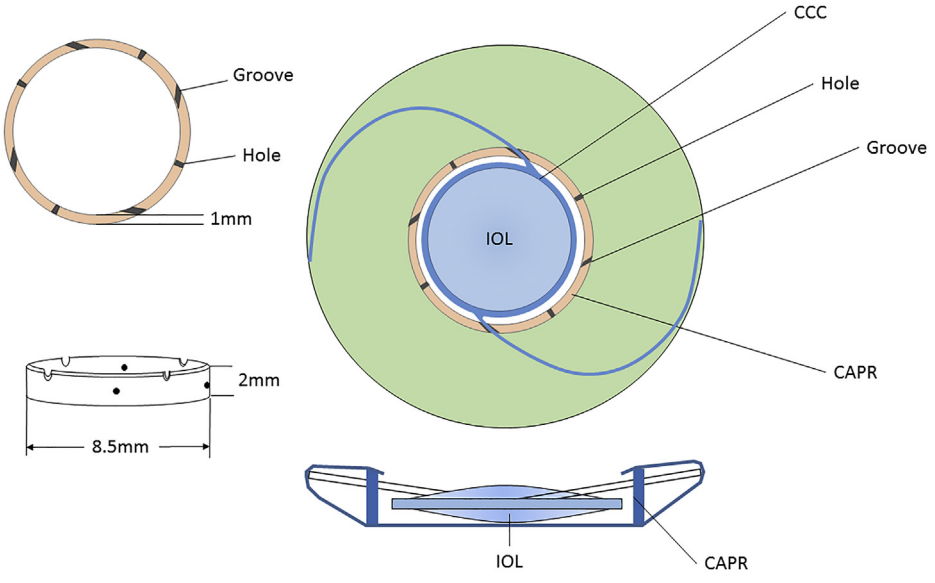

Figure 3. The design and in-the-bag placement of the capsular adhesion-preventing ring. *Left*: Schematic drawings of the ring showing the dimensions and the orientation of the 4 grooves and 4 holes (anterior and side views). *Right*: Schematic drawings of the ring together with an IOL implanted in the capsular bag (anterior and side views). Drawings modified from Nagamoto et al.[25] (CAPR = capsular adhesion-preventing ring; CCC = continuous cuvilinear capsulorhexis; IOL = intraocular lens).

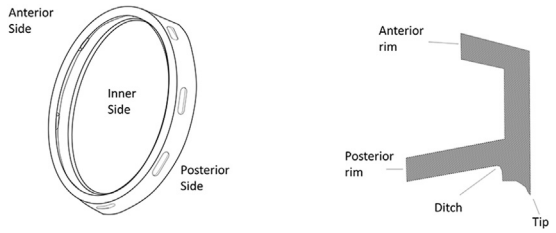

Figure 4. Illustration of the open-capsule device. *Left*: Overview. *Right*: Side view. The presence of the anterior rim or "roof" keeps the capsule away from the anterior IOL surface. Drawings modified from Alon et al.[26]

of aqueous humor to the capsule equator. This is thought to contribute to the inhibition of LEC proliferation in this area. Finally, this device maintains the capsular bag in an open configuration, as is similarly done by the other capsular ring devices.

Protective Membrane

The latest endocapsular device to prevent PCO through expansion of the capsular bag that was studied in our laboratory is designated as a protective membrane. Manufactured by Sharklet Technologies, Inc. from a silicone material, the protective membrane was designed to be implanted inside the capsular bag. The device acts as an artificial capsular bag in that once it is successfully implanted, a standard IOL is fixated inside it. The protective membrane features a square-edged haptic ring (outer diameter 9.5 mm) that fits the natural curvature of the lens capsule and provides a ridge (height 1.2 mm) to engage and retain the IOL haptics, including thicker haptics of single-piece IOLs. The anterior surface is completely open. The posterior surface (0.1 mm thick) has a central hole with a diameter of 5.5 mm. The sidewalls of the device (square-edged haptic ring) are 0.5 mm thick. On its posterior aspect, the protective membrane features a sharkskin-inspired micropattern (Figure 5). Engineered surface topographies, particularly geometries of ordered features designed with unique roughness properties, elicit specific predictable biological responses and have been shown to control bioadhesion.[27] The micropattern of the protective membrane is an example of such surface topographies. Studies have shown that this sharkskin-inspired microtopography more effectively inhibits bioadhesion than other ordered topographies (pillars, channels, other geometries).[27,28] In a similar manner, the protective membrane's designer postulated that the pattern of the protective membrane could interfere with the posterior LEC migration that leads to PCO.

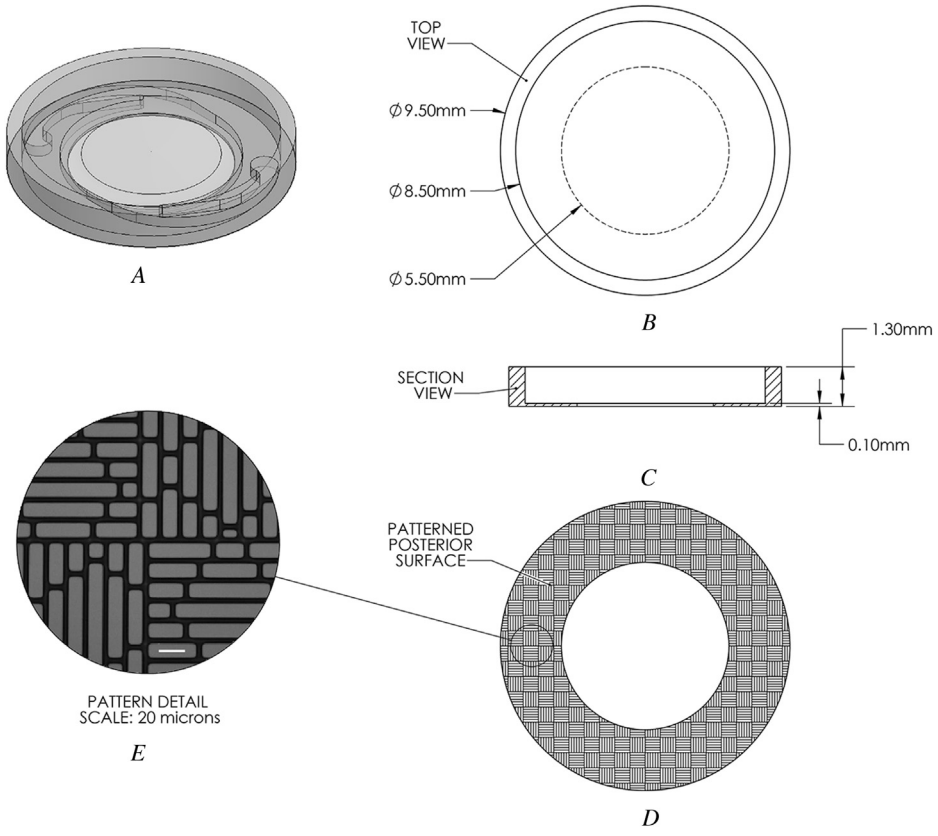

Figure 5. Schematic illustration of the protective membrane. *A*: Single-piece IOL contained within the protective membrane. *B*: Anterior view of the protective membrane. *C*: Side view of the protective membrane. *D*: Posterior view of the protective membrane showing the pattern on the posterior surface and the opening in the central 5.5 mm. *E*: The Sharklet pattern shown at high magnification (scale bar = 20 μm). Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[29]

A 2015 study[29] evaluated the stability and capsular bag opacification of both smooth and patterned silicone protective membranes implanted in the bag with secondary placement of an IOL in the rabbit eye. Twelve New Zealand rabbits had bilateral phacoemulsification with subsequent implantation of the Sharklet-patterned protective membrane and an IOL, the smooth protective membrane and an IOL, or an IOL alone. The protective membrane injection procedure was not optimal, and the nature of the silicone material used in the device's manufacture resulted in its rapid opening immediately following injection, making positioning of the protective membrane in the eye difficult to control. Some protective membranes were inverted in the capsular bag, resulting in different conformations of the IOL relative to the protective membrane's 5.5 mm posterior hole, located anteriorly (eg, partially injected through the protective membrane). Thus, a comparative analysis of PCO prevention by the patterned protective membranes versus the smooth protective membranes was not possible. However, when smooth and patterned protective membranes were combined into a single group, PCO scoring by slitlamp examination 4 weeks postoperatively was 0.64 $\pm$ 0.69 in eyes with a protective membrane and 2.33 $\pm$ 1.03 in eyes with the same IOL alone ($P = .0004$). Similar results were found on gross examination via the Miyake-Apple view, with central PCO scored as 0.28 $\pm$ 0.32 in eyes with a protective membrane and 2.08 $\pm$ 1.28 in eyes with the IOL alone ($P < .00001$). The presence of the protective membrane was associated with 86% less PCO than the group without a protective membrane. Histopathologic analysis confirmed a PCO preventive effect. Light microscopy showed widely dilated posterior capsules in the group of eyes with both smooth and patterned protective membranes (Figure 6). With the protective membrane, as with other devices discussed in this article, PCO is likely prevented through the complex interactions of various mechanisms.

INTRAOCULAR LENSES

Spring-Loaded Intraocular Lens

Hara et al.[30] designed a spring-loaded IOL to provide sufficient accommodation through dual optics and flexible closed loops. The IOL featured two 6.0 mm PMMA optics connected by 4 obliquely arranged polyvinylidene fluoride loops with a horizontal length of 10.0 mm. Initially, the distance between the optics was 4.38 mm. The refractive power of the IOL is contained in the anterior optic, which moves back and forth according to the degree of capsular bag tension. In contrast, the posterior optic was designed with no refractive power and remains stationary against the posterior capsule. Simultaneously pressing and twisting the anterior optic relative to the posterior optic reduces the IOL volume, facilitating IOL insertion through a 3.5 mm anterior capsule opening in an excised pig eye.

In a 1992 study in the rabbit model,[31] the distance between the optics was increased to 8.5 mm to fill the rabbit capsular bag more adequately (Figure 7). The modified spring IOL was implanted in 10 eyes that were followed from 2 to 26 months.[31] The surgical technique involved endocapsular phacoemulsification through a 4.5 to 5.0 mm "dumbbell" linear anterior capsule opening. Retention of posterior and anterior capsule transparency was observed in 9 of the 10 eyes. It was hypothesized that the transparency was secondary to the mechanical pressure against the capsule applied by the expanding spring inside the bag.

In a study conducted the following year,[32] ACO was assessed in rabbit eyes implanted with spring-loaded IOLs of different uncompressed anteroposterior thickness. In rabbit eyes with thin (4.38 mm) spring-loaded IOLs, the anterior capsules were opacified over their entire area. In rabbit eyes with thick (8.5 mm) spring-loaded IOLs, the anterior capsules were transparent at areas of contact. The thick IOLs were postulated to prevent fibrosis of the anterior capsule secondary to

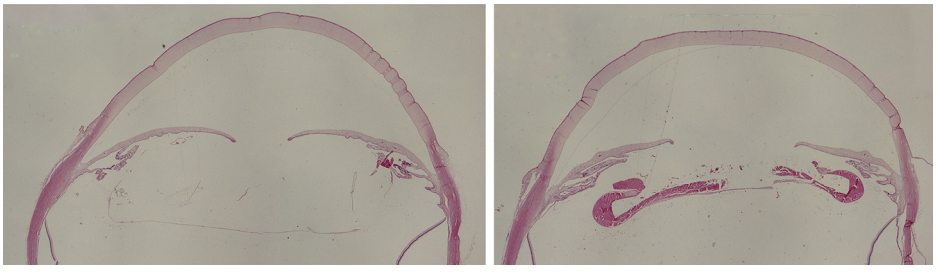

Figure 6. Photomicrographs of histopathologic sections cut from both eyes of the same rabbit. *Left*: Right eye with the protective membrane showing limited Soemmerring ring formation at the equatorial region and no proliferative material along the posterior capsule. The capsular bag is expanded with the anterior capsule at a distance from the posterior capsule. *Right*: Left eye with the control IOL showing considerable Soemmerring ring formation and PCO originating at the optic–haptic junctions. The proliferative cortical material extends onto the posterior capsule (*Left* and *right*: Composites of light photomicrographs; hematoxylin–eosin staining; original magnification ×20). Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[29]

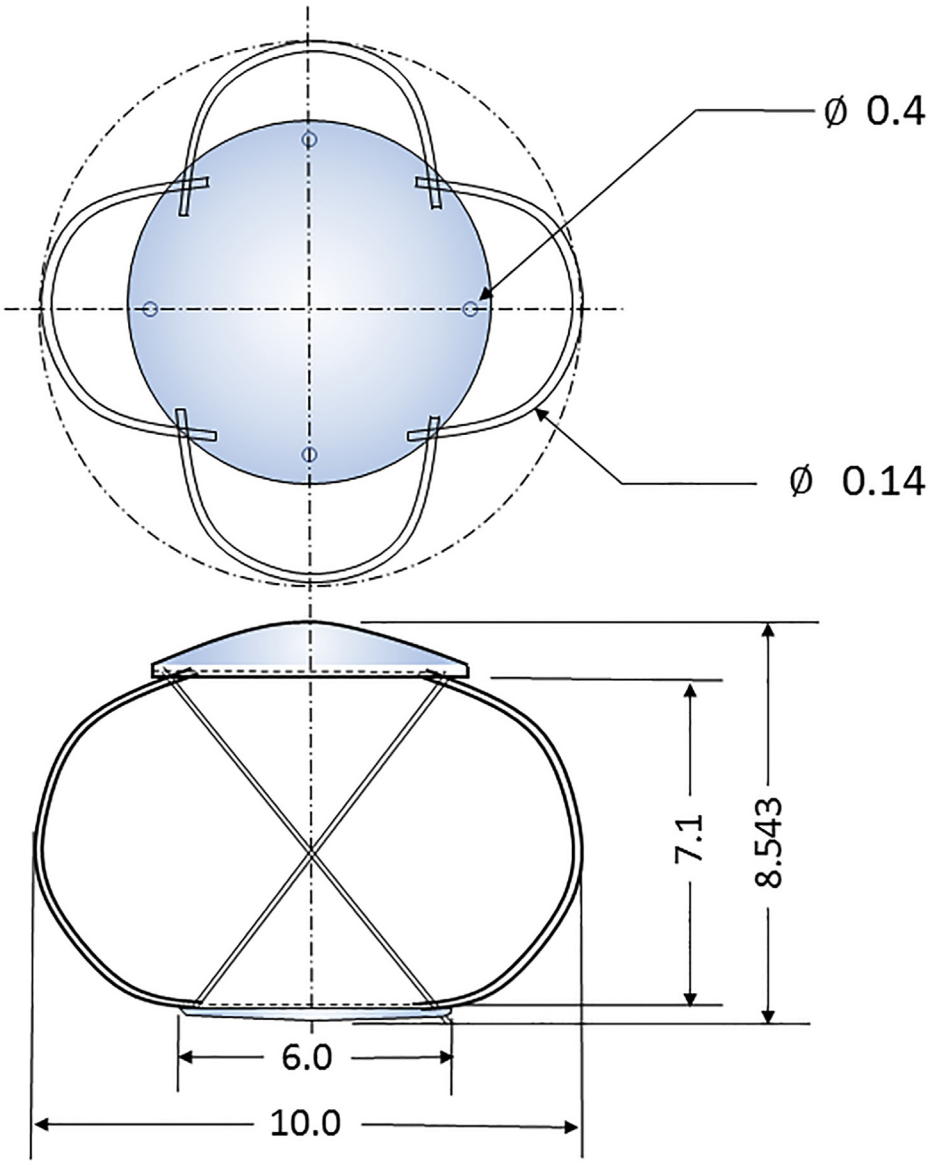

Figure 7. Schematic drawings of the spring-loaded IOL. *Top*: Anterior view. *Bottom*: Side view. Drawings modified from Hara et al.[31]

increased mechanical compression of LECs.[30,31] It is important to distinguish the compression inhibition that is described here from contact that can occur between the capsulorhexis edge of the anterior capsule and the anterior optic surface, which contributes to ACO formation.

Concept 360 Intraocular Lens

The Concept 360 (Corneal Laboratoire) is a single-piece foldable hydrophilic acrylic IOL with a water content of 26%. It is disk shaped with an optic diameter of 6.0 mm, an overall diameter of 11.5 mm, and squared optic and haptic edges. Six haptics emanate from the optic at 10-degree angles to the posterior surface, giving the IOL the appearance of a propeller (Figure 8). According to the developer, the Concept 360 was devised to keep the anterior capsule away from the IOL, simulate the effect of a CTR, and inhibit PCO. The design features are likely to influence the outcome of both ACO and PCO.[33]

The IOL features a configuration of haptic components that function similar to a broad, band-shaped CTR, holding the anterior capsule away from the optic surface. In a preliminary clinical study of 4 cadaver eyes, complete separation between the capsulorhexis margin and the anterior surface of the IOL optic was observed for 360 degrees. In the same study, the Concept 360 was associated with an absence of capsule striae.[33]

The design of the Concept 360 is associated with several factors that may contribute to PCO prevention. Spontaneous rotational movements of the disk-shaped IOL during irrigation/aspiration may help in the dislocation of residual cortical material and cells out

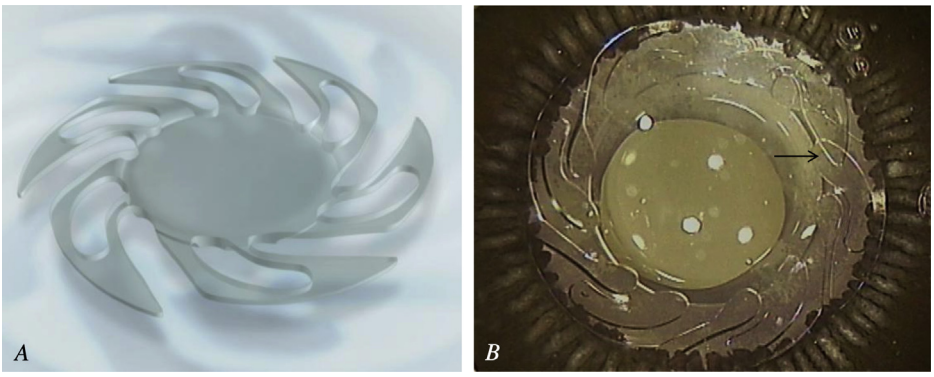

Figure 8. The Concept 360 IOL. *A*: Schematic illustration showing the IOL design (courtesy Corneal Laboratoire). The overall disk shape is similar to that of a propeller. The space between the haptic components decreases as a function of the capsular bag's diameter. *B*: Overview of the IOL fixated in the capsular bag from a posterior or Miyake-Apple view. The arrow denotes an area in which 2 haptic components of the IOL overlap. Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[33]

of the equatorial region of the capsular bag. This would make the material more accessible to the surgeon's view and therefore promote a more complete cortical cleanup. The square-edged haptic, in association with contact of the haptic periphery around the equatorial region of the capsular bag (CTR effect), may promote a significant barrier effect against cell proliferation. The contact between the square-edged posterior optic and the posterior capsule, further enhanced by the posterior optic–haptic angulation, is likely to represent another significant barrier against cell proliferation and thus PCO formation.[33]

It is important to note that the CTR effect of the Concept 360 is dependent on the size of the eye. In smaller eyes, the distance between the IOL haptics is minimized, as they come close together to conform to the capsular bag diameter. In this situation, the contact between the periphery of the IOL and the equatorial region of the capsular bag may produce the effect of a complete CTR. However, in capsular bags with larger diameters, the IOL haptics are not close together. The gaps between them may represent avenues for migration or proliferation of residual cells or cortical material in the capsular bag equator, eventually forming PCO. A similar phenomenon may occur in exceedingly small eyes. The influence of excess overlapping between the haptic components of the IOL on the CTR effect is unknown. To our knowledge, this IOL design has been discontinued.

Synchrony Intraocular Lens

The Synchrony (Visiogen, Inc./Abbott Medical Optics, Inc.) is a foldable single-piece dual-optic accommodating IOL manufactured from silicone. Two optic components, each in the design of a plate-haptic IOL, are attached at the haptics by a bridge with a spring function. The 6.0 mm posterior optic has a significantly larger surface area than the 5.5 mm anterior optic, and the 2 attached rectangular expansions help stabilize the capsular bag during the process of accommodation/unaccommodation. In this dual-optic IOL system, the anterior IOL has a high plus power and the posterior IOL has a minus power.[34–39] During accommodation, the ciliary body contracts and decreases capsular bag tension, allowing forward translation of the anterior optic. As contact between the anterior capsule and the IOL optic contributes to ACO development, which is essentially a fibrotic entity, the advent of accommodating IOLs has been accompanied by increased concern about the influence of postoperative fibrosis and opacification on the long-term functioning of these devices. The Synchrony IOL incorporates 2 small expansions of the anterior optic that project anteriorly, pushing the capsulorhexis edge away from the optic surface (Figure 9). In rabbit studies, the IOL has demonstrated significant reductions in ACO, capsulorhexis phimosis, PCO, and capsular bag contraction.[38,39] The degree of capsular bag expansion induced by this relatively bulky device may have contributed to the observed clarity of the capsular bag.[39]

The presence of a dual-optic system in the capsular bag also raises concerns about the potential for ingrowth of regenerative/proliferative crystalline lens material between the optics, forming ILO.[40–45] Rabbit studies have demonstrated that ILO characteristically occurs with in-the-bag implantation of 2 hydrophobic acrylic IOLs through a small capsulorhexis. In a 2006 rabbit study, Werner et al.[38] evaluated and compared the incidence of ILO in eyes with the Synchrony IOL and in eyes implanted with piggyback combinations of hydrophobic acrylic IOLs and silicone-plate IOLs. The highest rates of ILO were observed in eyes with piggyback hydrophobic acrylic IOLs. Gross and histopathologic examination confirmed the origins from proliferative cortical material within Soemmerring ring at the optic–haptic junctions of single-piece hydrophobic acrylic IOLs. In contrast, eyes implanted with silicone IOLs had significantly reduced rates of ILO and the Synchrony IOL was associated with the lowest amount of ILO

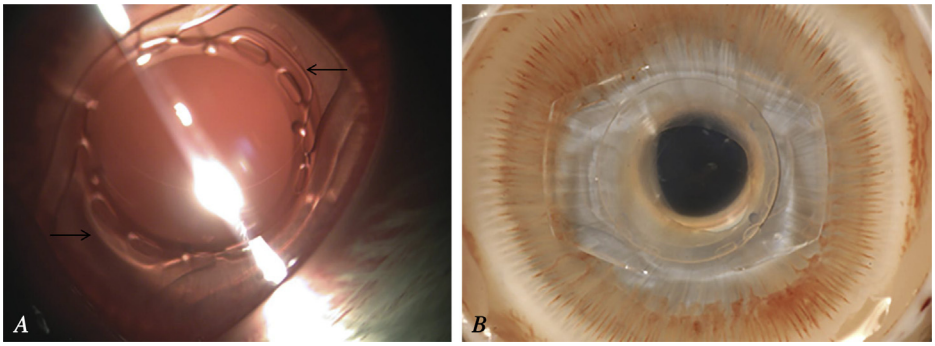

Figure 9. Slitlamp photograph of a rabbit eye with the Synchrony IOL taken 6 weeks postoperatively (*A*) and a corresponding gross photograph of the same eye obtained postmortem (posterior or Miyake-Apple view) (*B*). No capsular bag opacification is observed in the eye with the IOL. The arrows in *A* show lateral expansions off the anterior optic, which lifts the anterior capsule away from the anterior optic surface, minimizing contact between the 2 structures. Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[38]

formation. However, Soemmerring ring formation was similar in the 3 groups.

There are several important differences between the rabbit eye and the human eye that must be considered when interpreting studies of capsule fibrosis. In contrast to the rabbit eye, which lacks a mechanism of accommodation, the interlenticular space in humans is constantly changing as a result of accommodative efforts. Further clinical studies assessing a possible effect of dynamic interlenticular thickness on ILO formation are warranted. In a series of 25 human eyes that had the Synchrony IOL, ILO formation was completely absent at 12 months.[B]

The rabbit eye represents an accelerated model of PCO. With sufficient time postoperatively, the rabbit capsular bag will eventually exhibit complete filling with proliferative material. Extension of Soemmerring ring with protrusion into the interlenticular space may also occur. In contrast, the human eye has a much lower regenerative/proliferative lens capacity; 6 to 8 weeks in the rabbit eye correspond to approximately 2 years in the human eye.[46] Lower regenerative lens capacity combined with the careful cortical cleanup that occurs following IOL implantation make the occurrence of the same phenomenon unlikely in humans.

Zephyr Intraocular Lens

The Zephyr (Anew Optics, Inc.) is a single-piece hydrophilic acrylic monofocal IOL with a wheel-like configuration. The IOL optic is suspended between 2 complete haptic rings connected by a pillar of the haptic material, so the anterior ring rests against the anterior capsule at some distance from the capsule equator and the posterior ring rests against the posterior capsule also at some distance from the capsule equator. Originally, the design featured an overall diameter of 9.5 mm and an optic diameter of 6.0 mm.[47] The IOL was subsequently modified to include haptic perforations and a larger outer diameter of 10.02 mm. The haptic perforations function as conduits and enhance the endocapsular circulation of aqueous humor by permitting its flow to the capsular fornix and areas anterior and posterior to the IOL optic (Figure 10).[48]

In 2 rabbit studies, the peripheral haptic rings of this disk-shaped IOL prevented PCO and ACO by expanding the capsular bag and preventing contact between the IOL optic and the anterior capsule.[47,48] This was confirmed on ultrasonography, which demonstrated expansion of the capsular bag and a distinct separation between the anterior capsule and the IOL optic (Figure 10, *B*). Notably, the anterior capsule maintained its clarity for the duration of both studies. Soemmerring ring formation was limited to the equatorial region of the bag, between the peripheral rings.[48] Eyes with the Zephyr IOL had significantly less overall proliferative cortical material than eyes with the control IOL (Figure 11).

The maintenance of tight contact between the posterior surface of the IOL optic and the posterior capsule has been described as an IOL-related mechanism for PCO prevention. In a rabbit study evaluating the modified Zephyr IOL, there were 2 instances in which the optics bulged anteriorly instead of posteriorly.[48] It is possible that the modified IOL was slightly too large for the rabbit capsular bag, resulting in the forward displacement that was observed. Despite a lack of contact between the posterior optic surface and the posterior capsule, PCO in the eyes with anteriorly bulging optics did not differ from that in the eyes with the correctly positioned IOL. Thus, contact between the posterior optic surface and the posterior capsule is not required for PCO prevention providing the overall IOL design configuration is disk-shaped

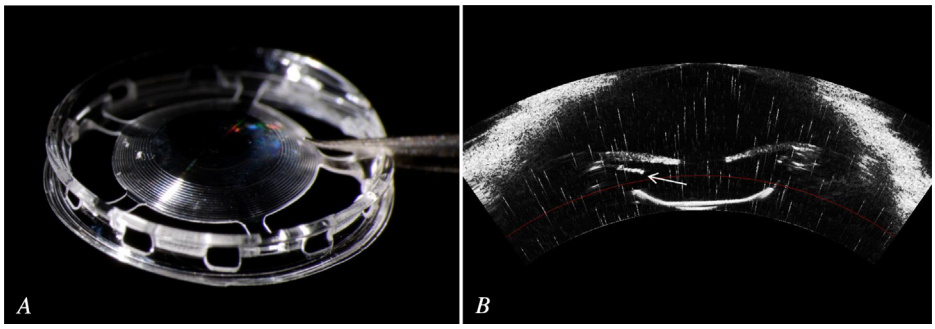

Figure 10. The Zephyr IOL. *A*: Anterior view of the modified Zephyr IOL. *B*: Ultrasound examination of an enucleated rabbit eye. The anterior capsule (*arrow*) is maintained at a distance from the anterior optic surface. Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[48]

with a large CTR effect around the equator, keeping the bag open and/or expanded. This effect has also been clinically demonstrated with the endocapsular equator ring.[12,13]

Fluidvision Intraocular Lens

The Fluidvision (Powervision, Inc.) is a new deformable accommodating IOL manufactured from a proprietary hydrophobic acrylic material. The design features hollow optic and haptic components that are filled with index-matched silicone oil. The haptics are especially large, keeping the anterior capsule at a distance from the posterior capsule (Figure 12). During accommodative efforts, fluid is driven from the haptics into the optic. As the optic fills with fluid, the surface curvature increases, resulting in higher optic power. In an initial clinical evaluation of an earlier prototype of this IOL, a limited number of sighted-eye patients achieved changes in optic power exceeding 5 diopters.[C]

In rabbit studies, the Fluidvision accommodating IOL effectively prevented capsular bag opacification. At the conclusion of a 6-week study, the IOL was associated with remarkable capsular bag clarity (Figure 13).[49] Although the high proliferative capacity of LECs in the rabbit model usually renders PCO comparisons difficult or impossible after a postoperative period of 4 weeks, evaluating the biocompatibility of new materials used in IOLs requires a 6-month in vivo study according to the requirements for IOLs set by the International Organization for Standardization (ISO).[50] Thus, a follow-up rabbit study assessing uveal and capsular biocompatibility of the silicone oil–filled accommodating IOL was performed in accordance with ISO requirements. Six months postoperatively, significantly less PCO was observed in eyes with the Fluidvision accommodating IOL than

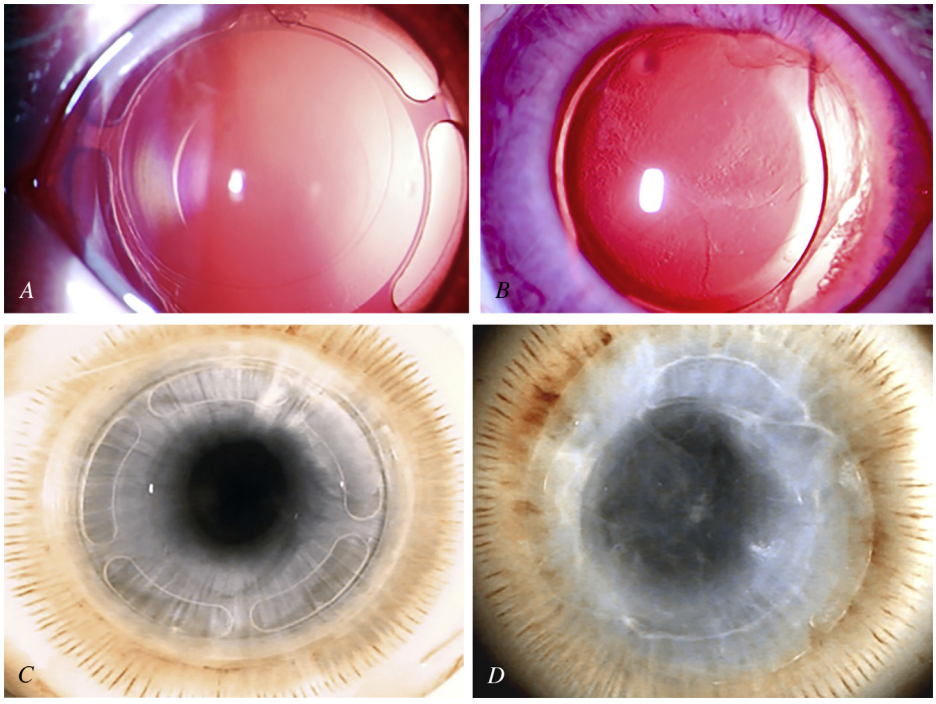

Figure 11. *A* and *B*: Slitlamp photographs from both eyes of the same rabbit. *A*: *Right* eye with the Zephyr IOL. *B*: *Left* eye with the control IOL. The right eye showed clarity of the posterior and anterior capsules. In contrast, the left eye developed diffuse PCO originating at the optic–haptic junctions. *C* and *D*: Miyake-Apple view of the anterior segments from the same rabbit. *C*: Postmortem examination of the right eye (study IOL) at 5 weeks showed overall clear posterior and anterior capsules. *D*: Postmortem examination of the left eye (control IOL) demonstrated diffuse PCO. Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[47]

Figure 12. Overall design of the Fluidvision IOL (courtesy of Powervision, Inc.).

in eyes with the control single-piece hydrophobic acrylic IOL.[51] No signs of untoward inflammation or toxicity was seen in any eye. The results in this study are especially encouraging as 6 months in the rabbit model are equivalent to several years in the human eye in terms of LEC proliferation and inflammatory response.

The Fluidvision IOL almost fills the capsular bag, resulting in an expanded bag configuration. In this configuration, it is unlikely that constant irrigation of the inner compartment of the capsular bag occurs and plays any role in preventing LEC proliferation. Other factors such as mechanical compression and/or stretching of the capsular bag are probably responsible for the significant prevention of capsular bag opacification relative to eyes implanted with control standard IOLs. Mild amounts of proliferative material, limited to the fornix of the capsular bag, were seen in some instances in rabbit eyes with the Fluidvision.[49] The presence of the haptics generally blocked extension of the proliferative material toward the optic except at the haptic gap sites. In those 2 areas, there was a lack of mechanical compression of the inner surface of the capsular bag; the shape and contour of the bag was also not maintained. However, the optic edge blocked the access of the material to the posterior capsule. The anterior capsule remained remarkably clear with the Fluidvision IOL throughout the 2 rabbit studies. The only contact between the study IOL and the anterior capsule was at the periphery of the capsular bag, at the level of the haptic components. A fine wrinkling of the anterior capsule was observed in that area in some eyes. The anterior capsule at and around the capsulorhexis edge was generally devoid of fibrosis as it was kept at a distance from the anterior IOL surface.

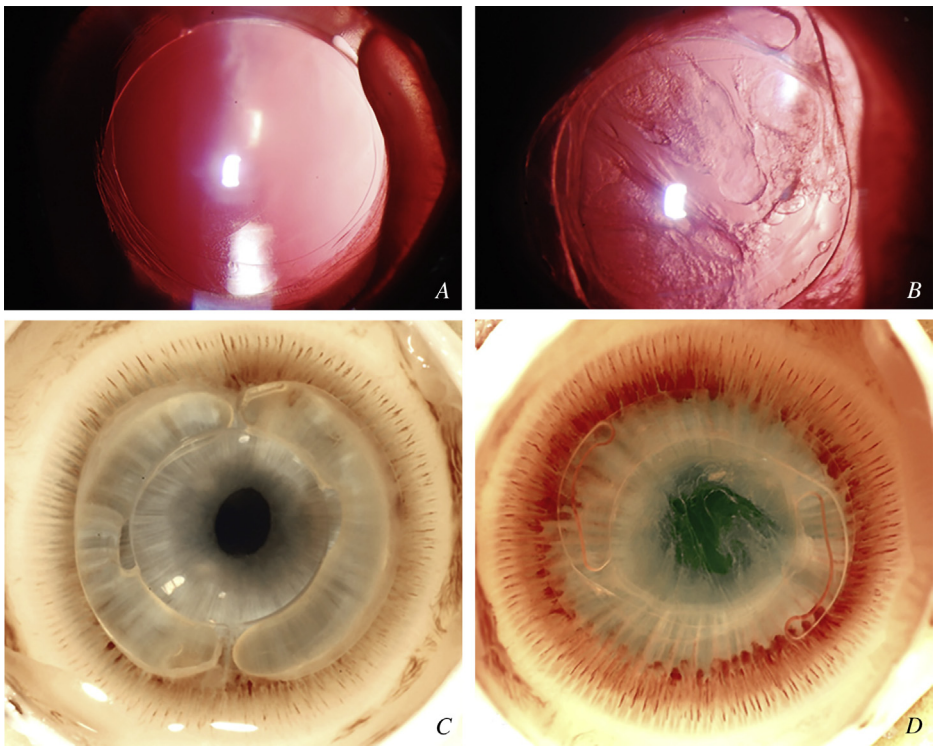

Figure 13. Clinical (*A* and *B*) and gross (Miyake-Apple view; *C* and *D*) photographs of both eyes of the same rabbit taken 6 weeks postoperatively. Clinical and gross examination of the eye with the study IOL (*A* and *C*) showed clear posterior and anterior capsules. Clinical and gross examination of the eye with the control IOL (*B* and *D*) showed diffuse PCO. Reprinted with permission of the *Journal of Cataract & Refractive Surgery*.[49]

Plate Torsion Haptic Intraocular Lens

The plate torsion haptic IOL was developed by Kuznetsov et al.[D] and is manufactured by Reper-NN Ltd. The IOL has an overall plate-haptic configuration and is manufactured from a hydrophobic acrylic material. The design was specifically conceived to restore the size and shape of the capsular bag after phacoemulsification and in-the-bag implantation. The plate-haptic elements have a less rigid area to ensure vaulting that follows the natural curve of the equatorial region of the capsular bag. Although versions with different dimensions have been tested, current dimensions are 15.5 mm and 5.5 mm for the overall diameter and the optic diameter, respectively (Figure 14).

At the 2014 European Society of Cataract & Refractive Surgeons meeting, 2 studies of this IOL were presented.[D,E] In the first study, 2 models of the plate torsion haptic IOL were used[D]: version MIOL-27 in 170 eyes of 146 patients, followed from 1 to 5.5 years; version MIOL-27 Soft in 20 eyes of 20 patients, followed from 6 months to 1 year. The IOLs were implanted after uneventful routine phacoemulsification through a 2.2 mm incision. Ultrasound biomicroscopy (UBM) was used to monitor the IOL position in all patients. The position of both IOL models was stable according to UBM data and did not change over the entire follow-up period. The MIOL-27 model completely restored the volume of the natural crystalline lens, and its position did not differ significantly from the preoperative position of the posterior capsule (Figure 15). The MIOL-27 Soft model did not completely replace the volume of the natural crystalline lens, and its optic was located more anteriorly. The rate of PCO was 2.35% in the MIOL-27 group and 15.0% in the MIOL-27 Soft group. The authors concluded that the higher haptic rigidity of the MIOL-27 version provided expansion of the capsular bag with better restoration of its volume as well as tighter contact between the IOL and the posterior capsule, resulting in better PCO prevention.

In the second study, a plate torsion haptic IOL version MIOL-27 with zero dioptric power was used in combination with various models of standard IOLs in 8 eyes of 8 patients.[E] The plate torsion haptic IOL was implanted in the bag through an incision of 2.2 to 2.4 mm after routine phacoemulsification, and the standard IOL was then implanted inside the open capsular bag in a piggyback configuration. The patients were followed from 6 months to 1.5 years. The UBM data showed an immediate effect of capsular bag shape recovery in all cases, which remained stable throughout the follow-up period. No PCO was observed in this study. The distance between the optics of the plate torsion haptic IOL and the standard IOL ranged from 0.02 to 1.5 mm.

POSSIBLE POSTERIOR CAPSULE OPACIFICATION PREVENTION MECHANISMS

No Space, No Cells

According to the "no space, no cells" theory, any gap between the IOL optic and the posterior capsule would represent a potential avenue for cellular ingrowth. Thus, tight contact between the posterior surface of the IOL optic and the anterior surface of the posterior capsule is an IOL-related mechanism effective in the prevention of PCO when standard IOLs are considered. Factors that increase capsular tension bring these 2 structures closer together. In a rabbit study by Hansen et al. comparing different IOL designs,[52] posterior convexity of the IOL optic and posterior angulation of the haptic loops were the design-related factors most effective in preventing PCO. Results of high-resolution laser interferometric studies have shown tighter contact between the posterior optic surface and the posterior capsule in eyes with a CTR combined with an IOL than in eyes with an IOL alone.[53] The relative stickiness of the IOL optic may also be a contributing factor. According to the "sandwich theory," the bioadhesive surface of some hydrophobic acrylic IOLs allows a single layer of LECs to bond to both the IOL optic and the inner surface of the capsules, forming a sealed structure that prevents further cell proliferation.[54]

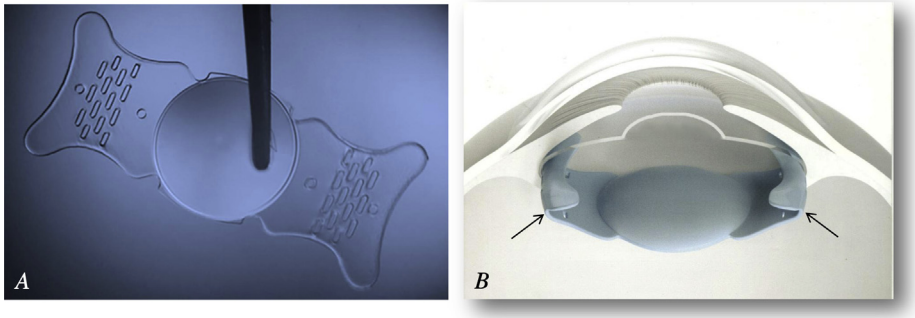

Figure 14. Gross photograph (*A*) and schematic drawing (*B*) showing the design of the plate torsion haptic IOL. The arrows in *B* show the sites of less haptic rigidity to ensure vaulting of the haptic elements following the natural contour of the capsular bag. Courtesy of Sergey Kuznetsov, MD, Department of Ophthalmology, Institute for Postgraduate Medical Studies of the Ministry of Health of Russian Federation, Penza, Russia.

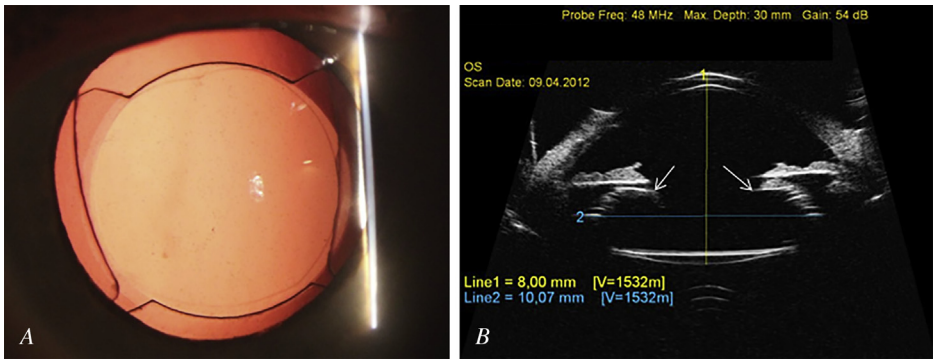

Figure 15. Slitlamp photograph (*A*) and ultrasound scan (*B*) showing eyes implanted with the plate torsion haptic IOL. *A*: Four days postoperatively. *B*: Five years postoperatively. The arrows in *B* show the anterior capsule. Courtesy of Sergey Kuznetsov, MD, Department of Ophthalmology, Institute for Postgraduate Medical Studies of the Ministry of Health of Russian Federation, Penza, Russia.

In association with in-the-bag IOL fixation and creation of a capsulorhexis with a diameter smaller than the optic diameter, the above factors create a shrink-wrap effect of the capsular bag around the IOL. This would consequently enhance the barrier effect of a design-related PCO prevention factor such as a square optic edge, which is the basis for PCO prevention as far as standard IOLs are concerned.[1]

Of the devices described in this review, the no space, no cells theory likely plays an important role in PCO prevention in relatively bulky IOLs such as the Fluidvision. However, studies of Hara et al.'s endocapsular equator ring[13] and the Zephyr IOL,[48] the single-piece disk-shaped IOL with a CTR effect, have shown effective PCO prevention in the absence of contact between the IOL optic and posterior capsule.[12,13,48] This finding emphasizes the importance of additional mechanisms in maintaining postoperative bag clarity in these devices.

Square-Edged Barrier Effect

In standard IOLs, various mechanisms have been postulated to explain the observed barrier effect of the square-edged optic and include contact inhibition by a capsular bend[55,56] or mechanical pressure exerted by the IOL edge against the inner capsular bag.[57,58] In culture studies by Nishi and Nishi,[59] LECs exhibited different proliferative patterns depending on the shape of the well in which they were cultured; U-shaped wells with round bottoms showed continuous LEC proliferation up the sidewalls of the well, whereas those with rectangular bottoms inhibited LEC proliferation at the sidewalls. In a similar manner, Menapace et al.[24] and Nishi and Nishi[59] postulated that the sharp discontinuous bend at the capsule equator would prevent PCO by inhibiting LEC migration via contact inhibition. However, Nagamoto and Fujiwara[57] and Bhermi et al.[60] conducted similar culture studies and found that the square-edged culture wells did not prevent the migration of LECs. In an in vitro study using mathematical modeling, Boyce et al.[58] showed that square-edged optics exerted approximately 70% more pressure on the capsular bag than round-edged optics. They suggest that the barrier to LEC migration results from the applied pressure of a square-edged optic against the capsular bag. The capsular ring and devices described in this review generally take advantage of the square-edged concept and enhance PCO prevention by shifting the capsular bend and pressure created by their square edges to the equatorial region.

Mechanical Compression of the Capsular Bag

Increased mechanical compression of the inner capsular bag by relatively bulky devices and IOLs has been hypothesized to contribute to retaining postoperative capsule transparency. This effect was originally described in association with the spring-loaded IOL developed by Hara et al.[31] Following in-the-bag implantation, the spring effect contributes to internal compression of the anterior and posterior capsules by the anterior and posterior IOL optics. In a 1990 study in the rabbit model,[30] mechanical compression of the anterior and posterior capsules was associated with retention of transparency of the same areas in 9 of 10 eyes. In contrast, the capsule equator region that did not undergo mechanical compression by the IOL was associated with LEC proliferation in all 10 eyes.

The notion of mechanical compression inhibition has been observed more recently in studies of the Fluidvision IOL, which likely complement the role of the no space, no cells theory. This accommodating IOL features 2 oversized haptics that expand the capsular bag and are overall effective in blocking the extension of proliferative cortical material toward the optic. However, there are 2 small sites in which migration of cortical material may occur. At these haptic gap sites, researchers noted a lack of mechanical compression of the IOL haptic against the inner surface of the capsular bag.[49]

Maintaining the Postoperative Contour of the Capsular Bag (Capsular Tension Ring Effect)

A CTR specifically designed to prevent opacification in the capsular bag was evaluated by groups in Japan and Austria.[22,24] Both studies reported significant reductions in ACO and PCO in eyes with a CTR and an IOL compared with eyes with the same IOL alone. Capsular tension rings and disk-shaped IOLs with a CTR effect exert a circumferential stretch on the capsular bag, with radial distention forces distributed equally. Formation of traction folds in the posterior capsule, which may be used as an avenue for cell ingrowth, is also avoided. Furthermore, the mechanical stretch imposed on the capsule equator functions to increase the space between the anterior and posterior capsules, maintaining the circular contour of the postoperative capsular bag and simultaneously enhancing the endocapsular circulation of aqueous humor in devices that keep the capsular bag expanded and open.

Enhanced Endocapsular Circulation of Aqueous Humor

Studies suggest that devices that maintain constant contact between fresh aqueous humor and LECs or enhance the endocapsular irrigation of aqueous humor have been effective in preventing the transformation and subsequent proliferation of residual LECs and the development of ACO and PCO.[15–21] Transforming growth factor β2, which is present in normal human aqueous humor, has demonstrated an inhibitory effect on the proliferation of LECs in vitro and corneal endothelial cells in vivo.[15,16] In rabbit studies, aqueous humor initially had an activating effect on LEC proliferation, which was maximum 1 day postoperatively. This effect gradually dissipated and was completely absent by 30 days postoperatively.[20,21] In a letter to the editor, Nishi[17] postulated that constant irrigation of LECs by aqueous humor may dilute certain proliferative cytokines in the capsular bag, preventing them from reaching the threshold concentrations required to have a proliferative effect. Studies by Nishi et al.[18,19] suggest that interleukin-1 is an example of such a cytokine. The expansion of the capsular bag secondary to devices described in this review results in a conformation of the capsular bag that often facilitates the flow of aqueous humor. In addition, certain devices incorporate holes in the IOL haptics or capsular rings that further enhance the circulation of aqueous humor throughout the capsular bag.

CONCLUSION

Prevention of opacification of the capsular bag after cataract extraction and IOL implantation, especially the fibrotic types of opacification, appears to be even more important now with the increased interest in the development of specialized IOLs such as accommodating IOLs. There are concerns that late postoperative capsular bag fibrosis might prevent long-term functioning of these IOLs. This may be associated with PCO and ACO development. Prevention of capsular bag collapse with maintenance of bag clarity has been associated with the various devices and IOLs described in this review. Although all the factors discussed appear to play a role in preventing capsular bag opacification in open or expanded capsule devices, it is difficult to determine which factor plays the most important role. It is also difficult to determine whether a particular device shows a superior preventive effect, as this would require studies making direct comparisons between the devices. Further research of the proposed preventive mechanisms of IOLs or devices maintaining an open or expanded capsular bag is warranted. Long-term experimental studies of the currently available devices will help discern between prevention and delay of capsular bag opacification. It is also important to stress that the ultimate success of these devices will depend on surgical aspects such as ease of implantation through small incisions.

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