

Biocompatibility of intraocular lens materials

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Current Opinion in Ophthalmology 2008, 19:41–49

Purpose of review

To provide an update on currently available materials used in the manufacture of intraocular lenses, as well as new materials under development, especially with regard to their uveal and capsular biocompatibility.

Recent findings

The biocompatibility of intraocular lens materials should be assessed in terms of uveal biocompatibility, related to the inflammatory foreign-body reaction of the eye against the implant, as well as in terms of capsular biocompatibility, determined by the relationship of the intraocular lens with remaining lens epithelial cells within the capsular bag. This situation may result in different entities, e.g. anterior capsule opacification, interlenticular opacification (between piggyback intraocular lenses), posterior capsule opacification and lens epithelial cell overgrowth. Reports on intraocular lens opacification suggest that the potential to calcify should also be taken into consideration when evaluating the long-term biocompatibility of a new material.

Summary

Intraocular lenses are being progressively implanted in much earlier stages of life (refractive lens exchange, pediatric implantation) and are expected to remain in the intraocular environment for many decades. Materials used in intraocular lens manufacture should, therefore, insure long-term uveal and capsular biocompatibility, as well as ultimate transparency after implantation.

Keywords

biocompatibility, hydrophilic acrylic, hydrophobic acrylic, intraocular lens, silicone

Curr Opin Ophthalmol 19:41–49
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1040-8738

Introduction

The article provides a review of recent findings regarding uveal and capsular biocompatibility of materials used in the manufacture of intraocular lenses (IOLs) that are currently available or under development. Aspects assessed include postoperative inflammatory reaction, opacification within the capsular bag (anterior capsule, interlenticular space, posterior capsule), cell overgrowth on the anterior IOL surface, as well as IOL opacification due to calcification. This review is timely, considering that IOLs are progressively being implanted in earlier stages of life and are, therefore, expected to remain transparent for many decades, without inducing inappropriate reactions from the host tissue.

Overview of biomaterials used in the manufacture of intraocular lens optics

Biomaterials (polymers) used for the manufacture of IOL optics can be divided into two major groups: acrylic and silicone. Acrylic lenses can be further divided as follows: rigid, e.g. manufactured from poly(methyl methacrylate) (PMMA); foldable, manufactured from hydrophobic acrylic materials, e.g. AcrySof (Alcon Laboratories, Fort

Worth, Texas, USA) and Sensar (Advanced Medical Optics, Santa Ana, California, USA) or manufactured from hydrophilic acrylics also known as hydrogels, e.g. Hydroview (Bausch & Lomb, Rochester, New York, USA), MemoryLens (Ciba Vision, Duluth, Georgia, USA) or Centerflex (Rayner Intraocular Lenses, Brighton-Hove, East Sussex, UK) [1–3].

Each currently available foldable acrylic lens design is manufactured from a different copolymer acrylic, with different refractive index, glass transition temperature (above this temperature the polymer exhibits flexible properties and below it remains rigid), water content, mechanical properties, etc. Hydrophobic acrylic lenses (as well as silicone lenses) have a very low water content, generally lower than 1%. Most of the currently available hydrophilic acrylic lenses are manufactured from copolymers with water contents ranging from 18 to 38% [2]. The Collamer material (Staar, Monrovia, California, USA) can also be included in the category of hydrophilic acrylic materials. This material is composed of a proprietary copolymer of a hydrophilic acrylic material and porcine collagen, with a water content of 34%.

The first silicone material used in the manufacture of IOLs was poly(dimethyl siloxane), which has a refractive index of 1.41. Latest generations of silicone materials have higher refractive indexes. While foldable acrylics display glass transition temperatures at around room temperature, the glass transition temperature of silicones can be significantly below room temperature. Another differentiating property between foldable acrylics and silicones is the refractive index, which is higher in the first group (1.47 or greater) so that acrylic lenses are thinner than silicone lenses for the same refractive power [1,2].

The surface properties of a polymer can be modified in order to ensure that it will be better adapted to its final use [4]. Basically, the surface energy of the polymer (hydrophilic vs. hydrophobic nature) can be modified according to three general methods: surface treatment, coating and graft of new molecules. Surface treatments can be used to create new chemical functions at the surface of the polymer, which will then be used for the grafting of new molecules. They can also be used to change certain surface characteristics of the polymer, such as roughness or hardness, without grafting of new molecules. A different polymer with appropriate properties can be used to coat the original polymer by adsorption, without real grafting of new molecules onto the surface of the latter. An example of this method in ophthalmology is the coating of PMMA IOLs with Teflon AF, rendering the surface of the PMMA IOL highly hydrophobic [5–8]. Different molecules can be permanently fixated or grafted onto the surface of the original polymer. The process may involve different steps, including an initial surface treatment in order to create new chemical functions that will be used to permanently graft the appropriate molecules. This method has been used in ophthalmology to render the surface of PMMA IOLs more hydrophilic by heparin surface modification [9,10], or more hydrophobic by surface passivation [11] or tetrafluorocarbon plasma treatment [12]. Although heparin-surface-modified lenses were found to have greater biocompatibility than unmodified PMMA lenses in terms of inflammatory reactions, especially in the pediatric population [10], there appears to be no advantage in terms of secondary cataract [9].

Other important elements of the IOL optic component are represented by the ultraviolet (UV)-absorbing compounds (chromophores). These are incorporated to the IOL optic in order to protect the retina from UV radiation in the 300–400 nm range, a protection normally provided by the crystalline lens. Two classes of UV-absorbing chromophores are used in general for the manufacture of pseudophakic IOLs: benzotriazole and benzophenone [2].

More recently, yellow hydrophobic acrylic IOLs containing a blue light-filtering chromophore (besides the

standard chromophore for protection against UV radiation) have become available in the market (AcrySof Natural) [13^{**},14^{**},15^{*},16^{*}]. The addition of a covalently bonded yellow dye results in an IOL UV/visible light transmittance curve that mimics the protection provided by the natural, precataractous adult human crystalline lens. There is indirect evidence showing that this addition may result in a reduction of the risk for macular degeneration or its progression. Clinical studies demonstrated that the biocompatibility of this yellow lens is overall similar to that of the same lens manufactured without the blue light-filtering chromophore. Only one study on pediatric implantation showed that transient inflammation is higher with implantation of yellow compared with non-yellow IOLs, but long-term inflammatory sequelae were roughly equal, as was the rate of posterior capsule opacification (PCO) [16^{*}].

Other manufacturers adopted the approach of a violet light-filtering chromophore (Bausch & Lomb). This approach was based on studies indicating that UV radiation and violet light (400–440 nm) have substantial potential acute UV/blue phototoxicity and provide negligible visual information, while blue light (440–500 nm) has significant potential acute UV/blue phototoxicity, but it is vital for scotopic vision [17,18^{**}].

Two new IOL materials currently being clinically investigated are materials with photochromic and light adjustable properties. The Medennium Inc. (Irvine, California, USA) hydrophobic acrylic material containing a photochromic chromophore has an UV/near blue absorption curve similar to the AcrySof Natural lens when exposed to UV light, while it behaves as a standard UV-absorbing IOL in an indoor or night environment [19^{**}]. The lens optic changes, therefore, from colorless to yellow when exposed to UV light and back to colorless in indoor environments. The Calhoun Vision (Pasadena, California, USA) silicone light adjustable material contains macromers and photoinitiators, besides the silicone matrix polymer and standard chromophore for UV protection [20,21^{*}]. The photosensitive silicone subunits (macromers) move within the lens optic upon fine tuning with a low-intensity beam of near-UV light. The refractive power of the lens can, therefore, be adjusted noninvasively after implantation to give the patient a definitive refraction. Biocompatibility studies involving at least 6 months of implantation in rabbit eyes were performed before clinical implantation of these two new materials, which were found to induce reactions similar to standard IOLs.

New methods of surface modification of IOLs currently being evaluated *in vitro* and *in vivo* include the covalent grafting of poly(ethylene glycol) on the surface of hydrogel IOLs [22^{*}], the covalent grafting of 2-methacryloyloxyethyl phosphorylcholine on the surface of

silicone IOLs through air plasma treatment [23^{*}] or grafting of the same molecule on the surface of hydrophobic acrylic lenses [24^{*}] and the active oxygen processing on the surface of hydrophobic acrylic lenses through UV/ozone or argon plasma irradiation [25^{*}]. All laboratorial analyses so far showed improvement in IOL biocompatibility, in terms of PCO formation.

Inflammatory response of the eye after intraocular lens implantation: uveal biocompatibility

Cataract surgery with IOL implantation produces a breakdown of the blood–aqueous barrier, with immediate release of proteins and cells into the anterior chamber. Protein adsorption on the surface of the IOL is the first phenomenon observed. It depends on factors such as the surface energy of the IOL biomaterial and its chemical structure. This phenomenon will influence subsequent cell interaction in the material–tissue interface observed in the following minutes or hours. The complement system is activated by the alternative pathway, with attraction of polymorphonuclear leukocytes and monocytes, which are at the origin of macrophages and giant cells constituting a foreign-body reaction directed against the IOL [26]. Surface specular microscopy confirmed that inflammatory cell deposits are a normal occurrence on the lens surface for up to 1 year after surgery [27]. This cellular response consists of two distinct processes: a response with small round, fibroblast-like cells, which peaks by 1 month, and a later giant cell response, which peaks at 3 months (Fig. 1). Giant cells then degenerate and detach from the IOL surface, and only an acellular proteinaceous membrane usually surrounds the IOL, isolating it from the surrounding ocular tissues.

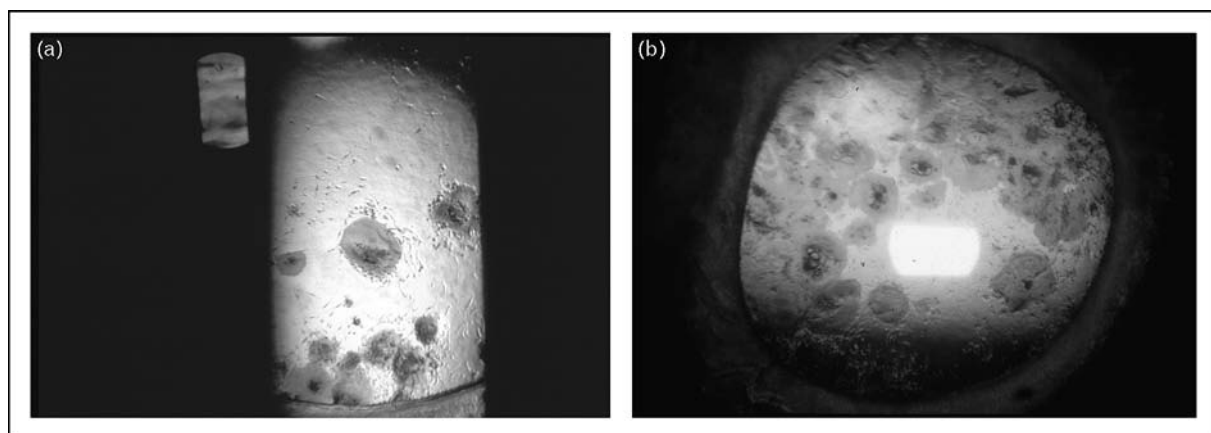
Different clinical studies compared the inflammatory reaction after implantation of IOLs manufactured from different biomaterials [28–35]. Comparison of postoperative flare values showed no clinically relevant differences among foldable biomaterials in patients with or without associated history of uveitis. Although absolute flare values and cell counts in eyes with uveitis were higher than in control eyes, primarily because of a damaged blood–aqueous barrier, postoperative recovery was similar. Also, no significant difference was observed in flare values between eyes having heparin-surface-modified PMMA IOL implantation or those having hydrophobic acrylic IOL implantation through the same-size incision in diabetic patients [36].

In terms of cellular inflammatory reactions, variations on the intensity and duration of each response (small cells or giant cells) may be found according to the IOL biomaterial evaluated. Some studies showed a tendency of the hydrophobic acrylic IOLs towards higher incidences of late foreign-body cell reaction [29,31], while others showed less giant cells with these lenses [27]. In all cases, however, the cellular reaction was low grade and clinically insignificant.

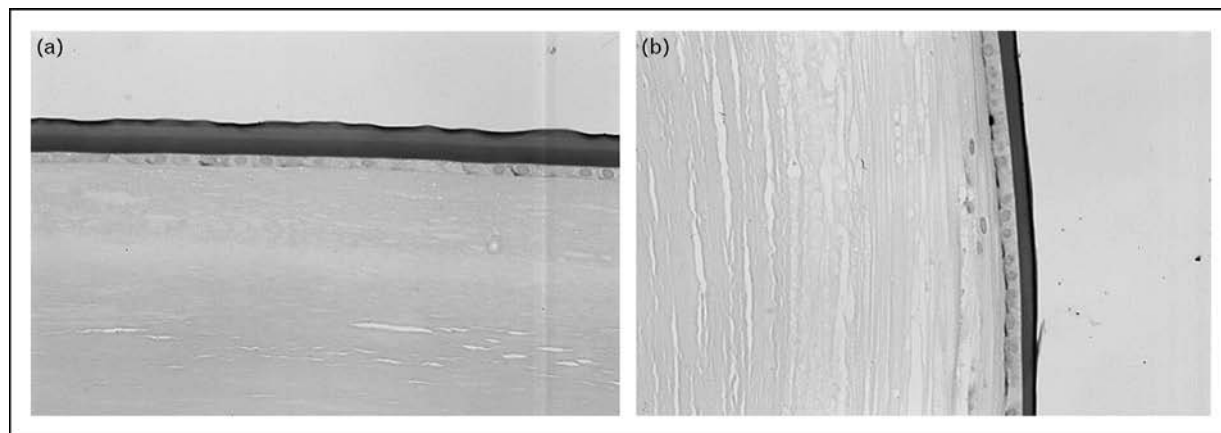
Lens epithelial cell proliferation after intraocular lens implantation: capsular biocompatibility

The epithelium of the natural crystalline lens consists of a sheet of anterior epithelial cells ('A' cells) that are in continuity with the cells of the equatorial lens bow ('E' cells) (Fig. 2). The latter cells comprise the germinal cells that undergo mitosis as they peel off from the equator. They constantly form new lens fibers during normal lens

Figure 1 Cellular reaction on the surface of intraocular lenses



Specular photomicrograph showing foreign-body giant cells, fibroblast-like cells and epithelioid cells on the surface of a hydrophobic acrylic intraocular lens, 3 months postoperatively (a). A foreign-body giant cell membrane can be observed on the surface of a hydrophobic acrylic lens in a case of uveitis, 1 year postoperatively (b). Courtesy: Professor Michael Amon, Vienna, Austria.

Figure 2 Histology of the human crystalline lens

High magnification light photomicrographs showing the A lens epithelial cells attached to the inner surface of the anterior capsule (a) and the E cells at the equatorial region of the crystalline lens (b).

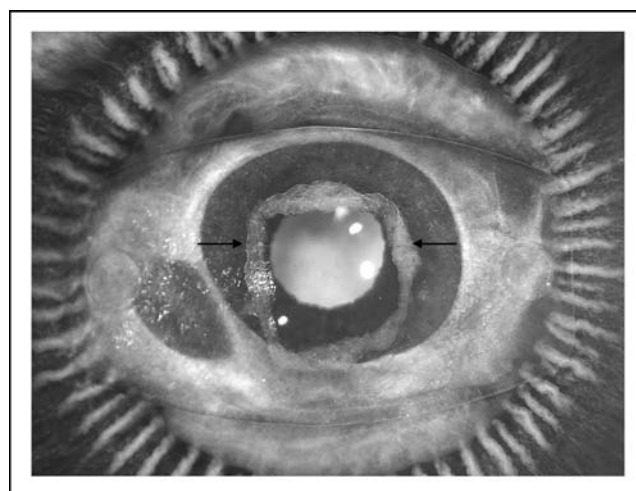
growth. Although both the anterior and equatorial lens epithelial cells (LECs) stem from a continuous cell line and remain in continuity, it is useful to divide these into two functional groups. They differ in terms of function, growth patterns and pathologic processes. The anterior, or 'A' cells, when disturbed, tend to remain in place and not migrate. They are prone to a transformation into fibrous-like tissue (pseudofibrous metaplasia). In contrast, in pathologic states, the 'E' cells of the equatorial lens bow tend to migrate posteriorly along the posterior capsule. In general, instead of undergoing a fibrotic transformation, they tend to form large, balloon-like bladder cells (the cells of Wedl), also known as Elschnig pearls. These are the cell types involved in the different forms of postoperative opacification of the capsular bag, including anterior capsule opacification (ACO), PCO and interlenticular opacification (ILO), in the interface between piggyback IOLs (Figs 3 and 4) [37].

Anterior capsule opacification

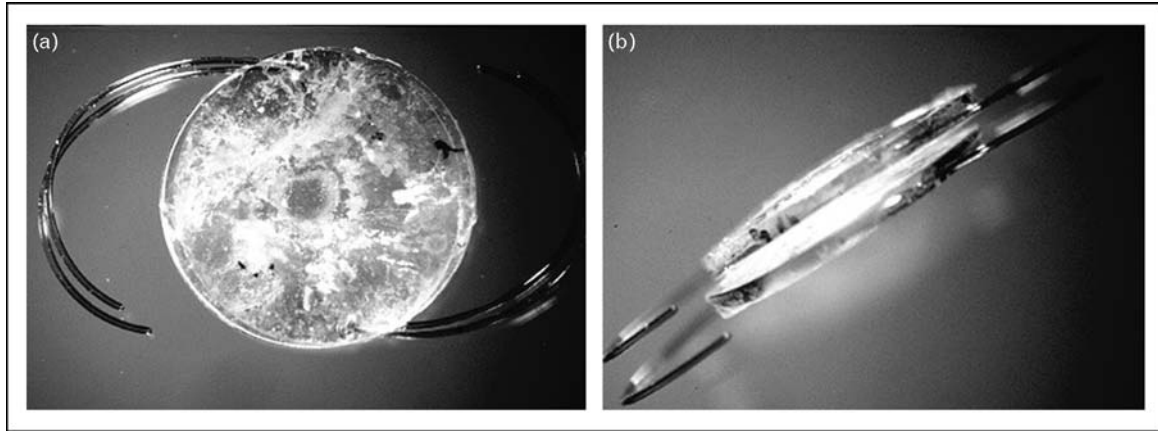
ACO has mostly been considered a clinical problem when anterior capsular shrinkage associated with constriction of the anterior capsulotomy opening (capsulorhexis contraction syndrome or capsular phimosis) accompanies excessive anterior capsule fibrosis. There has, however, been increasing concern about ACO due to the development of accommodating IOLs, generally designed to present a forward movement of the optic upon efforts for accommodation. Autopsy eye studies showed that ACO is more common with silicone IOLs, especially the plate designs, because of the larger area of contact between these lenses and the anterior capsule [38,39]. More recent studies, however, did not demonstrate statistically significant differences in ACO between hydrophobic acrylic and silicone lenses made of latest-generation

silicone materials [40**]. The edge of the anterior optic surface of the IOL (round or sharp) does not have an influence on the degree of ACO [40**]. This complication occurs in the area of contact between the inner surface of the anterior capsule and the anterior IOL optic surface; therefore, it has been used as an index of biomaterial biocompatibility. ACO may eventually be prevented by the use of an IOL that does not keep contact with the inner surface of the anterior capsule [41,42,43**]. Clinical studies also demonstrated that eyes in which the anterior capsule

Figure 3 Anterior capsule opacification and posterior capsule opacification (PCO)



Gross photograph of a human eye obtained postmortem, implanted with a plate silicone lens (Miyake-Apple view). The capsulorhexis rim is fibrotic and the anterior capsule is opacified where it keeps contact with the anterior intraocular lens surface. Soemmering's ring formation can be observed in the equatorial region of the capsular bag. A central posterior capsulotomy was performed due to PCO (arrows). Note the fibrotic tissue extending through the large fixation holes of the lens.

Figure 4 Interlenticular opacification (ILO)

Gross photographs of a pair of piggyback hydrophobic acrylic lenses explanted because of ILO (a: frontal view; b: side view). The lenses are attached to each other via the material within the interlenticular space. The pathology of this material is similar to the pearl form of posterior capsule opacification. Reproduced from [63], © 2002, with permission from Elsevier.

had been polished had significantly less ACO and reduced capsulorhexis aperture contraction 3 months after cataract surgery [44^{••},45[•]].

Posterior capsule opacification

Secondary cataract or PCO is the most common post-operative complication of cataract surgery [46[•],47^{••}]. This complication has been the object of a recently published review [47^{••}]. In terms of IOL material capsular biocompatibility, the ‘sandwich’ theory states that a hydrophobic acrylic IOL with a bioadhesive surface would allow only a monolayer of LECs to attach to the capsule and the lens, preventing further cell proliferation and capsular bag opacification. We performed two immunohistochemical studies on the adhesion of proteins to different IOLs that had been implanted in human eyes obtained postmortem, which confirmed the presence of greater amounts of fibronectin (protein mediating adhesion) on the surfaces of a hydrophobic acrylic lens (AcrySof, Alcon) [48,49]. Even though differences among materials exist, however, in terms of PCO prevention it appears that the geometry of the lens, with a square posterior optic edge, is the most important factor [50[•],51^{••},52[•],53^{••}]. Animal as well as clinical studies also demonstrated that this feature should be present for 360° around the optic, as the optic–haptic junction of single-piece lenses may represent sites where the edge barrier effect is absent [54,55,56[•]].

The ‘bag-in-the-lens’ concept, which involves the use of a twin-capsulorhexis IOL design, and performance of anterior and posterior capsulorhexis of the same size, significantly reduces the interaction of the lens with the capsular bag. If the capsules are well stretched around the optic of the lens, the LECs will be captured within

the remaining space of the capsular bag and their proliferation will be limited to this space, so the visual axis will remain clear [57^{••},58[•]–60[•]].

Interlenticular opacification

I consider it is important to re-assess factors leading to ILO, as there are dual-optic accommodating IOLs being developed [61[•]]. There is also an increased interest in the piggyback procedure, involving implantation of multifocal lenses [62[•]]. To date, all cases of ILO we have analyzed in our laboratory seem to be related to two hydrophobic acrylic IOLs (AcrySof, Alcon) being implanted in the capsular bag through a small capsulorhexis, with its margins overlapping the optic edge of the anterior IOL for 360° [63]. When these lenses are implanted in the capsular bag through a small capsulorhexis, the bioadhesion of the anterior surface of the front lens to the anterior capsule edge and of the posterior surface of the back lens to the posterior capsule prevents the migration of the cells from the equatorial bow onto the posterior capsule. This migration may be directed towards the interlenticular space. In this scenario, the two IOLs are sequestered together with aqueous and LECs in a hermetically closed microenvironment. In addition, the adhesive nature of the material seems to render the opacifying material very difficult to remove by any surgical means. The opacification within the interlenticular space is derived from retained/regenerative cortex and pearls, which is similar to the pathogenesis of the pearl form of PCO.

ILO can be prevented by two different surgical methods. The first option is to implant both IOLs in the capsular bag, but with a relatively larger diameter capsulorhexis. In this scenario, there is a possibility that the cut edge of the rhexis may fuse with the posterior capsule. This

fusion should help sequester the retained/proliferated equatorial LECs within the equatorial fornix. The other possibility is to implant the anterior IOL in the sulcus and the posterior IOL in the bag with a small rhexis. The rhexis margin will adhere to the anterior surface of the posterior IOL and the cells within the equatorial fornix will also be sequestered [62*,64*]. Clinical evidence, however, suggests that, in this case, the IOL fixated in the sulcus should have a smooth, rounded anterior optic edge, as well as thin haptics. This situation would minimize its interaction with the posterior iris surface, preventing complications such as pigmentary dispersion syndrome [65,66*]. According to the implantation site, the IOL design may significantly influence the overall IOL biocompatibility.

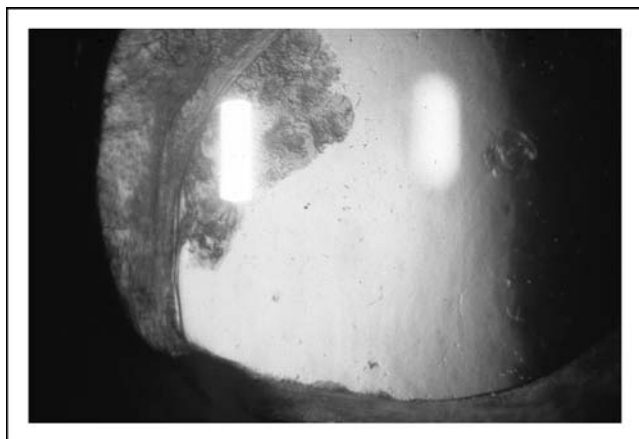
Lens epithelial cell ongrowth

In addition to being involved in capsular bag opacification, LECs located close to the capsulorhexis edge may proliferate onto the anterior IOL surface, a phenomenon known as LEC ongrowth, which usually does not cause opacification and has no influence on visual function [67–69]. This finding has been observed with different IOL biomaterials, especially with hydrophilic acrylic lenses and more particularly with the Hydroview design (Bausch & Lomb) (Fig. 5).

Long-term biocompatibility: biomaterial calcification potential

Long-term biostability of new IOL biomaterials may be assessed by tests such as those used in accelerated hydrolytic and UV aging studies, among others [70]. Considering the reports on IOL optic calcification of some hydrophilic

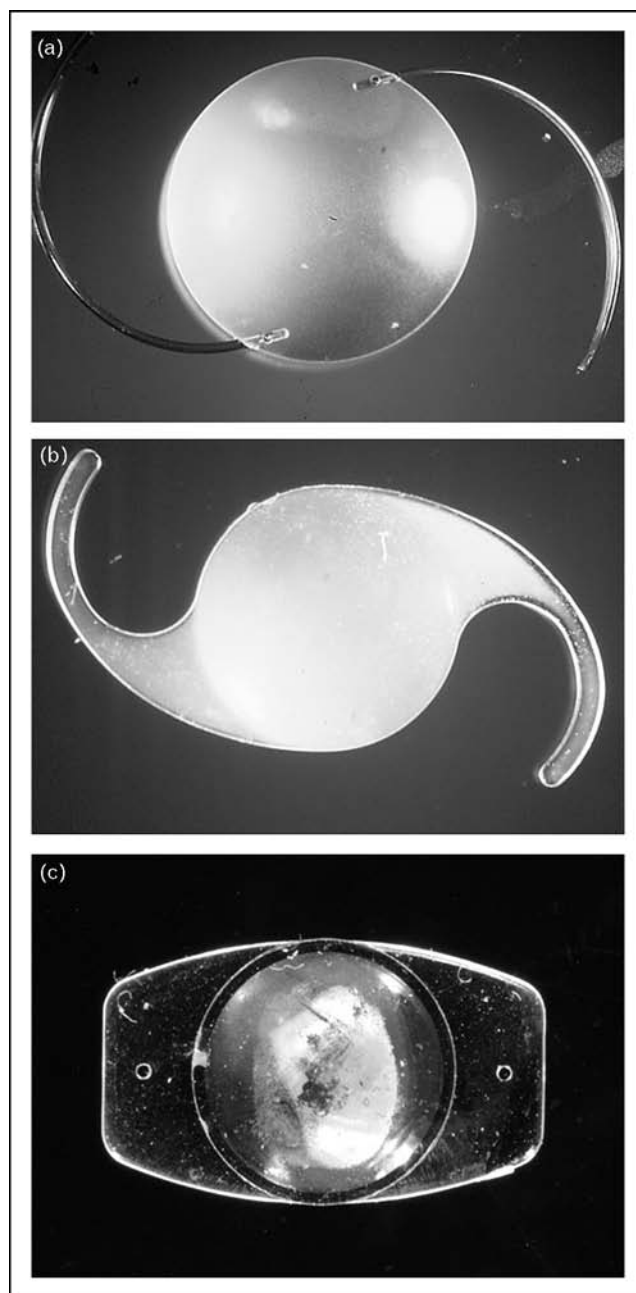
Figure 5 Lens epithelial cell (LEC) ongrowth



Specular photomicrograph taken 6 months postoperatively showing LEC ongrowth on the anterior surface of a Hydroview intraocular lens, originating from the capsulorhexis edge. Courtesy: Professor Michael Amon, Vienna, Austria.

acrylic designs appearing since 1999 [71,72**], it is reasonable to conclude that the potential of an IOL material to calcify should also be taken into consideration when evaluating the long-term biocompatibility of a new material. An experimental study demonstrated that subcutaneous and/or intramuscular rabbit implantation

Figure 6 Intraocular lens calcification



Gross photographs of hydrophilic acrylic (a and b), and silicone (c) lenses explanted because of calcification. Calcified deposits were found on the surface of the lens in (a) (MemoryLens; Ciba Vision), while they were predominantly found within the substance of the lens in (b) (Aqua-Sense, Ophthalmic Innovations International). The deposits were only observed on the posterior optic surface of the lens in (c) and were in relation to asteroid hyalosis.

appears to be an excellent model for screening new materials for calcification potential [73]. To date, the four major designs manufactured in the USA involved in the problem of dystrophic calcification were the Hydroview (Bausch & Lomb), the MemoryLens (Ciba Vision), the SC60B-OUV (Medical Developmental Research, Clearwater, Florida, USA), and the Aqua-Sense (Ophthalmic Innovations International, Ontario, California, USA). The calcified deposits causing the opacification were basically found on the optical surfaces of the Hydroview and the MemoryLens (Fig. 6a), while they were predominantly found within the substance of the SC60B-OUV and the Aqua-Sense (Fig. 6b). This problem appears to be multifactorial and the possibility of host environment factors (patient-related) cannot be ruled out at this point. Studies demonstrated that silicone lenses may also develop optic calcification in eyes with asteroid hyalosis (Fig. 6c). It is, however, still unclear why only a few cases have been observed, while there have probably been many implantations of silicone lenses of various designs in patients with asteroid hyalosis [74]. It is, therefore, difficult to proscribe silicone IOL implantation in the presence of asteroid hyalosis at this point.

Conclusion

The biocompatibility of IOL materials should be assessed in terms of uveal biocompatibility, related to the inflammatory foreign-body reaction of the eye against the implant, as well as in terms of capsular biocompatibility, determined by the relationship of the IOL with remaining LECs within the capsular bag [28]. Research on factors to optimize IOL biocompatibility, minimizing postoperative inflammatory reaction and preventing opacification within the capsular bag, as well as any form of IOL opacification, is increasing in significance with the increase in popularity of procedures such as refractive lens exchange.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 72–73).

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