Graefes Arch Clin Exp Ophthalmol (2008) 246:719–728
DOI 10.1007/s00417-007-0759-2

REFRACTIVE SURGERY

Crystalline lens changes in porcine eyes with implanted phakic IOL (ICL) with a central hole

Tetsu Shiratani · Kimiya Shimizu · Kunitoshi Fujisawa · Shigekazu Uga · Koichi Nagano · Yuuki Murakami

Received: 24 May 2007 / Revised: 26 August 2007 / Accepted: 15 December 2007 / Published online: 26 February 2008

Abstract
Background We calculated the smallest diameter of a hole in the center of the optic at which the optical character of a phakic IOL (ICL) may be maintained. The changes induced in the aqueous humor dynamics and the pathology of cataract development with such a hole were investigated.
Methods A simulation was performed using ZEMAX software to calculate the hole diameter that makes possible the maintenance of a stable optical character of a phakic IOL. After a hole of calculated diameter was trepanned in the center of the optic of the ICL, the latter was implanted into one eye of a 5-month-old minipig, and an unperforated ICL into the other. The postoperative course was observed for 3 months. Then, Evans blue was injected into the vitreous body under general anesthesia to stain the anterior capsule of the crystalline lens. Within 30 min, the eye was enucleated and the tissues removed were fixed.
Results The MTF of the perforated ICL (hole diameter, 1.0 mm) in the center of the optic resembled that of the unperforated ICL. In all cases with non-perforated ICLs, subcapsular turbidity developed, but no staining caused by EB was observed in the anterior capsule. On the other hand, the anterior capsules of the eyes fitted with ICLs with a 1.0-mm hole were stained, but exhibited no turbidity.
Conclusion An ICL with a central hole of diameter 1.0 mm in the optic is similar to an unperforated ICL. The size of the hole influenced the aqueous humor dynamics and increased the aqueous humor perfusion volume over the entire anterior surface of the crystalline lens. The possibility of preventing cataracts was therefore suggested.

T. Shiratani (✉) · K. Shimizu · K. Fujisawa · K. Nagano · Y. Murakami
Department of Ophthalmology, School of Medicine,
Kitasato University,
1-15-1 Kitasato,
Sagamihara, Kanagawa 228-8555, Japan
e-mail: tetyu-metal@y3.dion.ne.jp

S. Uga
Department of Orthoptic and Visual Science,
School of Health Sciences,
International University of Health and Welfare,
Otawara, Tochigi, Japan

Introduction

The use of a phakic IOL for eyes with high refractive errors that cannot be corrected with refractive surgery has become increasingly popular. Implantation of a phakic IOL involves no optical invasion because the optical region of the cornea is not incised, and lens exchange may be possible if an error or a change of refraction occurs as a result of a reversible maneuver. ICL (Staar Surgical, Monrovia, CA, USA) is a posterior-sac type of phakic IOL that can be used to correct a wide range of refractive errors (-20D to +20D). It can be implanted into the eye through a corneal incision of only 3.2 mm. A current issue of concern, however, is a secondary cataract as a postoperative complication [1, 3, 4, 11, 13, 17]. According to the reported results of ICL clinical trials in the US, the incidence of secondary cataract is 2.1% within 1 year and 2.7% within 3 years after surgery [8, 16]. However, the reasons for this are not yet understood. Fujisawa et al. implanted several types of ICL into the eyes of pigs, and reported changes in aqueous humor dynamics and in the crystalline lens. Implantation of ICLs of the ordinary type into porcine eyes was followed in all cases by turbidity as an anterior subcapsular cataract. Similar, but milder, symptoms were seen after the implantation of all ICLs with four holes around the optic. On the

other hand, ane ICL with a 3.0 mm hole in the center of the optic improved the aqueous humor circulation, and no turbidity is reported in any instance beneath the anterior capsule [2]. Although this method revealed the risk of turbidity in the anterior capsule, such a large hole in the optic compromises lens function. We therefore calculated the diameter of the central optic hole that would not affect the optical character of the lens, and conducted an experiment in which such perforated lenses were implanted into porcine eyes in order to observe the changes in aqueous humor dynamics and the occurrence of secondary cataract.

Materials and methods

Calculation of hole diameter

To calculate the diameter of the hole in the center of the optic that does not affect the properties of the ICL, a simulation was performed using ZEMAX software (ZEMAX Development Corporation, Bellevue, WA, USA). As a basic specification of eyeball models, the pupil diameter was set at 3.0 mm using the Gullstrand model eye. Then, the modulation transfer function (MTF) was set to the maximum level occurring at the location of the retinal image. Four lenses of the same size as the optical diameter of the ICL were added to this eyeball model, one with no hole at all, the others with holes of 2 mm, 1.5 mm and1.0 mm respectively. We then compared and reviewed the contrast at a spatial frequency of 100 cycles/mm to evaluate ocular performance [9].

Implantation experiment

The study was performed on 12 eyes of six minipigs (Göttingen strain) aged 5 months. Each minipig was raised in an animal room 6 m^2 in area and maintained with 12-h light-dark cycles. The animal was fed twice a day and given water freely. After about 1 month, the center of the optic of the perforated ICL was implanted into one eye using a trepan of a diameter that caused no problems during the computer simulation. An unperforated ICL was implanted into the other eye. After implantation of the lenses, the animals were raised in the same room for 3 months, during which their progress was observed. The eyeball was then extirpated. For that period, the anterior ocular segment was photographed and the course was observed. Regarding ICL, a minus lens 13.0 mm in diameter was used. Although there were individual differences, we took the average of the actual values of the white-to-whites and used it to decide the lens size.

Implantation method

Endotracheal intubation was performed after anesthesia was induced with an infusion of pentobarbital sodium. Inhalation anesthesia was administered using nitrous oxide laughing gas. Temporal keratotomy of 3.2 mm in length was performed, and the anterior chamber and a cartridge for ICL implantation were filled with a viscoelastic substance. The ICL was pressed into this substance, and the cartridge was then slid into a special injector. The cartridge was inserted from its front end into the wound, and the injector was operated with great care to avoid contact of the cartridge with the crystalline lens, so that the ICL entered the anterior chamber. The four haptics were positioned behind the iris. During surgery, we operated with care so as, again, to avoid any contact with the crystalline lens. After the haptics were securely in place, the viscoelastic substance was removed. Finally, the corneal wound was sutured with 10-0 nylon.

Follow-up

Postoperatively, instillation of 0.5% levofloxacin, 0.1% diclofenac sodium and 0.5% betamethasone sodium phosphate was carried out four times a day for 1 week. The anterior ocular segment was photographed 1 week, 1 month, 2 months, and 3 months after surgery, and the course was observed.

Pigment injection and extirpation of eyeball

To determine the hemodynamics of the aqueous humor before the extirpation of the eyeballs, 10 μl of 20% Evans blue pigment dissolved in physiological saline (molecular weight 960.8) was injected into the anterior part of the vitreous body of each minipig eye from the ciliary ring, using an Ito microsyringe with a 31 gauge needle under general anesthesia. After 30 min, the pigment was circulated in the aqueous humor. The eyeball was then extirpated and fixed with 4% glutaraldehyde-0.1 M phosphate buffer. After extirpation, the minipigs were treated according to the ARVO resolution regarding animals used in research.

Fixing the eyeball

After the extirpated minipig eyeballs were fixed with 4% glutaraldehyde-0.1 M phosphate buffer, the eyeball was cut in half, and the ICL and crystalline lens were removed from the eyeball. At this time, the torn surface of the eyeball, the anterior and posterior surfaces of the extirpated crystalline lens, and the ICL were observed under a stereoscopic microscope. In addition, the eyeballs were left in fixative for 3 days to fix the eye tissues thoroughly. The extirpated crystalline lens was cut in half again, and the torn surface was observed under the stereoscopic microscope.

The specimen was fixed with 1% osmic acid-phosphate buffer 4 h after washing with 0.1 M phosphate buffer. After being dehydrated with an ethanol series, it was further dehydrated three times with propylene oxide and was embedded into Quetol 812. Semithin sections were stained with toluidine blue and then observed under a light microscope. Thin sections were stained with uranyl acetate and lead citrate, and examined by electron microscopy.

Calculation of crystalline lens turbidity area

For the turbid part of the anterior surface of the crystalline lens observed under a stereoscopic microscope, an image of the anterior surface of the porcine crystalline lens was cropped using "Adobe Photoshop" (an image-editing program) according to the size of the ICL optic, and the cropped image was subjected to black-and-white processing. Then, a border was drawn with the computer mouse immediately around the area of turbidity, the image was pixelized, and the number of pixels in the turbid part (which was black) was counted to make possible calculation of the ratio between the turbid and cropped optical areas. We calculated the proportions of the unperforated and perforated lenses represented by the turbid areas, and used Student's *t*-test to compare these proportions.

Results

Hole diameter

The simulation results obtained using the optical design software ZEMAX are shown in Fig. 1. In the table, the ordinate represents contrast and the abscissa, the waveform region. Fig. 1d shows the simulation in which the lens has no hole, and the contrast is 0.45 when the MTF is 100 cycles/mm. As Fig. 1a shows, the contrast is 0.15 (rate of decrease, 67%) when MTF is 100 cycles/mm, and in Fig. 1b, it is 0.23 (rate of decrease, 49%) when the MTF is 100 cycles/mm. These rates of decrease were much greater than those seen with an unperforated lens. On the other

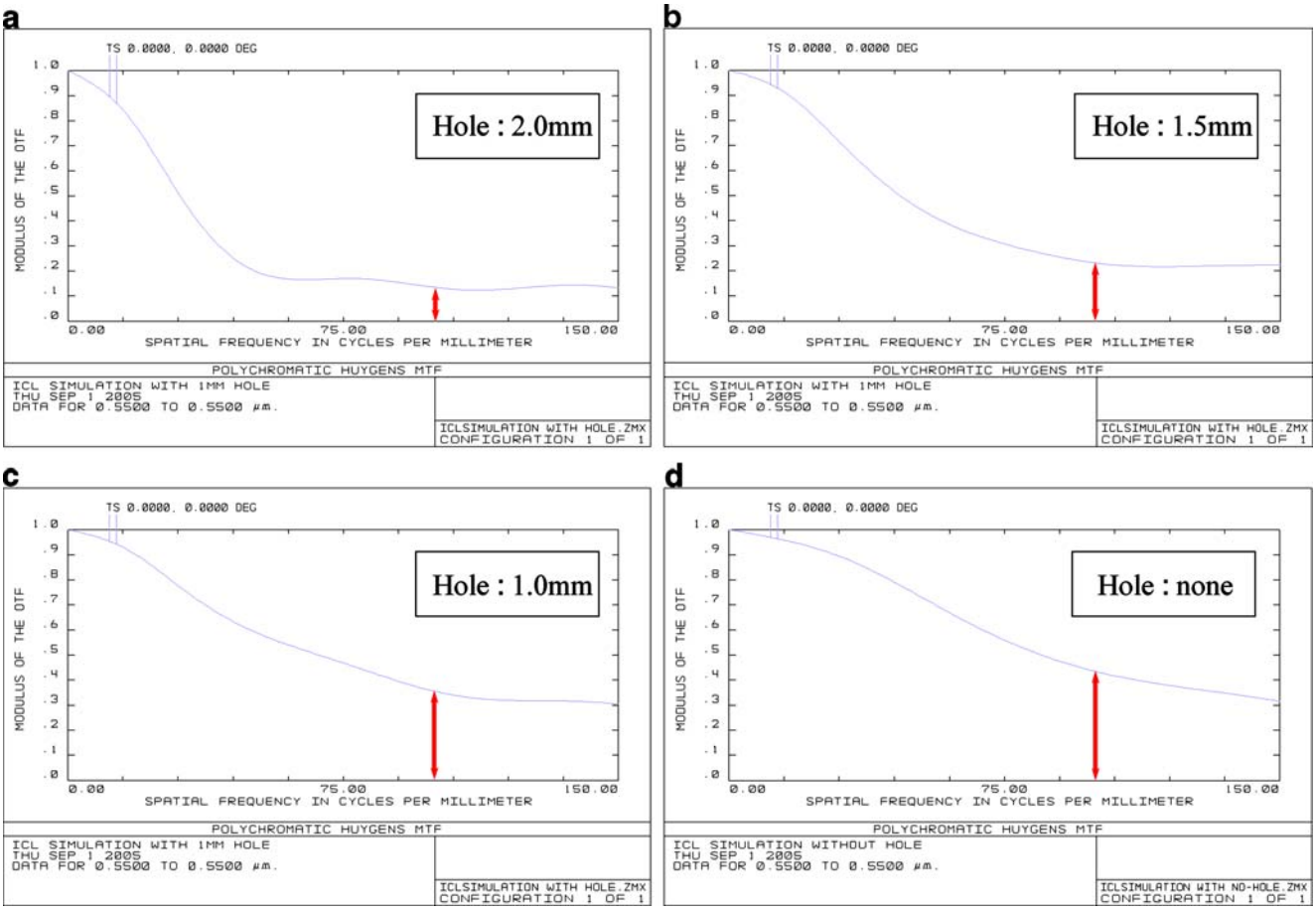

Fig. 1 Results of simulation by ZEMAX. *Red arrows* represent contrast level when MTF is 100 cycles/mm. **a** Contrast level: 0.15. **b** Contrast level: 0.23. **c** Contrast level: 0.39. **d** Contrast level: 0.45

hand, since the contrast was 0.39 (rate of decrease, 13%) when MTF was 100 cycles/mm, there was a smaller decrease (Fig. 1c).

According to simulation using ZEMAX, the degrees of contrast depicted in Figs. 1c,d were similar. On the basis of this result, a 1.0-mm hole was made in the center of the ICL optic using a trepan, and subsequently, the implantation experiment was conducted (Fig. 2).

Crystalline lens turbidity area

In the slit-lamp microscope image 1 month after ICL implantation, both the unperforated and the perforated lenses were free of turbidity in the crystalline lens (Fig. 3a,d). However, 3 months after the ICL was implanted, the unperforated ICL had induced turbidity on the anterior surface of the crystalline lens, while the perforated-ICL showed no turbidity (Fig. 3b,e). After eyeball extirpation, stereoscopic microscope examination showed light turbidity consistent with the turbidity on the anterior surface of the crystalline lens observed using a slit-lamp microscope for the unperforated ICL, but no turbidity or any other abnormality was found with the perforated ICL (Fig. 3c,f). The proportion of each turbid area is shown in Table 1. The cases shown in *gray* were excluded from the review because there were postoperative complications. All cases in which unperforated ICLs were implanted had turbidity covering 4.7–31.3% of the area of the anterior crystalline lens and located in its center, while all cases in the group with perforated ICLs had no turbidity whatsoever, and there was a significant statistical difference in the area of turbidity between the two groups of cases.

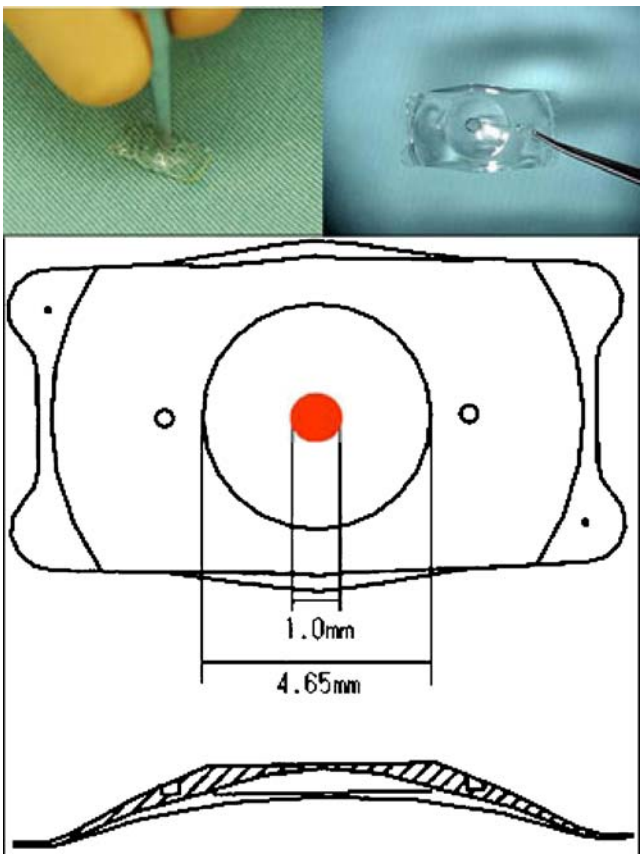

Fig. 2 A hole of 1.0 mm diameter was prepared in the center of the optic using a trepan

Stain state in cranial sac by pigment injection

Pigment was injected into the anterior part of the vitreous body to compare the degree of staining on the anterior surface of the crystalline lens. In the unperforated ICL, the posterior capsule of the crystalline lens was strongly stained, but the anterior capsule, only slightly (Fig. 4a). On the other hand, in the perforated ICL, the posterior capsule of the crystalline lens was strongly stained and its anterior capsule was also comparatively well stained (Fig. 4b).

Histopathological findings

Light-microscopic observation of the equator of the crystalline lens in the eye into which a perforated ICL had been implanted showed a mixture of light cells and dark cells in the crystalline lens epithelial cells (Fig. 5a). Electron-microscopic observation of these epithelial cells showed no remarkable changes in the cytoplasm in either light or dark cells. However, the enlarged cisterns of the granular endoplasmic reticulum were observed in the dark cells (Fig. 5b, 6). Examination at high magnification showed accumulations of stringy material in the cisterns (Fig. 6). In the dark cells, unlike the light cells, there were many filaments in the cytoplasm. In the stella lentis iridica, light cells and dark cells were mixed, as they were at the equator, but the proportion of dark cells was greater than in the latter region (Fig. 7a). Electron-microscopic examination showed no structural abnormality in the organelles of epithelial cells, but the contrast between light cells and dark cells was marked, and enlarged cisterns were present in the granular endoplasmic reticulum of the dark cells (Fig. 7b). In the layers of fibrocytes under the epithelial cells, considerable amounts of granular material suggesting organellar denaturation were observed (Fig. 7d). The cortical fibers in the stellae lentis hyaloidea of both eyes with perforated, and those with unperforated lenses exhibited no abnormality (Fig. 7c).

In the eyes containing an ICL with a central hole, there were few dark epithelial cells at the equator of the crystalline lens (Fig. 5c). Electron-microscopic observation showed no structural abnormality in the organelles of the

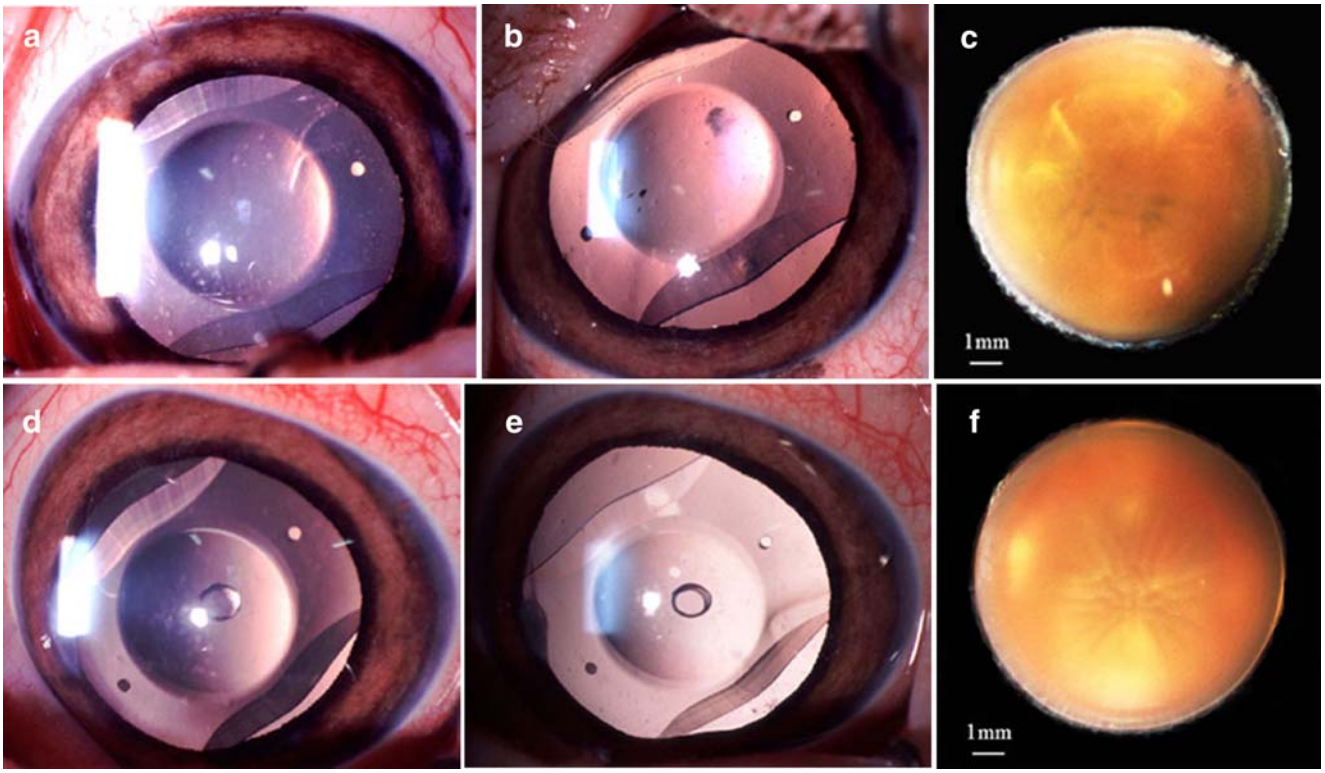

Fig. 3 **a** Slit-lamp microscope image 1 month after an unperforated ICL was implanted. The crystalline lens has no turbidity. **b** Slit-lamp microscope image 3 months after an unperforated ICL was implanted. The anterior of the crystalline lens shows turbidity. **c** Stereoscopic photomicrograph of the anterior surface of the crystalline lens in an eye with an unperforated ICL. The anterior surface of the crystalline lens exhibits slight turbidity. **d** Slit-lamp microscope image 1 month after a perforated ICL was implanted. The crystalline lens shows no turbidity. **e** Slit-lamp microscope image 3 months after a perforated ICL was implanted. The crystalline lens shows no turbidity. **f** Stereoscopic photomicrograph of the anterior surface of the crystalline lens in an eye fitted with a perforated ICL. The anterior surface of the crystalline lens is not turbid

Table 1 Fractions of the total anterior surface of the crystalline lens occupied by the turbid material in eyes bearing perforated ICLs

Unperforated ICL opacity area (%)	Perforated ICL opacity area (%)
2.7	4.3
25.8	0.0
16.0	0.0
12.1	0.0
4.7	0.0
31.3	2.0

t-test $P<0.05$*

The cases with gray shading were excluded from the review because there were postoperative complications (2 cases of severe postoperative inflamation 1 of displacement of the haptics). The turbid areas have statistically significant differences.

epithelial cells of the crystalline lens and almost no enlarged cisterns in the granular endoplasmic reticulum, which was observed in the eyes with an ICL without a hole (Fig. 5d). In the stella lentis iridica, as well as at the equator, scarcely any dark cells were seen, and the rest of the crystalline lens had a normal structure (Fig. 8a). In the stellae lentis hyaloidea of eyes with perforated and with unperforated lenses, the cortical fibers showed no abnormality (Fig. 8b).

Discussion

Fujisawa et al. have reported that ICLs with a 3.0 mm hole in the center of the optic improved the aqueous humor circulation, and that there was no turbidity in any instance beneath the anterior capsule, but they did not examine the optical character of the lens [2]. It is a matter of course that a 3.0 mm hole should affect the optical character of the lens. We therefore examined the clinical application of the ICL with the central optic hole, and calculated the maximum diameter of the central optic hole that would not affect the optical character of the lens, and conducted an

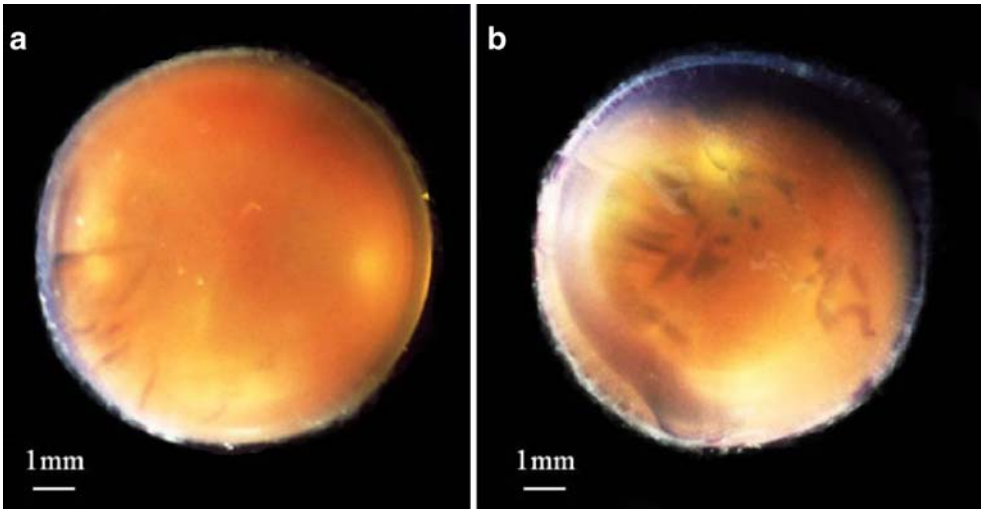

Fig. 4 **a** Stereoscopic photomicrograph of the anterior surface of the crystalline lens in an eye containing an unperforated ICL. The anterior surface of the crystalline lens was slightly stained by Evans blue. **b** Stereoscopic photomicrograph of the anterior surface of the crystalline lens in an eye containing a perforated ICL. The anterior surface of the crystalline lens was relatively well stained by Evans blue

experiment in which such perforated lenses were implanted into porcine eyes in order to observe the changes in aqueous humor dynamics and to see whether a secondary cataract would occur. To calculate a hole diameter that will not affect the optical character of an ICL, a computer simulation was performed using the commercial optical design software ZEMAX, and the results were compared with those of ICLs without holes. In a 1.0-mm-diameter perforated ICL, the rate of decrease in contrast was reduced, as in the case of unperforated ICLs. This result suggests that it is desirable for maintaining good image formation that the size of the central hole in the ICL optic be 1.0 mm or less. In this experiment, a trepan of the minimum diameter (1.0 mm) was selected, and a hole was

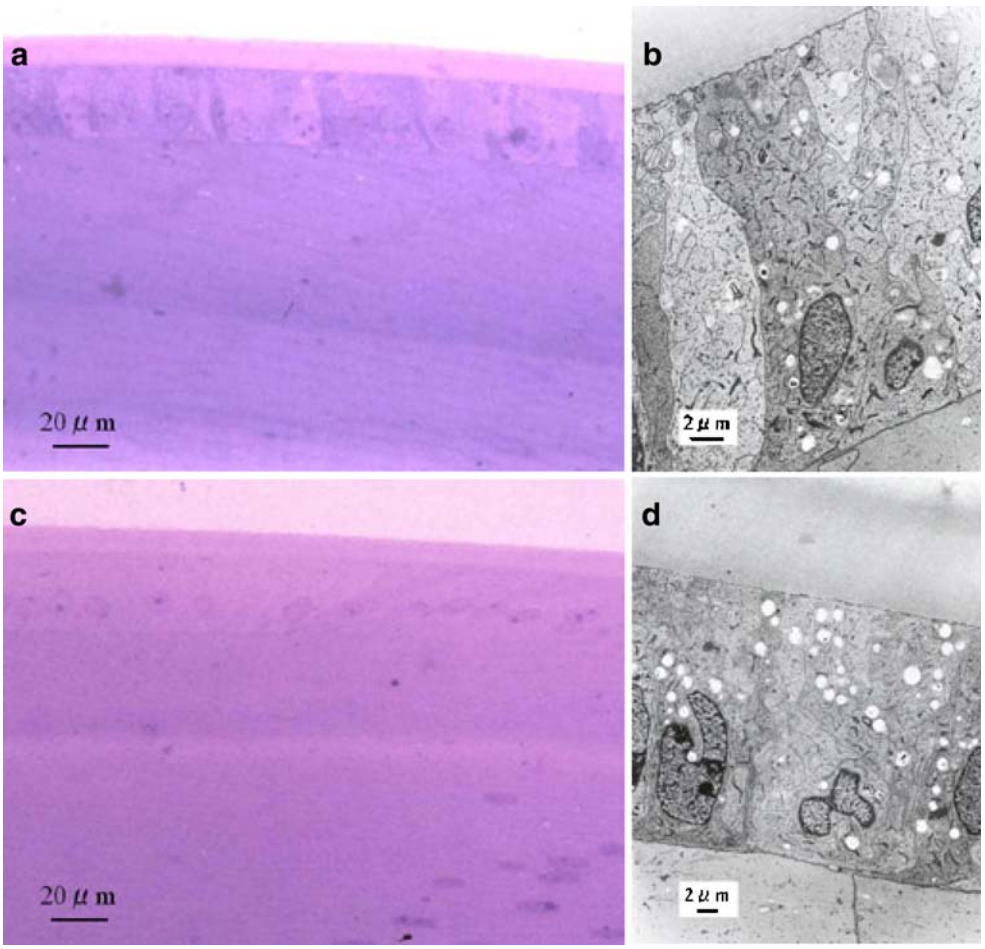

Fig. 5 **a** Photomicrograph of epithelial cells at the crystalline lens equator in an eye bearing an unperforated ICL. A mixture of light cells and dark cells is present. **b** Electron-microscope image of epithelial cells at the crystalline lens equator in an eye containing an unperforated ICL. Neither light nor dark cells exhibit any structural abnormality in their organelles. However, in the granular endoplasmic reticulum of the dark cells there are many enlarged cisterns. **c** Photomicrograph of epithelial cells at the equator of the crystalline lens in an eye with a perforated ICL. Few dark cells can be seen. **d** Electron-microscope image of epithelial cells at the equator of the crystalline lens in an eye bearing a perforated ICL. There is no structural abnormality in the organelles

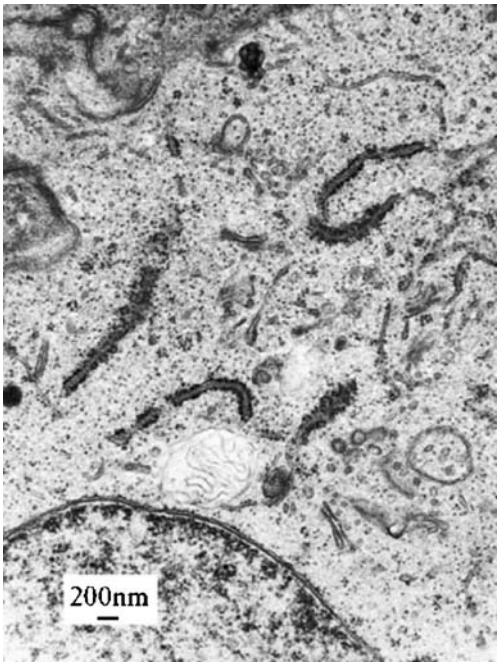

Fig. 6 Electron-microscope image of dark cells in the crystalline lens equator in an eye bearing an ICL without a hole. Enlarged cisterns in the granular endoplasmic reticulum are present, and it can be seen that they contain a stringy material. Many fibrous bodies can be seen in the cytoplasm

made in the center of the ICL optic to implant an ICL. One focus of this study was an optical simulation model, with the eventual aim of investigating the usefulness of perforating an ICL for implantation into a human eye without aggravating aberration or the quality of the retinal image. The perforation is intended to correct the aqueous humor circulation dynamics currently encountered behind an unperforated ICL. The next stage of this research will seek to demonstrate in humans that the degree of aberration and the quality of the retinal image achieved with a perforated lens are desirable. In addition, it is necessary to develop a new design in which the lens does not become displaced, because its displacement will probably prevent it from correctly fulfilling its function.

All cases of unperforated ICL had turbidity with an area ratio of 4.7–31.3% in the center of the anterior surface of the crystalline lens. In contrast, all cases of perforated ICL with a 1.0-mm hole in the center of the optical part were entirely free of turbidity. Fujisawa et al. have reported the possible reasons for the far higher speed and frequency of cataract development in minipigs than that in human eyes, and that turbidity with an area ratio of 15 to 21% developed in all pigs with an unperforated ICL of lens diameter 13.0 mm implanted into the eye. They have also reported that, for an ICL with a 3.0 mm hole in the center of the ICL optic, no eye showed turbidity because the aqueous humor perfusion on the anterior surface of the crystalline lens increased, resulting in an adequate provision of the substances needed for the metabolic activity of the crystalline lens [2]. The present experiment yielded findings similar to those in the report by Fujisawa et al. In other words, unperforated ICLs cause cataracts, but placing a hole in the center of the optic appears to prevent the

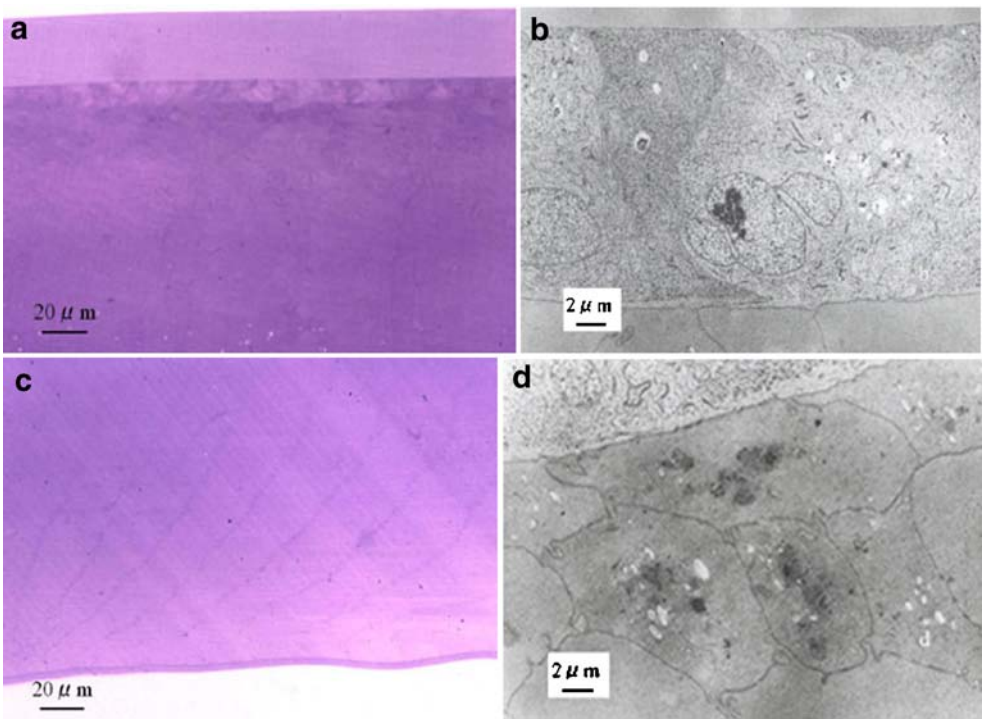

Fig. 7 **a** Photomicrograph of epithelial cells in the stella lentis iridica in an eye with an unperforated ICL. There is a mixture of light and dark cells, and the cells appear to have a markedly irregular morphology. **b** Electron-microscope image of epithelial cells in the stella lentis iridica in an eye containing an unperforated ICL. The organelles show no structural abnormality, but there is a distinct contrast between light and dark cells, and the latter have many enlarged cisterns in the granular endoplasmic reticulum. **c** Photomicrograph of the stella lentis hyaloidea in an eye bearing an unperforated ICL. No particular abnormality can be seen. **d** Electron-microscope image of subepithelial fiber cells in the stella lentis iridica in an eye fitted with an unperforated ICL. The cells vary in size and contain granular material

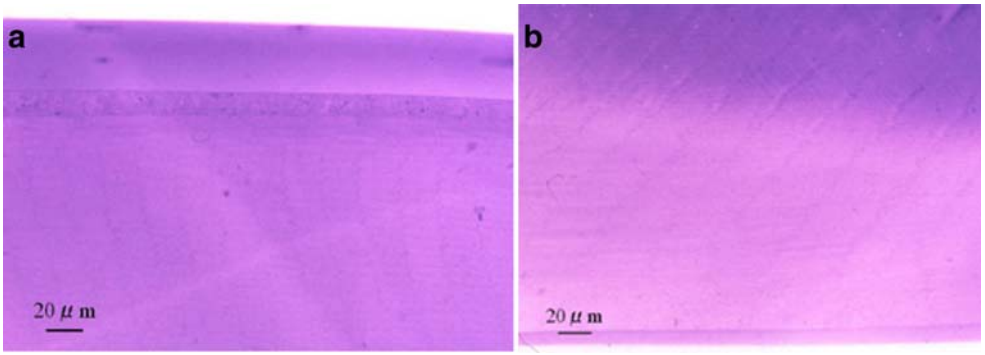

Fig. 8 **a** Photomicrograph of epithelial cells in the stella lentis iridica in an eye containing a perforated ICL. Small dark cells are present. **b** Photomicrograph of the stella lentis hyaloidea in an eye fitted with a perforated ICL. No particular abnormality can be seen

development of a secondary cataract. In addition, it was found that, even if the hole diameter is only 1.0 mm, cataracts can be prevented. The mechanism of cataract prevention is considered to be related to the aqueous humor circulation. When pigment was injected into the anterior part of the vitreous body, and staining of the anterior capsule of the crystalline lens was confirmed, in the unperforated ICL the anterior capsule was only slightly stained, while in the perforated ICL it was relatively well stained. This slightly stained state is thought to result from changes in the aqueous humor circulation dynamics resulting from implantation of the unperforated ICL, and from inadequate perfusion of the aqueous humor through the space between the anterior of the crystalline lens and the ICL. However, it is considered that the 1.0-mm hole in the center of the ICL optic allowed aqueous humor perfusion from the posterior side onto the anterior surface of the crystalline lens and out through the ICL into the anterior chamber via the 1.0-mm hole, resulting in staining of the anterior capsule. This indicates that the aqueous humor spreads out between the anterior surface of the crystalline lens and the ICL.

In this experiment, periodic examinations were conducted using the slit-lamp microscope, and each time the anterior ocular segment was photographed and recorded (Fig. 9a,b). Of all cases in both eyes with unperforated ICLs and perforated ICLs, the distance between the anterior surface of the crystalline lens and the ICL (vaulting) was maintained at about 1/4 to 1/3 of the corneal thickness. Since the thickness of the cornea of the minipigs used in this experiment was about 800 μm, at least 150-μm vaulting was needed. In humans, one report states that the vaulting is 0.15 mm or more [3], and thus the present vaulting was considered adequate. In addition, only as a guide, at examination time the eyes with perforated ICLs appeared to have narrower vaulting than those with unperforated ICLs. In the latter eyes, the vaulting was slightly enlarged because of stagnation of aqueous humor between the crystalline lens and the ICL. In contrast, in the perforated ICL, the space was narrowed because the aqueous humor flowed out via the hole in the optic. These results suggest the possibility that a small difference in vaulting occurs.

Usually, in the crystalline lens, the state of high K^+ and low Na^+ is maintained by Na-K ATPase. It has been reported that, from this concentration difference, an electrochemical potential of 24 mV is generated at the epithelial side, and that ions and nutrients such as amino acid were incorporated in the crystalline lens [10]. In the Nakano mouse (cac mouse), which is well known as a hereditary cataract model, it has been reported that since its cataracts result from the inhibition of Na-K ATPase,

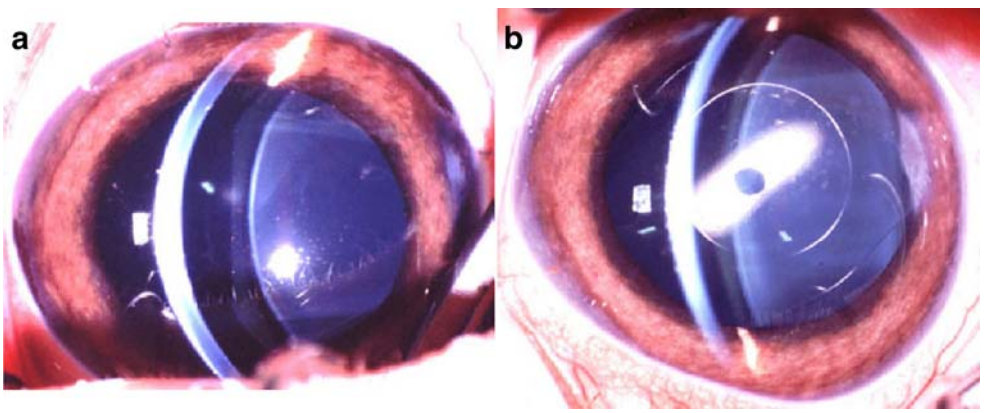

Fig. 9 **a** Slit-lamp microscope image of an eye bearing an unperforated ICL. The ICL is not in contact with the crystalline lens, and the vaulting measures about 1/4 to 1/3 of the thickness of the cornea. **b** Slit-lamp microscope image of an eye containing a perforated ICL. The ICL is not in contact with the crystalline lens, and the vaulting measures about 1/4 to 1/3 of the thickness of the cornea

swelling, disruption, and vacuolation of the fiber cells in the stellae lentis iridica and hyaloidea occur [6]. In addition, in relation to changes in the crystalline lens due to trauma, it has been reported that when trauma occurred, reduplication of the crystalline lens also took place [7, 18]. In this study, the cataracts caused by implantation of unperforated ICLs were always anterior subcapsular cataracts. The histopathological findings were a mixture of light and dark epithelial cells on the crystalline lens and many enlarged cisterns in the granular endoplasmic reticulum. The disturbance has progressed beyond not only the epithelial cells but also the fiber cells. Normal fiber cells have almost the same shape and size, while the morphology of the fiber cells in the crystalline lens of the eye fitted with an unperforated ICL shows cells of varying size containing much granular material. In short, we consider that the tissue abnormalities that we observed are similar to the abnormalities in cataracts resulting from the inhibition of Na-K ATPase, rather than to those in cataracts due to trauma. This is thought to be because the presence of an unperforated ICL suppressed adequate perfusion of the aqueous humor, and the metabolic activity in the epithelial cells of the crystalline lens was disturbed, which resulted in a lack of normal protein synthesis and in changes in the epithelial cells. Fujisawa et al. have reported that cataracts are caused by degeneration of the epithelial cells of the crystalline lens and by the consequent enlargement of the capsules of the granular endoplasmic reticulum [2]. Although these have been reportedly caused by prolonged circulatory disturbance of the aqueous humor, no such dramatic changes were observed in this study. However, the abnormality in the granular endoplasmic reticulum is consistent in type but not in amount, and we consider that it is involved in some metabolic disturbances.

Turbidity occurred in the stella lentis iridica only, but histopathological examination showed the same abnormality in the epithelial cells at the equator of the crystalline lens, although it was milder than that in the stella lentis iridica. It has been shown that in a normal monkey eye, ^{35}S-L-cystein is absorbed from near the equator of the crystalline lens, especially the germinative zone, into the crystalline lens, and is transported to the stellae lentis iridica and hyaloidea [15]. In another report, it was shown that when iodoacetic acid, which is harmful to the crystalline lens, was intraperitoneally administered into rats, it was transferred via the blood from the ciliary body into the posterior chamber, and was absorbed by the epithelial cells of the crystalline lens at the equator of the crystalline lens [14]. In short, the equator of the crystalline lens plays an important role in the absorption of nutrients. In this result, it is possible that the metabolic disturbance was accelerated by changes in the epithelial cells at the equator.

On the other hand, for the stella lentis hyaloidea, neither the eyes with unperforated ICLs nor those with perforated ICLs had any histopathological abnormality. This is a very interesting finding when considered together with the cell growth factors. One of the cell growth factors, transforming growth factor β (TGF_β), is present in the anterior chamber and the vitreous body, and promotes and inhibits cell growth depending on the types and quantities of the cells affected. Although it is reported that anterior subcapsular cataract is induced by TGF_β [5, 12], it mainly modulates cell differentiation. TGF_β absorbed from the posterior capsular side is transferred to the stella lentis iridica, where it affects the epithelium of the crystalline lens to differentiate them from fiber cells. In this experiment, when either a perforated or an unperforated ICL was implanted, there was no histopathological abnormality whereby the absorption and transport of TGF_β occurred in the stella lentis hyaloidea, but unperforated ICLs caused mild differentiation abnormalities in the stella lentis iridica and at the equator. It may be that, although TGF_β absorption from the stella lentis hyaloidea was normal, inhibition of TGF_β absorption from the anterior chamber led to this mild differentiation abnormality.

This study indicated that, in eyes bearing unperforated ICLs, the epithelial cells of the stella lentis iridica and the equator of the crystalline lens consisted of a mixture of light and dark cells, and suggested that the cisterns of the granular endoplasmic reticulum of these dark cells became enlarged as a result of disturbances of normal protein synthesis. Although the morphology of fiber cells showed a wide variation in size, and although degenerated organelles were found here and there, there was no abnormality in the stella lentis hyaloidea. On the other hand, for eyes in which perforated ICLs had been implanted, there was little abnormality in the stella lentis iridica or hyaloidea, or at the equator.

In short, there is no need for a hole of as much as 3 mm in the center of the ICL optic, because a hole of only 1.0 mm in diameter adequately increased the aqueous humor perfusion volume on the anterior surface of the crystalline lens, resulting in the prevention of cataract. In addition, it was found that a hole of 1.0 mm in diameter in the center of the optic had no optical effect on vision.

Acknowledgments The authors wish to thank Mr. C. W. P. Reynolds for his careful linguistic assistance with this manuscript.

References

1. Arne JL, Lesueur LC (2000) Phakic posterior chamber lenses for high myopia: Functional and anatomical outcomes. J Cataract Refract Surg 26:369–374

2. Fujisawa K, Shimizu K, Uga S, Suzuki M, Nagano K, Murakami Y, Goseki H (2007) Changes in the crystalline lens resulting from insertion of a phakic IOL (ICL) into the porcine eye. Graefes Arch Clin Exp Ophthalmol 245:114–122
3. Gonvers M, Bornet C, Othenin-Girard P (2003) Implantable contact lens for moderate to high myopia. Relationship of vaulting to cataract formation. J Cataract Refract Surg 29:918–924
4. Gonvers M, Othenin-Girard P, Bornet C, Sickenberg M (2001) Implantable contact lens for moderate to high myopia short-term follow-up of 2 models. J Cataract Refract Surg 27:380–388
5. Hales AM, Chamberlain CG, McAvoy JW (1995) Cataract induction in lenses cultured with transforming growth factor-β. Invest Ophthalmol Vis Sci 36:1709–1713
6. Hara A, Matsumoto M, Uga S (1999) Morphological study on cataractogenesis of the Nakano mouse lens. Graefes Arch Clin Exp Ophthalmol 237:249–255
7. Hirayama S, Wakasugi A, Morita T, Sakai Y, Mukuno K, Uga S, Shimizu K (2003) Repair and reconstruction of the mouse lens after perforating injury. Jpn J Ophthalmol 47:338–346
8. ICL in Treatment of Myopia (ITM) Study Group (2004) United States Food and Drug Administration clinical trial of the implantable collamer lens (ICL) for moderate to high myopia: three-year follow-up. Ophthalmology 111:1683–1692
9. International Organization for Standardization (ISO) 11979-2. Ophthalmic implants - Intraocular lenses - Part 2: Optical properties and test methods: 1999(E)
10. Kinsey VE, Hightower KR (1978) Studies on the crystalline lens. XXV. An analysis of the dependence of the components of the potential on sodium-potassium fluxes based on the pump-leak model. Exp Eye Res 26:157–164
11. Lackner B, Pieh S, Schmidinger G, Simader C, Franz C, Dejaco-Ruhswurm I, Skorpik C (2004) Long-term results of implantation of phakic posterior chamber intraocular lenses. J Cataract Refract Surg 30:2269–2276
12. Liu J, Hales AM, Chamberlain CG, McAvoy JW (1994) Induction of cataract-like changes in rat lens epithelial explants by transforming growth Factor β. Invest Ophthalmol Vis Sci 35(2):388–401
13. Masket S (2003) Cataract surgical problem. J Cataract Refract Surg 29:1058–1059
14. Matsumoto M, Morita T, Hirayama S, Uga S, Shimizu K (2002) Morphological analysis of iodoacetic acid-induced cataract in the rat. Ophthalmic Res 34:119–127
15. Sweeney MHJ, Garland DL, Truscott RJW (2003) Movement of cysteine in intact monkey lenses: the major site of entry is the germinative region. Exp Eye Res 77:245–251
16. The Implantable Contact Lens in Treatment of Myopia (ITM) Study Group (2003) U.S. Food and Drug Administration clinical trial of the implantable contact lens for moderate to high myopia. Ophthalmology 110:255–266
17. Uusitalo RJ, Aine E, Sen NH, Laatikainen L (2002) Implantable contact lens for high myopia. J Cataract Refract Surg 28:29–36
18. Wakasugi A, Uga S, Sakai Y, Matsumoto M, Hirayama S, Shimizu K (2002) Response of the mouse lens to varying sizes of lnjured area. Jpn J Ophthalmol 46:391–400