TITLE: CHANGING THE APPARENT COLOR OF THE EYE: A REVIEW ON SURGICAL ALTERNATIVES, OUTCOMES AND COMPLICATIONS

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ABSTRACT

Background. There is an increasing number of people asking for the elective change of eye color. We review the surgical techniques, outcomes and complications arising from the different existing surgical alternatives, including the cosmetic iris implants -which should be considered based on the available evidence as malpractice-, the laser iris depigmentation and the cosmetic keratopigmentation.

Main text. Laser iris depigmentation has been in clinical use for aesthetic purposes without obtaining a license yet; it can be performed in an outpatient clinic thanks to the use of Nd:YAG laser but literature data about this treatment are poor. Cosmetic iris implants are not CE marked or FDA approved, and lead to severe complications arising from their placement including uveitis, hyphema, glaucoma, cataract, corneal endothelial damage and severe vision loss. Management of complications resulting from iris implants might require several surgical procedures, and the follow-up is difficult among these poorly informed patients. Keratopigmentations are one of the most widely studied techniques and have long been investigated before being introduced into clinical practice: already introduced centuries ago, it was developed and perfected up to an excellent level of safety and efficacy. The medium and long-term cosmetic outcomes of keratopigmentation are highly appreciated by the patients.

Conclusions. The available level of evidence makes cosmetic keratopigmentation the surgical choice for patients asking for a permanent eye color change. Still, more investigation and work should be carried out to decrease the postoperative complications and investigate the long-term outcomes of the new surgical alternatives.

KEYWORDS

Eye Color Change; Keratopigmentation; Cosmetic Iris Implants; Laser Depigmentation.

BACKGROUND

Different surgical techniques have been proposed for the treatment of patients requiring an elective and permanent change of eye color. Keratopigmentation (KTP) [1-3] has long been investigated before being introduced into clinical practice; nevertheless, other techniques such as laser iris depigmentation, even if interesting in the results, are been in clinical use even before there are relevant data in the literature. [4, 5] Finally, cosmetic iris implants have been surrounded by growing malpractice: even if not approved, they are continuously used in some countries, leading to their tremendous complications. [6-9] No previous review reports are available on the topic of the different surgical alternatives to changing the apparent color of the eye. In the current review, we are going to provide the technical and surgical characteristics of the various alternatives, the level of evidence existing today for their practice and a broad view of what is reported in the literature concerning the corresponding outcomes and complications. This review is important to help doctors and patients to choose wisely between the different surgical alternatives, knowing the state of the art of each of them and their level of effectiveness and any eventually associated complications.

LASER DEPIGMENTATION

Surgical Techniques. The procedure uses a device mounted onto the slit-lamp biomicroscope that produces a frequency-doubled 532 nm wavelength neodymium: yttrium-aluminium-garnet (Nd:YAG) laser with a different spot diameter. Yildrim et al [4] conducted an animal study using a 900 µm spot size: they applied 200 laser shots (A.R.C. Laser, Germany) in 2 groups of rabbits divided according to the energy levels (group A, 0.8 mJ; group B, 1.2 mJ) with a time application laser of 3 nanoseconds. 120 pulses were administered at the first session; the same dose and pulses were repeated at the second session, which was two weeks after the first application; finally, both groups received 200 laser pulses at the third session to fill the gap between spots. Thus, in total, the laser was applied minimally as 352 mJ in group A (0.8 mJ ×440 pulses/3 sessions) and maximally as 660 mJ in group B (1.5 mJ ×440 pulses/3 sessions).

Basoglu et al [5] treated sectorial heterochromia in a 22-year-old man with a 400-mm spot diameter. The energy level was adjusted to 0.5 mJ. They divided the area of treatment into 3 zones and 100 pulses/d were applied on each zone to complete the treatment in 3 days. 1 month after the first session, the patient returned to repeat the session and complete the treatment. In both studies, pupils were constricted before laser application with miotic eyedrops.

STRŌMA® Laser System (available at https://www.stromamedical.com) is another investigational device that is not currently approved for commercial use. It uses a laser procedure that generates a low-energy laser beam that heats the brown pigment on the front surface of the iris, revealing the natural underlying blue or green eye. However, the STRŌMA Laser procedure is not commercially available anywhere in the world and does not have a commercial release date since its under investigation and no literature is available on it.

Clinical Application, Outcomes and Complications. Laser iris depigmentation has been in clinical use for aesthetic purposes without obtaining a license yet, and literature data about this treatment are poor. Its use was introduced based on the satisfactory cosmetic results observed in the treatment of oculodermal melanocytosis [10] as well as in the dermatological treatment of cutaneous pigmentation.[11] It is proposed that eye color could be changed with this laser by reduction or elimination of melanin pigments on the anterior iris surface; however, because the procedure can only reveal the natural underlying grey stromal fibers, the patient cannot choose a blue or green eye as the procedure cannot change a blue eye to green or a green eye to blue. To our knowledge, in the only single case study about the human treatment with Nd:YAG laser, the authors reported an excellent cosmetic result with no side effects, and flare formation that disappeared after 3 days; however, data about intraocular pressure and other safety parameters are missed. [5]

In the animal investigation about this novel technique, the authors reported the presence of a patchy appearance in iris tissue at the first week in group A, as well as areas showing hyperpigmentation, that diminished at the end of the eighth week. In group B, mottling became more extensive on day 30 with a grayish appearance; hyperpigmented granular areas diminished on day 60 with a broken white appearance. They also observed ciliary injection and mild anterior chamber reaction in all groups on the first day, which became more prominent in group B and eventually disappeared after the first week. Nevertheless, they did not administer anti-inflammatory treatment, and there was no hypopyon or prolonged anterior chamber reaction. [4]

We report the case of a 25-year-old Caucasian female that was referred to our clinic because of binocular photophobia. She was treated in another clinic with laser iris depigmentation to change the apparent color of the eyes. At the slit-lamp examination, an extensive iris subatrophy was present in both eyes and was confirmed with anterior segment optical coherence tomography (AS-OCT) (Figure 1). The patient was also dissatisfied with the achieved eye color: we performed a cosmetic KTP to reduce the photophobia and, at the same time, achieved the desired cosmetic aspect.

COSMETIC IRIS IMPLANTS

Surgical Techniques. A variety of prosthetic iris implants have been used for functional, traumatic or congenital iris deficiencies since the first prosthetic iris was implanted in 1956: [12,13] nowadays, two medical devices are used for cosmetic purposes. The NewColorIris (Kahn Medical Devices, US patent 2006 #7025781 2B, available at https://www.google.com/patents/US7025781) is a silicone iris diaphragm with 6 rounded flaps at the periphery designed to hold it in place, between 11.0 mm to 13.0 mm in diameter with a pupillary aperture of 3.5 mm and a thickness of 0.16 mm. The BrightOcular (Stellar Devices LLC, US patent 2012 #8197540, available at http://www.google.com/patents/US8197540) presents some slight differences in size (11.5 to 13.5

mm in diameter and 0.16 to 0.18 mm in thickness). It is held in place by 5 peripheral triangular flaps and its posterior face presents grooves to facilitate the flow of the aqueous humor. [6, 8]

Both implants do not have a CE marking or FDA approval and, as will be discussed later in the review, lead to disastrous post-operative complications. Their use is strongly discouraged; therefore, we do not consider it in the interest of the review to proceed with the specifics about the surgical implant technique and their clinical application, but only with the management of their complications.

Clinical Application, Outcomes and Complications. Complications arising from the placement of cosmetic iris implants are serious and include uveitis, hyphema, glaucoma, cataract, corneal endothelial damage and severe vision loss. [6-9, 14-23] Corneal complications are the most common (figure 2), related to corneal edema because of loss of endothelial cell density (ECD) that may require a corneal transplant, as well as ocular hypertension because of three main mechanisms: direct trauma to the trabecular meshwork, peripheral anterior synechiae (figure 3) and iris pigment dispersion. [8,9] Corneal graft surgery may be required in eyes with previous glaucoma surgery, being more challenging as the anterior segment is usually abnormal either due to synechiae or the presence of a glaucoma tube. [24]

Despite both implants are not CE marked or FDA approved, the growing malpractice leads to continuous implantation of such device, and it is common to deal with patients reporting such complications. Hoguet et al [9] reported the presentation and management of fourteen eyes of 7 patients who had NewColorIris cosmetic iris implants in Panama City, Panama: all 14 eyes were eventually treated with explantation of the iris prosthesis (between 4 to 33 months after implant placement). Intraoperative complications included suprachoroidal hemorrhage during explantation in 1 eye and his vision was limited to hand motion. Postoperative complications included corneal edema in 8 eyes, early cataract development in 9 eyes and increased IOP/glaucoma in 7 eyes. Descemet-stripping automated endothelial keratoplasty was performed in 5 eyes, penetrating keratoplasty in 1 eye, cataract extraction with intraocular lens placement in 7 eyes, trabeculectomy in 3 eyes, and glaucoma drainage implant placement in 3 eyes.

Mansour et al [6] collected a collaborative case series of 12 patients who had bilateral cosmetic iris implants placement contacting authors who previously published about this topic: three cases of this series were previously presented in part as surgical videos or PubMed.[25, 26] 11 subjects had ocular manifestations including anterior uveitis (83.3%), glaucoma (58.3%) and corneal decompensation (50%). 4 patients, even if advised of the necessity to explant the prosthesis, refused because of the positive cosmetic effect achieved. A single patient had no ocular signs and symptoms but requested prophylactic removal of the implants.

Recently, El Chehab et al[8] reported a multicenter retrospective observational questionnaire-based study about the safety, complications and therapeutic management in a large French series of 65 eyes who had cosmetic iris implant placement. Of the 65 eyes analyzed, only 5 eyes (7.7%) did not experience any complication and 60 eyes (92.3%) had at least 1 complication. The most commonly reported complication was corneal decompensation (78.5%) and 13 eyes (20%) had a keratoplasty: of them, 11 eyes had Descemet's membrane endothelial keratoplasty (DMEK) and 2 eyes (one patient) had penetrating keratoplasty (PKP). The diagnosis of glaucoma was made in over half of the cases (52.3%) and a filtering surgery was needed in 15 eyes (21%). 16 eyes had cataract surgery with a mean age of 34.2 years. Explantation was needed in 81.5% of cases on average 2.3 ± 0.4 years after implantation. Among all explantation, 51 eyes had a complication and 2 eyes were explanted preventively. The remnant patients had been advised but refused explantation. The mean final visual acuity was 0.45 ± 0.08 logarithm of the minimum angle of resolution (logMAR) (0 to 2 logMAR).

Table 1 shows our series of 10 eyes of 5 patients referred for the management of complications derived from cosmetic iris implants (2 eyes had implantation of NewColorIris, 8 eyes had implantation of BrightOcular). All the eyes had been eventually explanted because of dangerous post-operative complications between 1 to 60 months after implantation. ECD was 848±227.5 and 30% of eyes required a corneal transplant: of them, 2 eyes had DMEK and 1 eye had PKP, while 3 patients have been advised of the necessity to perform a corneal transplant surgery (1 PKP and 2 DMEK) but they have not been performed yet (figure 4). 90% of the eyes had ocular hypertension or showed signs of glaucomatous neuropathy and filtrating surgery was needed in 2 cases (20%) to control the raised IOP. Early development of cataract was a common complication, as 40% of our patient required cataract surgery with the implant in one case of a Morcher iris-IOL device (Morcher GMBH, Stuttgart, Germany) because of the severe iris atrophy (figure 3.C): mean age at the time of cataract surgery was 36 years.

COSMETIC KERATOPIGMENTATION

Surgical Techniques. Three main surgical techniques have been described for KTP, which can be divided between intrastromal and superficial KTP. The recommended and most used in cases of cosmetic KTP is the femtosecond laser-assisted intrastromal technique (FAK),[1] in which a circular stromal tunnel is created with a femtosecond-laser: the tunnel is eventually opened to the periphery of the cornea until reaching the limbus with a lamellar dissector (KTP corneal dissector; Epsilon, Irvine, CA), followed by the injection of the pigment through the superior incision using a 27G flat cannula. [1-3, 27, 28]

Manual intralamellar KTP (MIK) is a surgical alternative for those clinics that do not have a femtosecond laser. Two to four freehand incisions are performed from the limbus to the border of a previously marked pupil. The cornea is then dissected intralamellarly and circumferentially using a microcrescent blade and helicoidal intrastromal corneal dissectors. [2]

Afterward, the pigment is injected as described above. [29, 30] We recommend the use of a femtosecond laser for the creation of the stromal tunnel as it allows a precise cut that can be created at any depth of the stroma.

Finally, superficial automated keratopigmentation (SAK) used a special micropuncture device [Vissum Eye MP System, Madrid, Spain (Apl. No. 2.949.539), provided by Blue Green Medical, Spain] with a customized set of power and depth according to the individual case, to deliver the pigments to the superficial layers of the cornea.[2, 31-33] The center of the cornea is previously marked with a caliper and the pupil size determined by an optic zone marker (Katena, New York, USA). SAK is recommended in cases of deep and dense corneal opacities or fine-touching the details of the iris pattern, but not as the first treatment choice for a patient seeking the elective change of the eye's color.

Third generation customized mineral micronized pigments were manufactured following the Ministry of Health and the Annex IV of European Regulation of Cosmetics: the CE mark certificated pigments (Blue Green Company, Spain) are composed of different amounts of lactic acid, propanediol, and micronized mineral pigments [color index: 77007, 77491, 77499, 77492, 77288, and 77891]. Mineral micronized pigments were prepared in agreement with the cosmetic desires of the patients, according to a proposed list of colors and computer simulations were also performed in most of the cases using the patient's picture and the proposed or selected color, to decide the most suitable one in agreement with the surgeon.[1]

Clinical Application, Outcomes and Complications. This technique has the largest number of scientific evidence, in addition to high quality in its therapeutic and cosmetic application. Alio et al in 2016 reported for the first time the outcomes of 7 patients treated with cosmetic KTP for elective change of eye color.[3] The authors reported excellent stability of the pigmentation pattern with a follow-up of up to 2.5 years, without signs of ocular toxicity and changes in patients' vision and astigmatism, thus representing a valid and safe surgical option for patients motivated to change the eyes color. In 2020, D'Oria et al prospectively reported the medium and long-term outcomes of 79 normally sighted eyes of 40 patients who performed a cosmetic KTP, with an average follow-up of 29 months up to a maximum of 69 months.[1] Observer's evaluation was excellent in 90% of cases, defined as the agreement with the proposed and the achieved color and a very natural appearance, patient's satisfaction was excellent in 92.5% of cases, and all the patients would repeat the surgery. No significant changes in topographic, pachymetric and refractive values and visual acuities had been reported, thus confirming the safety of the procedure. About complications, 2 patients experienced an intraoperative pigment dispersion at the site of a previous LASIK flap interface; no other intraoperative complications or any other intraoperative problems related to the surgical procedure were observed in any case. 12 patients (30%) complained about excessive light sensitivity, which eventually disappeared during the first postoperative month and was absent in those newest patients treated deepening the stromal pocket at more than 250 µm, not to stimulate the subbasal corneal nerve plexus. One patient (2.5%), who had a prior LASIK surgery, developed after 6 months a bilateral and progressive corneal ectasia and was successfully treated performing a standard epithelium-off corneal collagen cross-linking (CXL), being stable throughout 2 years of follow up following the CXL procedure. We recommend not to performed KTP in a LASIK patient as LASIK might represent a contraindication according to our evidence; nevertheless, according to our evidence, PRK does not represent a contraindication to KTP. Failure to meet the cosmetic expectation can cause dissatisfaction for patients after cosmetic procedures: we recommend to use a preoperative photo-editing software and discuss the color in agreement with the patient.

DISCUSSION

Individuals who wish to change the cosmetic appearance of their eyes can recourse to various surgical techniques that achieve it through a permanent change of the apparent eye color. However, different techniques have been described but the level of evidence available, the level of development and their safety rate make some of them not yet advisable or contraindicated. Complications arising from the placement of cosmetic iris implants are serious and have been described secondary to both BrightOcular and NewColorIris implantation. [6-9,19-21] The reported case series documented the occurrence of severe complications related to anterior segment damage, such as uveitis glaucoma and corneal decompensation, that can lead to severe and permanent visual loss and the need for secondary treatments;[6-9] also, patients usually reported no follow-up after surgery in the country where they have been implanted as they have been poorly informed. [8] Based on the retrospective nature of the literature available, it is not possible to determine the exact incidence of complications; however, since this is a cosmetic procedure, the presence of serious complications with devastating visual consequences would not be considered acceptable and makes this cosmetic implant not recommended for any patient. Laser iris depigmentation represents an innovative technique that is emerging in the clinical panorama, but it has not yet been extensively studied: data on animals' study and a single human case report are available in the literature,[4,5] and still needs to be improved not to determine a certain permanent degree of photo sensibility. KTP is the most widely studied technique of all: already introduced centuries ago, it was developed and perfected by our research team up to an excellent safety and efficacy profile, and has been used for a wide range of therapeutic, functional and cosmetic applications. [1-3, 27-29, 34-37] The outcomes of 79 eyes treated for purely cosmetic purposes have been reported by the authors, [1] showing the complications that have emerged in the course of the learning and study curve of this new technique and which have now disappeared in its most modern version: the functional, topographical and pachymetric parameters of the treated eyes are not modified by this technique, no eye has undergone complications that permanently compromise vision, and all patients have been extremely satisfied with the aesthetic outcome, thanks to the duration and resistance of the new micronized minerals pigments in use. [29, 30]

CONCLUSION

Patients seeking to change eye color permanently can recourse to various surgical techniques. Placement of cosmetic iris implants represents a surgical option that carries a high risk of definitive loss of vision as well as other fearsome complications that should be emphasized to patients. However, this surgical practice is still used in many countries, and it is necessary to be prepared to face any problems connected with it. Laser iris depigmentation represents an innovative and promising technique that is emerging in the clinical panorama. It has the advantage of being able to be performed in an outpatient clinic thanks to the use of Nd:YAG laser, but it has not yet been extensively studied. KTP is the most widely studied technique of all: the safety and efficacy level of this technique make its elective application the best option for an adequately selected patient who wishes to change the apparent color of the eye.

Abbreviations

AS-OCT: Anterior segment optical coherence tomography; DMEK: Descemet membrane endothelial keratoplasty; ECD: Endothelial cell density; FAK: Femtosecond laser-assisted keratopigmentation; KTP: Keratopigmentation; LogMAR: logarithm of the minimum angle of resolution; MIK: Manual intrastromal keratopigmentation; Nd:YAG: neodymium: yttrium-aluminium-garnet; PKP: Penetrating keratoplasty; SAK: Superficial automated keratopigmentation

Availability of data and materials

All data analyzed during this study are included in this published article and its supplementary information files.

TABLES AND FIGURES

Figure 1. 25-year-old female that underwent laser iris depigmentation. A-B) Iris subatrophy at both eyes, saving the peripupillary rings. C-D) AS-OCT shows the loss of iris tissue in correspondence with the treated areas.

Figure 2. 32-year-old female with iris implant in both eyes. A-B) Slit-lamp image of both eyes, showing the cosmetic iris implants with severe corneal edema in the left eye. C) AS-OCT of the right eye shows the endothelial cell loss with the implant resting on the iris. D) AS-OCT of the left eye shows the corneal edema.

Figure 3. 41-year-old female with iris implant in both eyes. A-B) Post-operative condition of both eyes, showing severe bilateral iris atrophy. C) Right eye had cataract surgery with Morcher iris-IOL

device placement and Ahmed valve. D) Left eye had Descemet's membrane endothelial keratoplasty (DMEK). E) AS-OCT of the left eye showing clear cornea with the resolution of the edema after DMEK surgery, iris atrophy and peripheral anterior synechiae.

Figure 4. 37-year-old female with a cosmetic implant in her left eye. A-B) pre-operative condition of the eye, showing the presence of the cosmetic device and an apparent clear cornea with a dramatic endothelial cell loss (1163 cells/mm^2); C-D) Post-operative presentation, with iris atrophy most evident in the superior sector and a relatively conserved endothelial cell density after the explant (1054 cells/mm^2).

Table 1. Clinical summary of 5 patients with cosmetic iris implant.

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Ethics Declarations

Ethics approval and consent to participate. This study adhered to the tenets of the Declaration of Helsinki for research on human subjects. Informed consent was obtained from all participants.

Consent for publication. Not applicable.

Competing interest. The authors declare they have no competing interests.

Authors' contributions.

FD and JLA participated in the design of the study and data collection, drafted the manuscript and revised it. All authors read and approved the final manuscript

Table 1. Clinical summary of 5 patients with cosmetic iris implant.

Patient/Eye	Age at implant	Model	Explantation/ Months After Implantation	ECD (cells/mm^2)	Corneal Trasplant	Iris Atrophy	Cataract Surgery	HTO	Glaucoma Surgery
1/R	35	NewColorIris	Yes/1	778	No	Yes	No	No	No
1/L	35	NewColorIris	Yes/2	1026	No	Yes	No	Yes	No
2/R	37	BrightOcular	Yes/12	444	DMEK	Yes	No	Yes	No
2/L	37	BrightOcular	Yes/12	1054	Advised	No	No	Yes	No
3/R	44	BrightOcular	Yes/32	814	PKP	No	Yes	Yes	Trabeculectomy+Ex PRESS shunt
3/L	44	BrightOcular	Yes/32	NA	No	No	Yes	Yes	No
4/R	41	BrightOcular	Yes/40	NA	Advised	Yes	Yes	Yes	No
4/L	41	BrightOcular	Yes/40	NA	DMEK	Yes	Yes	Yes	1° Trabeculectomy+ ExPRESS shunt; 2° Ahmed Valve
5/R	27	NewColorIris	Yes/60	972	No	Yes	No	Yes	No
5/L	27	NewColorIris	Yes/60	NA	Advised	Yes	No	Yes	No

Abbreviation: DMEK, Descemet membrane endothelial keratoplasty; ECD, endothelial cell density; HTO, Hypertension; L, Left eye; NA, information not available; PKP, Penetrating keratoplasty; R, Right eye

Figure 1

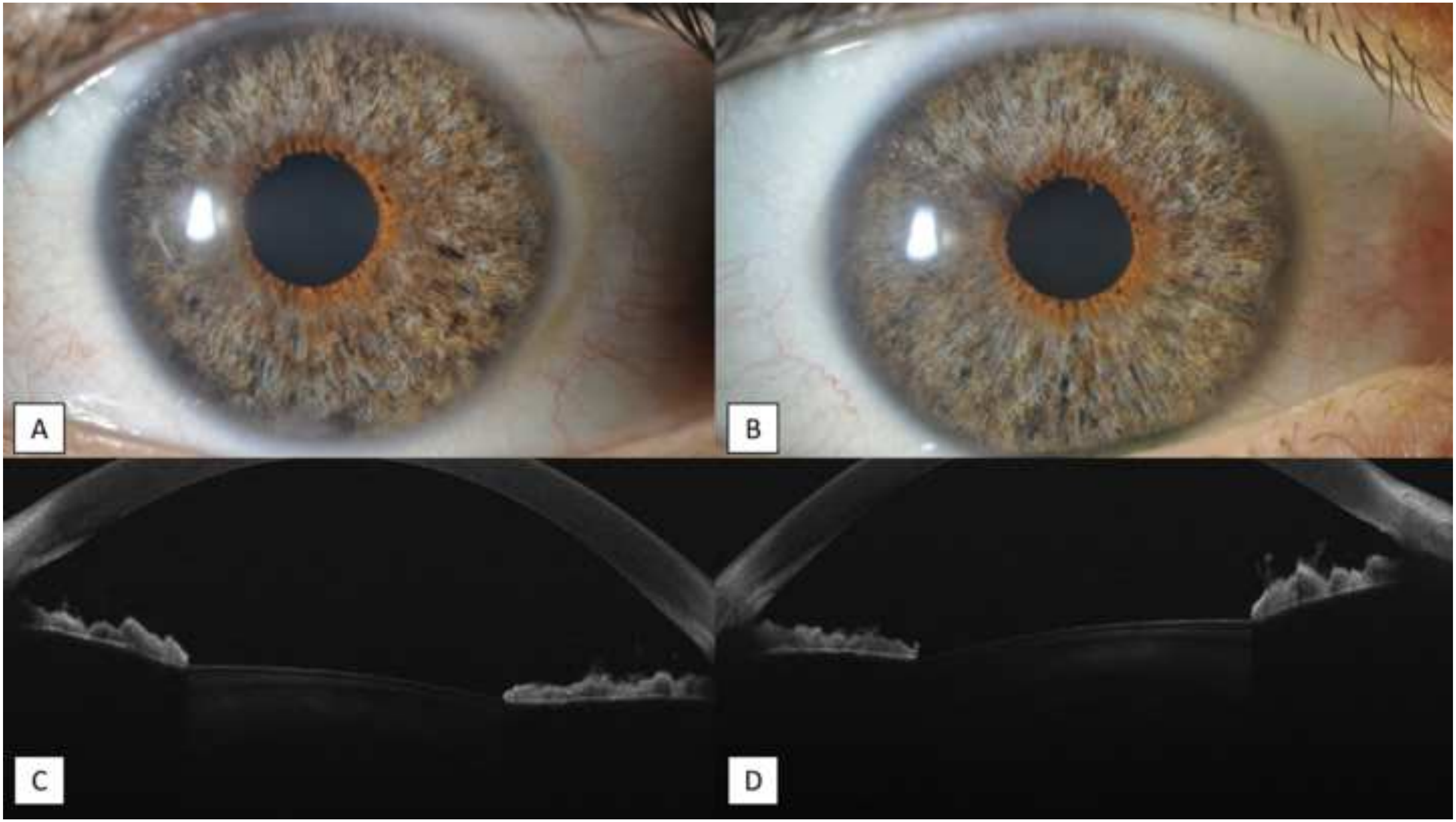


Figure 2

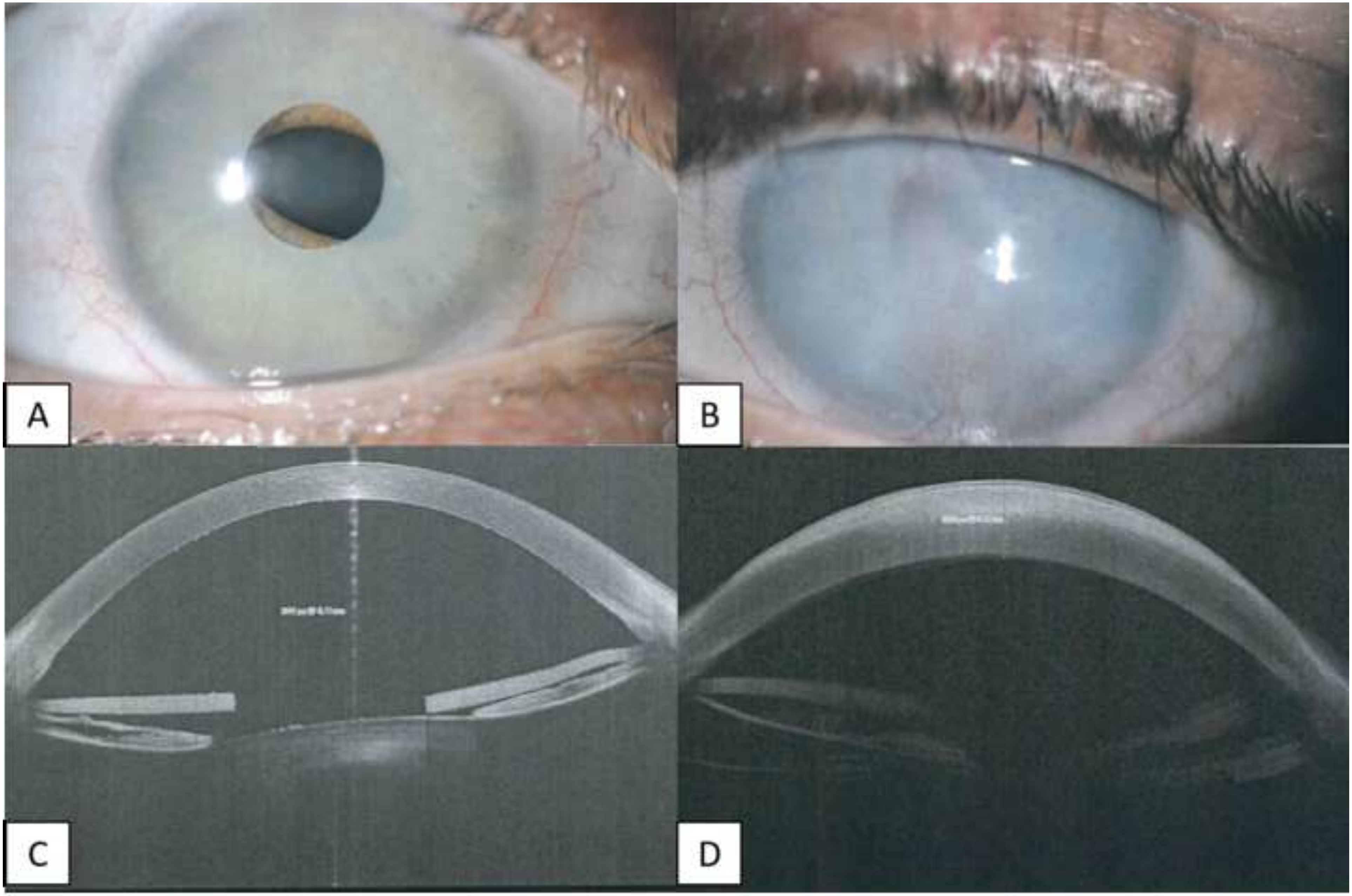
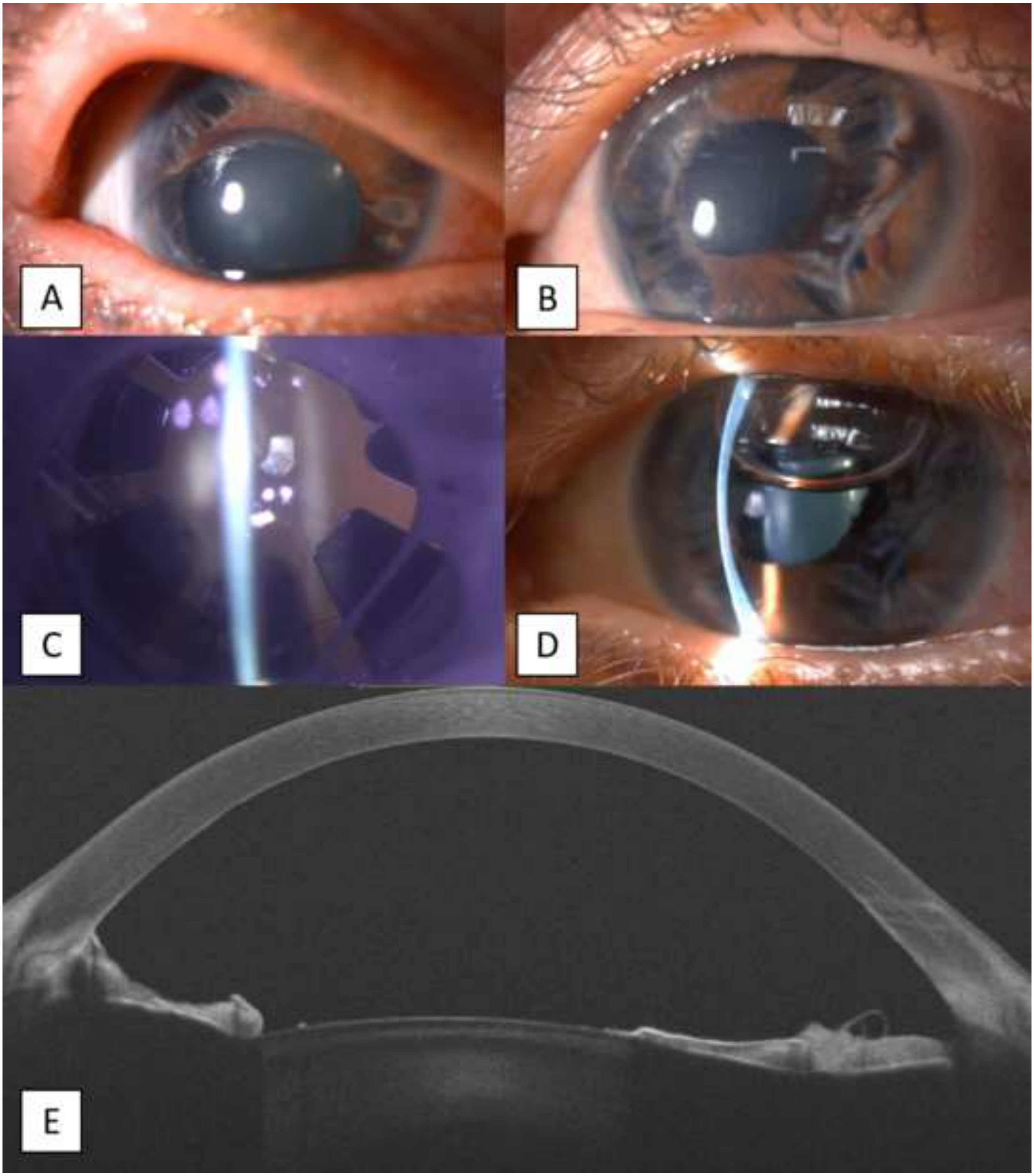
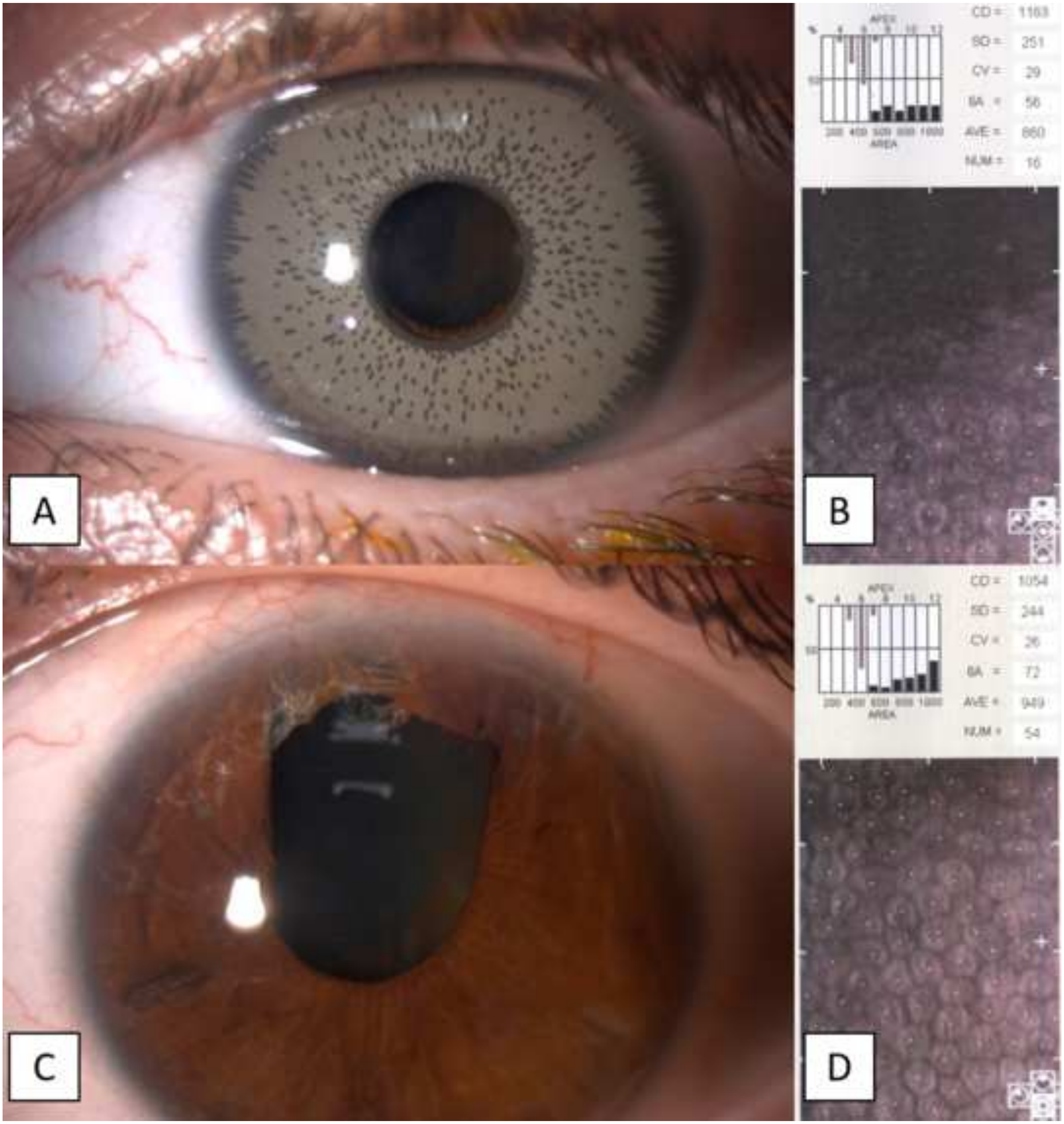


Figure 3

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CV = 29
6A = 56
AVE = 860
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APEX
AREA
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6A = 72
AVE = 949
NUM = 54
C
D