



Full Length Article

Late postoperative opacification of a new type hydrophilic acrylic intraocular lens

Jin Xie^{a,b}, Xinyi Zang^{a,c}, Shilan Mao^{a,b,d}, Jie Sun^e, Ting Liu^{a,b}, Yunhai Dai^{a,b,*}^a State Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory of Ophthalmology, Qingdao, Shandong, China^b Eye Institute of Shandong First Medical University, Qingdao Eye Hospital of Shandong First Medical University, Qingdao, Shandong, China^c Weifang Medical University, Weifang, Shandong, China^d Shandong First Medical University, Jinan, Shandong, China^e People's Hospital of Yinan, Linyi, Shandong, China

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ABSTRACT

Background: To report the clinical consequences and laboratory characteristics of late postoperative opacification of a hydrophilic acrylic intraocular lens (US-860UV IOL) as well as the prognosis of IOL replacement.**Methods:** Forty medical records (42 eyes) of patients with US-860UV IOL opacification reporting decreased or lost vision who underwent IOL explantation between 2017 and 2019 were reviewed. Explanted IOLs were analyzed by slit-lamp examination, confocal microscopy, scanning electron microscopy (SEM) and energy-dispersive X-ray spectroscopy (EDS) at the Shandong Key Laboratory of Ophthalmology, Shandong Eye Institute, Shandong First Medical University, and Qingdao University of Science and Technology, Qingdao, China.**Results:** The mean age of the 40 patients was 74.83 ± 7.57 (63–92) years. The mean interval between cataract surgery and diagnosis of opacification was 32.38 ± 8.76 (17–48) months. Systemic diseases were found without statistical correlations, the most frequent being arterial hypertension, coronary heart disease, and diabetes mellitus. Visual acuity improved from 1.42 ± 1.03 to 0.31 ± 0.16 (logMAR) after IOL replacement. SEM, EDS and alizarin red staining showed uniformly distributed, diffuse, milk-white opacification, with calcium and phosphorus deposits on the optic and haptic surfaces that could be dissolved in 1% HCl.**Conclusions:** Calcium and phosphorus deposition was the main cause of hydrophilic acrylic US-860UV IOL opacification. IOL replacement can safely and effectively improve the visual acuity of patients.

1. Introduction

Cataracts are one of the most common causes of blindness worldwide. There are no recognized treatments to delay or reverse progression of cataracts; the most effective method for treating cataracts is phacoemulsification and intraocular lens (IOL) implantation. With the improvement of medical technology, small-incision phacoemulsification cataract surgery with the implantation of various foldable IOLs has become the main treatment for cataracts. IOL implantation, a safe and cost-effective surgery, can greatly improve the vision of cataract patients, and the incidence of complications is approximately 1%.^{1–4} IOL dislocation, incorrect refractive power selection, problems related to multifocal IOLs (such as glare, optical aberrations, and neural adaptation failure), and IOL opacification are the main causes of IOL replacement

after implantation.

Since IOL opacification was first reported in 1994,⁵ it has gradually attracted the attention of clinicians and been discussed in depth. To date, different mechanisms may explain the opacification process in IOLs of different materials.⁶ Hydrophilic acrylate IOLs, which have a high water content (between 18% and 38%), have good flexibility and biocompatibility.^{6,7} However, to date, late postoperative opacification has been reported for many models of hydrophilic acrylate IOLs.^{8–10}

This study confirms late postoperative opacification for a new IOL (US-860UV, Aaren Scientific Inc, Ontario, US). The US-860UV IOL is a hydrophilic acrylate IOL, which is a single piece, posterior chamber intraocular lens, foldable, with an improved loop shape of C. To our knowledge, our study is the first to describe a case of calcification in relation to the US-860UV IOL design.

* Corresponding author. State Key Laboratory Cultivation Base, Shandong Provincial Key Laboratory of Ophthalmology, Qingdao, Shandong, 266071, PR China.
E-mail addresses: 15971795751@163.com (J. Xie), slanmaojx@163.com (S. Mao), 18265986631@163.com (J. Sun), lxmbest@126.com (T. Liu), yunhaidai@163.com (Y. Dai).

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2. Methods

2.1. Study design and patients

This retrospective case series study analyzed 42 eyes from 40 patients with IOL opacification acquired from January 2019 to June 2021 at the Qingdao Eye Hospital of Shandong First Medical University, which is the largest tertiary specialty hospital with ophthalmic services in Qingdao. All patients with late postoperative hydrophilic acrylic US-860UV IOL opacification and visual acuity impairment were included in the study. They were identified by careful slit-lamp examination in the consultation room of Qingdao Eye Hospital. Statistical analysis was based on data from the department's medical records and further information provided by the patients' ophthalmologists. The exclusion criteria were posterior capsule opacification (PCO), IOL dislocation and incorrect IOL power.

The following clinical information was registered in detail for all patients with IOL opacification: age; sex; affected eyes; systemic diseases, such as hypertension and diabetes mellitus (DM); and ophthalmic conditions, such as glaucoma, uveitis, and high myopia. In addition, the history of ocular trauma or surgery was recorded.

All retrospective data of IOL implantation and replacement were collected. We analyzed associated ophthalmological characteristics and the details of cataract surgery and IOL replacement, such as the axial length, noncontact intraocular pressure, dilated fundus examination findings, corrected distance visual acuity (CDVA), optical coherence tomography findings, date of IOL implantation, and intraoperative and postoperative complications. In our study, CDVA was measured with the Snellen chart at 5 m and was then converted to logarithm of the correct minimum angle of resolution (logMAR) values for statistical calculations. Patients who could only perceive hand motion at 2 feet (or less) were considered to have Snellen equivalent 20/20000 (3.0, logMAR) vision.

2.2. Laboratory examination

The material, type, serial number, and implant position of previous and new IOLs were also analyzed. In addition, the opacity IOLs were carefully examined in the laboratory. In the first stage, three IOLs were removed from the eyes in the optical department with surgical scissors. Subsequently, some of them were sent to the Shandong Key Laboratory of Ophthalmology, Shandong Eye Institute, Shandong First Medical University, China, where the opacity of the IOL was observed and imaged by light and confocal microscopy (Leica LMD7, Germany). Next, the IOLs were immersed in 1% alizarin red solution for histochemical staining and observed by microscopy. The rest of the cut IOLs were kept in 1 mL of 2.0% formaldehyde containing 0.1 M sodium cacodylate buffer and sent to Qingdao University of Science and Technology for analysis. The IOLs were removed from the preservation solution and allowed to dry naturally in a cool and ventilated environment. With the opacity surface facing upward, the IOLs were sprayed with gold to increase their conductivity. Subsequently, the IOLs were put examined by scanning electron microscopy (SEM, HITACHI S-3500 N, Japan) to observe the details of IOL opacification at different working distances and magnifications. Moreover, the element composition and content of sediment in different areas of the IOLs were analyzed by energy-dispersive X-ray spectroscopy (EDS, HITACHI E-1020, Japan). In addition, changes in the surface of another 2 opacified IOLs dipped into 1.0% hydrochloric acid (HCl) were observed.

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 22, IBM Corp.). Data are reported using descriptive statistics (absolute [n] and percentage [%] frequencies, mean \pm SD), and significance was assumed when the P value was less than 0.05.

3. Results

As showed in Table 1, a total of 40 patients (42 eyes) were included in this study. From 2017 to 2019, all patients underwent phacoemulsification and hydrophilic acrylic IOL (US-860UV, USA) implantation at different hospitals in Qingdao. Among them, 29 patients (29 eyes) were from the Qingdao Eye Hospital Affiliated with Shandong First Medical University, and 11 patients (13 eyes) were from three other medical institutions in Qingdao. The average age of the patients at IOL opacification was 75.13 ± 7.50 (60–92) years, and there were 13 males (32.5%) and 27 females (67.5%). Initially, 28 patients underwent bilateral cataract surgery, but only 2 patients had bilateral IOL opacification. In all, 25 right eyes (59.52%) and 17 left eyes (40.48%) were affected. The mean interval between hydrophilic acrylate IOL implantation and diagnosis of opacification was 32.38 ± 8.76 (17–46) months. In 2017, a total of 4000 IOLs of this type were implanted at the Qingdao Eye Hospital, 27 of which were found to be opacity. Due to the patient's own reasons (such as patients died, IOL opacification does not affect daily life, etc.), we are not able to detect some IOLs opacification. Thus, the opacification rate of this type of IOL might be larger than 27/4000. According to the clinical examination results and medical history, 25 patients (62.5%) with IOL opacification had systemic diseases to varying degrees; the most common of these diseases were arterial hypertension (20 patients [50%]), DM (14 patients [33.3%]), and coronary heart disease (12 patients [30%]). The diagnosis of DM mainly depends on past diabetes history and the results of blood sugar analysis (hemoglobin A1c percentage greater than 6%). By careful case collection, only 2 of the patients were diagnosed with an associated ophthalmic pathology (glaucoma and high myopia), and there were no patients with uveitis.

29 of 40 patients underwent cataract surgery by senior physicians at our hospital, with stable results. The intraocular pressure, ocular axis and fundus were examined preoperatively. An ophthalmic operating microscope and phacoemulsification instruments were used for the operation. The conjunctival sac was rinsed with normal saline/Anerdian (1:1) solution. The anterior capsule was entered through a 2.8-mm corneoscleral tunnel incision. The crystalline lens was phacoemulsified after water separation, and the cortex was removed with the phaco tip of the phacoemulsifier. Then, the hydrophilic acrylate US-860UV IOL was implanted into the capsule, and the position of the IOL was adjusted. After the operation, antibiotics and steroid eye drops were used for 2 weeks (5 times/day), and nonsteroidal anti-inflammatory eye drops were used for 4 weeks (4 times/day). No patients experienced significant postoperative complications.

In this study, 42 IOLs had a cloudy or ground-glass appearance by slit-lamp examination, and the average best-corrected visual acuity was 1.42 ± 1.03 (0.40–3.00) (logMAR). 38 eyes of 38 patients underwent IOL replacement surgery at our hospital. In these patients, after peribulbar anesthesia was established, a viscoelastic agent was injected into the anterior chamber through the corneal incision, the adhesion between the IOL and capsule was separated with 1 ml needle and lens dialer, and the optical area of the IOL was cut into two halves, which were then removed. Subsequently, a new IOL was implanted, the anterior chamber was lavaged, and the incision was closed in a watertight manner. Several intraoperative complications occurred in 9 patients, including 7 cases of posterior capsule rupture and 2 cases of suspensory ligament rupture. Finally, there were 6 cases (6 eyes) of IOL implantation in the ciliary sulcus. All replacement IOLs were hydrophobic IOLs, including 22 AR40e IOLs (Abbott Medical Optics, Inc., US), 5 Akreos Adapt AO IOLs (Bausch & Lomb Inc., US), 3 SoftecHD IOLs (LensteC, Inc., US), 3 iSert251 IOLs (Hoya Corporation, Japan), 4 SZ-1 IOLs (NIDEK Co., Ltd., Japan), and 1 A1-UV IOL (Eyebright Medical Technology, Inc., China). Patients recovered well postoperatively, with no complications. The best-corrected visual acuity after IOL replacement was 0.00–0.80 (logMAR), with an average of 0.31 ± 0.16 (logMAR). Therefore, IOL replacement surgery greatly improved visual acuity.

Moreover, we noticed that all 29 IOLs implanted at our hospital were made between July 2016 and May 2018, while 16 IOLs were made in

Table 1
Characteristics of the 42 cases opacity hydrophilic acrylic IOLs.

PT	Age	HbA1c	IOL SN	IT	CDVA-1	CDVA-2	E-1	E-2	Order
1/M	75	5.1	O-28416001-029	20	0.52	0.52	U	D	2
2/F	81	5.8	O-34416007-085	25	3.00	0.22	U	D	2
3/F	76	6.3	O-21116050-006	31	0.82	0.15	U	D	2
4/F	80	6.9	O-34916034-086	28	0.70	0.30	U	S	2
5/F	79	5.8	O-04817001-005	27	1.70	0.15	U	S	2
6/F	88	7.2	O-28816007-081	22	0.92	–	U	D	2
7/F	88	5.5	O-20117028-023	17	–	–	S	S	–
8/F	68	–	–	26	0.40	0.52	S	S	–
9/F	78	–	–	32	3.00	0.40	U	D	2
10/M	68	–	–	24	3.00	0.52	S	S	–
11/F	73	4.9	O-04717025-033	25	1.00	0.70	U	D	1
12/M	60	–	–	29	0.52	0.22	U	S	2
13/F	79	5.9	O-12317034-044	27	0.52	0.80	U	S	1
14/M	81	6.9	O-22116039-040	40	0.60	0.30	U	S	1
15/M	73	–	O-33316047-044	36	0.60	0.30	D	D	–
16/M	76	5.7	O-10717012-022	23	0.40	0.10	U	S	2
17/F	79	–	–	35	1.00	0.22	U	S	–
18/F	72	6.6	O-04817001-019	38	0.92	0.15	D	D	–
19/F	76	8.1	O-03717016-083	46	0.92	0.00	U	D	1
20/M	78	6.2	O-31217025-042	19	0.60	0.22	U	D	2
21/M	74	6.8	O-03018006-A-040	21	0.52	0.22	D	D	–
22/F	72	8.7	O-04717025-023	33	3.00	0.40	U	S	2
23/F	88	5.2	O-03717016-068	37	3.00	0.40	U	D	2
24/F	65	5.1	O-11517019-073	34	0.82	0.10	D	D	–
25/F	78	5.4	O-33716019-058	38	3.00	0.30	U	D	2
26/F	82	5.3	O-14118012-025	17	3.00	0.40	U	S	1
27/M	70	7.6	O-33716005-002	39	3.00	0.30	U	D	2
28/F	74	7.3	O-36416030-062	28	0.82	0.22	D	D	–
29/M	73	5.7	O-04817001-015	42	1.00	0.30	U	S	1
30/M	68	6.6	O-34416005-030	44	0.52	0.30	S	S	–
31/F	70	5.3	O-33716017-004	45	1.00	0.22	D	D	–
32/F	89	4.9	O-14118012-017	24	1.00	0.30	U	D	2
33/F	67	5.2	O-36516010-006	37	1.30	0.30	U	D	1
34/F	92	–	–	32	3.00	0.30	U	D	1
35/M	70	–	–	38	1.00	0.15	U	D	2
36/M	63	–	–	42	–	–	U	U	–
					0.70	0.40			–
37/F	71	–	–	44	3.00	0.40	U	D	2
38/M	78	–	–	46	–	–	U	U	–
					0.52	0.22			–
39/F	63	–	–	38	1.00	0.40	S	S	–
40/F	70	6.4	O-04817001-014	46	3.00	0.30	D	D	–

PT = patient; SN = serial number; IT = interval time;
 CDVA-1 = CDVA before IOL replacement (logMAR);
 CDVA-2 = CDVA after IOL replacement (logMAR);
 E-1 = eyes of cataract surgery; E-2 = eyes of IOL replacement;
 “–” express no accurate information;
 M = male, F = female, U=Ocular utro, D = oculus dextrus, S = oculus sinister.

December 2016 (8 IOLs) and February 2017 (8 IOLs). Moreover, several IOLs originated from the same batches.

To clarify the morphological characteristics and composition of the surface of those IOLs, some were sent to the Shandong Eye Institute for observation after they were removed. Light and confocal microscopy showed that the opacity area of the IOLs was mainly located in the front surface of the optical area, with a rough and uneven appearance and a gully-like shape. The amount of opacity sediment was positively correlated with the degree of opacification, and a large number of particles formed clusters that were gully-like or cerebriform in shape. Conversely, the back surface was smooth, with no or minimal deposition.

Other IOLs observed by SEM at Qingdao University of Science and Technology showed that the central opacity area accumulated sediment layer by layer to form a hilly shape and that only a few particles were scattered around the edge of the optical area. Interestingly, a transparent, arc-shaped band was found at the junction of optical and haptic parts in several IOLs. In the follow-up operation, we confirmed that the band corresponded to the adhesion site between the anterior capsule and IOL.

It was easily to observe that in those transparent bands, some particles were completely or partially embedded in the surface layer of the IOL, while more were attached to the surface of the IOL. Careful observation of the particles on the surface of the IOL revealed that individual particles appeared similar to red cells, with a concave area in the middle (Fig. 1).

To determine the elemental composition of the sediment, energy spectrum analysis was performed. We found that the sediment in the opacity area of the IOL had a high content of calcium and phosphorus, which was positively correlated with the degree of opacification. Meanwhile, EDS analysis showed that traces of silicon were also present in the IOLs (Fig. 2). The alizarin red test results of two removed IOLs were positive, and the opacity area on the surface of the IOLs was dyed orange red. To understand whether the opacity precipitation on the IOL surface could be dissolved in hydrochloric acid, the opacity IOLs were placed in 1% diluted hydrochloric acid. Over time, the transparency of the IOL increased while the opacification decreased. After 10 min, the IOL became completely transparent under the naked eye, and the optical quality was significantly improved (Fig. 3).

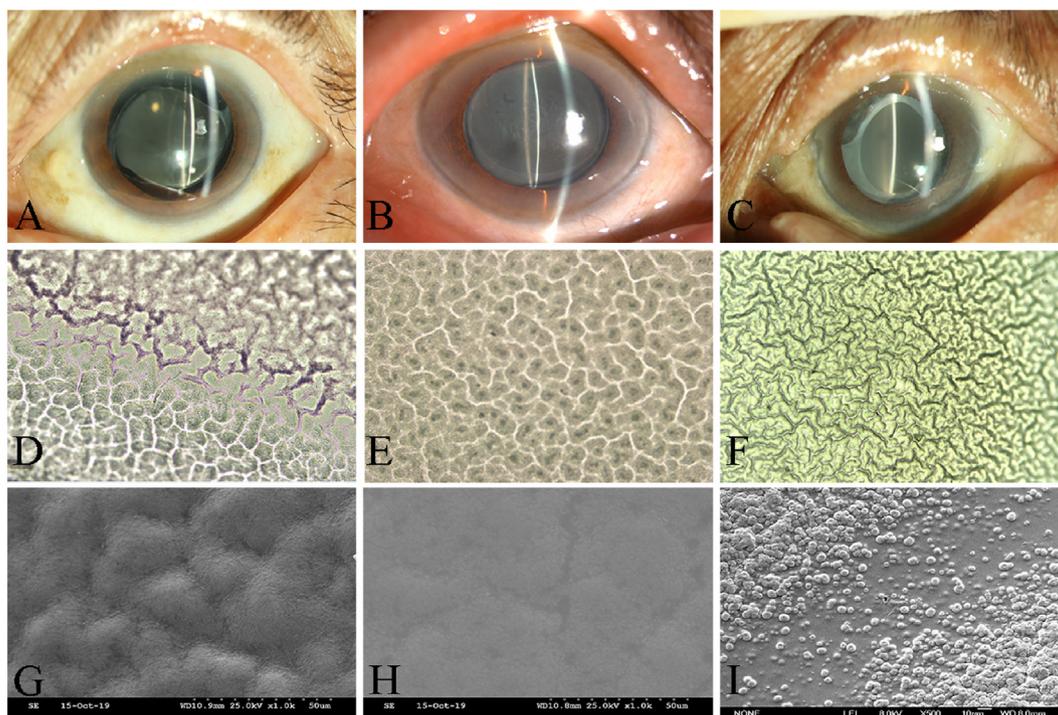


Fig. 1. Calcification of the implanted IOL. Slit-lamp photographs (A–C) from the three patients, showing a dusty haze present on the anterior surface of the lens. (A–C) Obtained from case 2,3,8. Confocal microscope of an IOL shows granular (D), gully(E), and cerebriform (F) appearance of the surface of an explanted IOL (original magnification 200). Scanning electron photomicrographs (G–I) from the surface of an explanted opacified hydrophilic IOL showing massive deposits on the IOL surface (original magnification 1000).

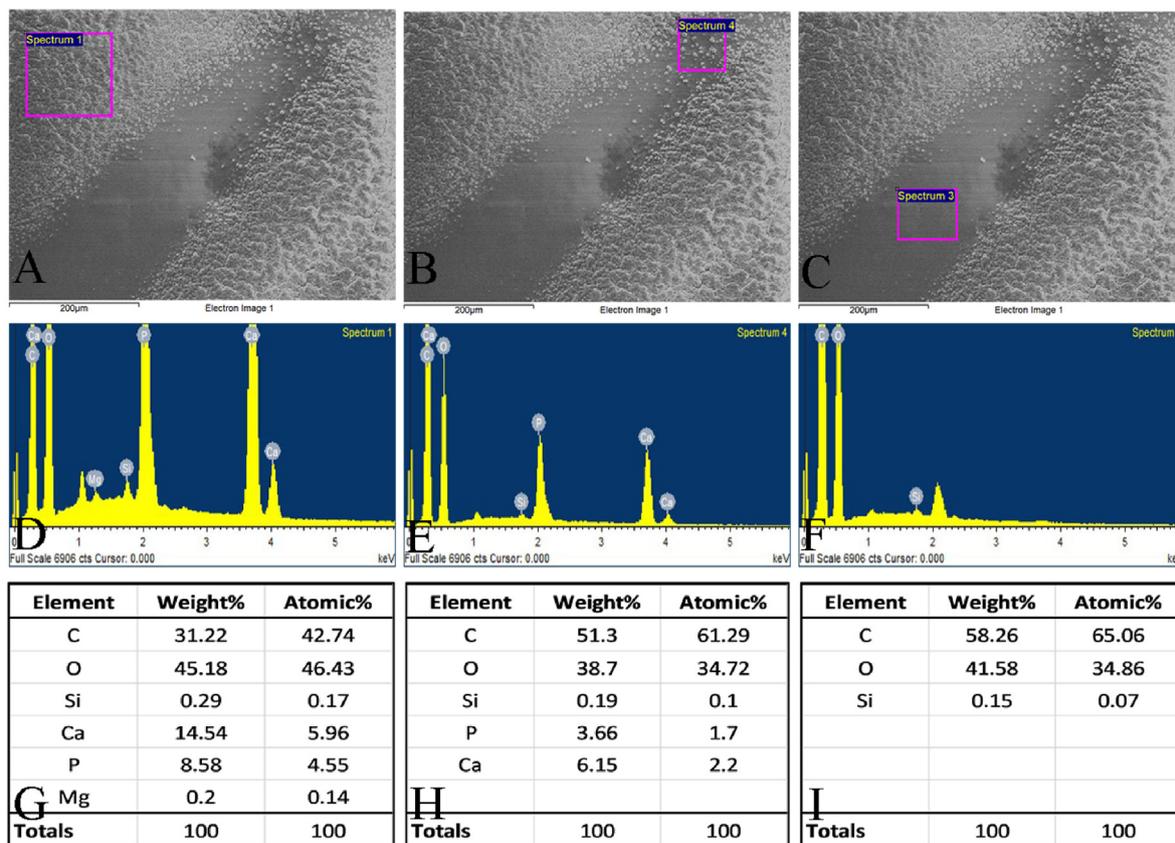


Fig. 2. EDS from different areas of case 14 revealed the presence of calcium and phosphorous in the cloudy IOL (C, carbon; O, oxygen; P, phosphorus; Ca, calcium; Mg, Magnesium; and Si, Silicon).



Fig. 3. Light photomicrographs of an IOL explanted because of postoperative IOL opacification. A: The granules within the IOL stained positive for calcium after direct alizarin red staining (original magnification 40). (B-C): The transparency of removed IOL improved after immersed in 1% diluted HCL 10 min.

4. Discussion

IOL opacification is a rare postoperative complication that seriously affects the vision and living standards of patients. With the popularization of IOL implantation, the number of cases of IOL opacity is also increasing, which has gradually attracted the attention of clinicians. Hydrophilic acrylate IOLs have many advantages,¹¹ including good mechanical and optical properties, good elasticity and hydrophilicity, excellent surface biocompatibility, surface flexibility, surface stability during the folding and implantation process, and low immunogenicity, so they are widely used in clinical practice. However, the high hydration of hydrophilic acrylate IOLs leads to ionization of the hydrophilic functional groups, which promotes the formation of calcium ion complexes and contributes to the formation of calcium complexes on the surface and inside of the material.¹² Therefore, hydrophilic acrylate IOLs are more prone to opacification.^{13–15} In our study, nearly all of the patients underwent IOL replacement, which can significantly improve the vision of patients and is an effective treatment.

Although many researchers have performed many studies describing IOL calcification, most of them have included only a few cases. Our study of the US-860UV IOL includes 42 cases; additionally, opacification related to this new IOL design has not previously been described. In recent decades, different degrees of opacification have been described for IOLs of most materials (polymethylmethacrylate, silicone, polyhydroxyethylmethacrylate, acrylic), but the statistics show that opacification is more common in hydrophilic acrylic IOLs than hydrophobic acrylic or silicone IOLs.⁶

According to the time of postoperative IOL opacification, some scholars divided it into early and late postoperative opacification.¹⁶ Late postoperative opacification has been reported for multiple types of hydrophilic acrylic IOLs, but this is the first report of opacification for the hydrophilic acrylic US-860UV IOL, and it represents a rare, short-term outbreak. On the basis of the above classification standard, these are considered cases of late postoperative opacification. The hydrophilic US-860UV IOL is a one-piece, foldable IOL; its main body and the supporting part are made from the copolymerization of hydroxyethyl methacrylate, methyl methacrylate, and ethylene glycol dimethacrylate (EGDMA), among others, with the addition of an ultraviolet absorber.

In 2008, in light of the underlying pathological mechanism, some scholars classified IOL calcification into primary, secondary and false-positive calcification.¹⁷ Calcification associated with the IOL itself is called primary calcification, and the sources of calcification are related to its own manufacturing, packaging, transportation, and storage processes.¹⁸ Secondary calcification refers to IOL opacification caused by environmental factors. In patients with diabetes, uveitis or water vapor exchange in vitreous body surgery may cause blood-water barrier destruction, which in turn causes changes in the intraocular environment, resulting in secondary calcification on the IOL surface.^{13,19} False-positive calcification represents the misdiagnosis of other pathologies, such as calcification, or cases of false-positive calcium staining.

The most common IOLs affected by primary calcification are the LS-502^{12,18} and SC60B-OUV.²⁰ Irmingar²¹ reported that the special polishing techniques used in the manufacture of these IOLs may cause changes in the lens surface, which may in turn lead to calcium deposition on the

surface. Some studies have reported that during the production and packaging of different batches of hydrophilic IOLs, the silicone and phosphate residues produced by detergent promote IOL opacification and that the silicone on the IOL surface provides a binding site for calcium and phosphorus deposition.^{12,22,23} Frohn proposed that the energy absorbed by the UV absorber may lead to the decomposition of some UV absorber molecules and the production of living free radicals and that aging of the UV absorber inside the IOL may lead to opacification.²⁴ A UV absorber was added during the production of US-860UV IOLs, and in this study, trace amounts of silicone were found on the surface of IOLs by energy spectrum analysis. Moreover, we consulted the medical records and found a total of 29 IOLs with information on the production batch, and 16 (55.17%) of these were produced on certain days in December 2016 and February 2017. Therefore, we considered that the surface opacity of these hydrophilic US-860UV IOLs is more consistent with the characteristics of primary calcification.

In fact, there is a closer relationship between secondary IOL calcification and the patient's condition. It has been found that the entry of air during Descemet's stripping [automated] endothelial keratoplasty (DSAEK/DMEK) or pars plana vitrectomy and repeated surgery lead to destruction of the blood-water barrier, which is an important risk factor for hydrophilic IOL calcification.^{15,25–30} Jeffrey³¹ found that the intraoperative use of ophthalmic visual devices (OVDs) can promote the formation of late calcification in Hydroview IOLs. The residual crystalline cortex after phacoemulsification is rich in calcium and phosphate, which can promote calcium deposition on the surface of IOLs.^{16,32} From the results of the case analysis, only 1 patient had uveitis, and none of the patients underwent multiple eye surgeries, causing damage to the blood-water barrier. In addition, as diabetes is a systemic disease, the effects on the left and right eyes are similar. In this study, 38 patients underwent phacoemulsification cataract surgery in both eyes, but there were only 2 cases of IOL opacification occurring in both eyes. Therefore, there is insufficient evidence for the secondary calcification of US-860UV IOLs.

In this study, the average age of the patients was 75.13 ± 7.50 years. Nicolas¹⁸ found that age at the time of implantation may be a risk factor for IOL calcification through statistical analysis, while posterior capsulotomy may be a protective factor. Through a laboratory analysis, the opacification of the US-860UV IOL was found to be caused by the deposition of calcium and phosphorus compounds on the crystal surface, which is consistent with the opacification of most other types of hydrophilic IOLs. We found that significantly more patients were female than male (13:7). A significant sex difference in patients with IOL opacity has been reported in domestic and foreign studies, with a ratio of males to females of approximately 1:2~3:4.³³ Part of the reasons may be due to the reduced estrogen secretion in elderly women affecting normal bone calcium metabolism, which increases the blood and aqueous humor calcium concentration,³⁴ thereby accelerating calcification and deposition and promoting IOL opacification. Most patients with IOL opacity choose IOL replacement, which greatly improves their vision. Thus far, this method is the only safe and effective way to change visual function.

The transparent area of IOL (Fig. 3A) had been confirmed to be the region where the IOL and capsule were closely apposed, and the area is not in full contact with the aqueous humor. On the contrary, the turbid

regions of IOL soaked in aqueous humor, it could fully interact with trace elements (calcium, phosphorus, etc.) in the aqueous humor. Therefore, we believed that the aqueous humor is also an important influencing factor. By the way, the solutions and materials used during surgery are unlikely to be independently related to the IOL opacification process because they were the same in all cataract surgeries.

This study has several limitations. The review of case records may produce some data deviations, and some information was provided by the contacted external ophthalmologists. In addition, because not all older patients revisit a doctor due to vision loss, not all patients could be included. Thus, some calcification cases may have been omitted, or some patients may not have yet been able to see a doctor, prolonging the time interval for opacity detection. At the same time, more studies are needed to investigate the real impact of individual patient factors and determine whether IOL calcification is indeed related to some situations or whether IOL calcification is purely due to subtle differences in the production of each IOL.

5. Conclusions

In conclusion, we believe that the late opacity after hydrophilic US-860UV IOL surgery is a form of primary calcification and is affected by the aqueous humor. The occurrence of opacification is the result of the comprehensive influence of the IOL material itself and patients' intraocular conditions. The opacification is not isolated and cannot be observed at a single site. The involvement of manufacturers, clinicians and patients is needed to further investigate the causes of this serious complication. After IOL opacity, IOL replacement can significantly improve the visual acuity and quality of vision of patients. This study enriches the understanding of types of hydrophilic IOLs affected by opacification and provides support for clinicians to select appropriate IOLs according to clinical practices and patients' conditions. In future work, we will further explore and research the mechanism of IOL opacity to better understand the specific mechanism of IOL opacity and prevent the occurrence of postoperative complications.

Study approval

The authors confirm that any aspect of the work covered in this manuscript that involved human patients or animals was conducted with the ethical approval of all relevant bodies and the study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Qingdao Eye Hospital [approval number:(2020)58].

Author contributions

JX, JS and SLM collected and analyzed the data. JX and JS wrote the manuscript. YHD TL and JX designed the research. All authors contributed to the article and approved the submitted version.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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