Long-term evaluation of anterior lens density after implantable collamer lens V4c implantation in patients with myopia over 40 years old

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ABSTRACT

Purpose To investigate the long-term safety and efficacy of implantable collamer lens (ICL) V4c implantation and changes in the anterior lens density (ALD) in patients with myopia ≥40 years of age.

Methods This prospective study included 104 eyes of 52 patients >40 years of age before ICL V4c implantation. Spherical equivalent (SE), uncorrected distance visual acuity, corrected distance visual acuity (CDVA), intraocular pressure, endothelial cell density, anterior chamber depth, anterior chamber volume and anterior chamber angle preoperatively, at 1 and 3 months, and at 3 years postoperatively were recorded. Pentacam HR was used to analyse ALD changes at a depth of 0.5, 1.0 and 1.5 mm within a 3 mm diameter range around the pupil’s centre.

Results The overall follow-up was uneventful at 42±7.1 months; the safety index at last follow-up was 1.26±0.35 and the efficacy index was 0.91±0.41. No eye lost the Snellen line of CDVA, 76% of the eyes had an increase in CDVA for ≥1 line and 62% had an SE within ±0.50 dioptre. The increase in ALD at 0.5, 1 and 1.5 mm was 16.52%±10.46%, 16.72%±9.85% and 17.28%±11.93%, respectively. Preoperatively, 1-month and 3-month postoperative ALDs showed correlations with SE and age, and ALD at last follow-up was correlated only with age. There was no correlation between ALD and any other parameters.

Conclusion ICL V4c shows long-term safety and efficacy in people ≥40 years of age. ALD increased in such patients, which may be related to age and SE.

INTRODUCTION

In the past two decades, a number of studies have demonstrated the short-term and long-term safety and efficacy of implantable collamer lens (ICL),1 which have a 20-year history of clinical application. Further, long-term stability towards intraocular pressure (IOP), endothelial cell density (ECD) and vault after ICL V4c implantation has been demonstrated.2–4

Anterior lens density (ALD) is an objective parameter that evaluates the opacity of the anterior part of the lens. Previous research on ALD has highlighted its close correlation with age, and a linear correlation between ALD and age was reported for people >40 years old.5 6

Lens contact, lower vault and changes in aqueous humour circulation are increasingly recognised as factors affecting ALD changes after ICL implantation. Therefore, increased ALD is an essential component of lens opacity monitoring and may be related to cataract formation.

ICL V4c (STAAR Surgical, Monrovia, California, USA) is a phakic intraocular lens with a central perforation,7 which maintains aqueous circulation8 9 and decreases risk of complications such as cataract and glaucoma.10 Studies on long-term safety and efficacy have been mostly restricted to limited samples at ages ranging 25–45 years, and only one study has estimated ALD change in patients aged ≤40 years.11 However, existing accounts failed to deal with the long-term safety, efficacy and ALD changes in patients ≥40 years of age. With the ageing population, ICL V4c application has become a central issue for myopia correction in the population >40 years of age. Hence, this study aimed to investigate the long-term safety and effectiveness of ICL V4c implantation in patients with myopia ≥40 years of age and to ascertain changes in ALD and related factors associated with ICL V4c implantation.

MATERIALS AND METHODS

Participants This prospective, observational, consecutive case study comprised 104 eyes of 52 patients who underwent bilateral ICL V4c implantation for myopia correction and myopic astigmatism at the Department of Eye and ENT Hospital of Fudan University between April 2016 and December 2017. Informed consent was obtained from all patients.

The inclusion criteria were as follows: (1) ≥40 years old; (2) unsatisfactory correction with spectacles or contact lenses, stable refraction for ≥2 years (increase of ≤0.50 dioptre (D)/year); and (3) no contact lens use for ≥2 weeks and no rigid gas permeable contact lens use for ≥4 weeks.

Patients were excluded if they had any of the following: (1) history of ocular surgery, progressive corneal degeneration, cataract, glaucoma, uveitis or diabetic retinopathy; (2) history of systemic diseases; and (3) a preoperative anterior chamber depth (ACD) <2.6 mm or preoperative ECD <2000 cells/mm².

Examinations Preoperatively, all patients underwent complete ophthalmological examinations as follows: uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), non-contact IOP measurement by Canon Full Auto Tonometer TX-F...
(Canon, Tokyo, Japan), ECD by SP-2000P (Topcon Corporation, Kyoto, Japan), axial length, corneal thickness, corneal diameter as white-to-white (WTW) distance, ACD, anterior chamber volume (ACV), anterior chamber angle (ACA) and angle-to-angle distance (ATA). ALD was measured in a 3 mm diameter around the pupil’s centre at a depth of 0.5, 1.0 and 1.5 mm; all were measured using the Pentacam HR (Oculus Optikgeräte, Wetzlar, Germany). Objective 360° lens density measurement results can be obtained by Pentacam HR imaging, a system with high repeatability and accuracy. The lens density measured by this system ranges from 0 (fully clear) to 100 (fully opaque). A detailed description of these methods has been previously reported.

Lens power and size calculation
All eyes included in this study had either myopic or toric V4c ICLs implanted. ICL V4c power calculation was carried out using the manufacturer’s software (STAAR Surgical). Eyes of patients with myopia without presbyopia were targeted for emmetropia, and intentional undercorrection was selected in eyes of patients with myopia with presbyopia. The dominant eyes were targeted for emmetropia and the non-dominant eyes for around −2.25 to −0.50 D, and −18.00 D was selected as the target refraction correction for eyes ≤−18.00 D at the spectacle plane. The ICL size was also chosen by the manufacturer’s nomogram based on the horizontal WTW distance, the horizontal or vertical ATA, and ACD.

Surgery
All surgeries were performed by two experienced surgeons (XZ and XW). The patients received ophthalmic antibioticinstillation for 3 days (four times a day) preoperatively, and on the day of the surgery dilating and a topical anaesthetic. The anterior chamber was filled with sodium hyaluronate 1%, which was completely removed at the end of the surgery, and an ICL V4c was inserted through a 3 mm clear corneal incision using an injector cartridge. The ICL V4c haptics were fixed into the ciliary sulcus using a manipulator, and the viscoelastics were completely washed out of the anterior chamber with a balanced salt solution. Details of the procedure have been previously described. After surgery, antibiotic and steroid eye-drops were administered four times a day for 2 weeks and tapered gradually.

Follow-up
Postoperative follow-up visits were conducted at 1 month, 3 months and 3 years. The following parameters were collected at each follow-up: (1) UDVA, CDVA, IOP and ECD (only at 3 months postoperatively and at last follow-up); (2) corneal thickness, WTW, ACA, ACD, ACV and vault (the distance from the posterior surface of ICL V4c to the lens); and (3) ALD in a 3 mm diameter around the centre of the pupil at a depth of 0.5, 1.0 and 1.5 mm. Safety index was defined as postoperative CDVA/preoperative CDVA; efficacy index was defined as postoperative UDVA/preoperative CDVA; predictability was defined as the comparison between postoperative spherical equivalent (SE) and the target SE; and stability was defined as change in postoperative SE at long-term follow-up.

Statistical analysis
All statistical analyses were performed using the Statistical Package for the Social Sciences (V25.0). The results are expressed as mean±SD. The Shapiro-Wilk test was used to assess the normality of variables. The Wilcoxon signed-rank test was used to compare pretreated and post-treated non-normally distributed data and one-way analysis of variance for normally distributed data. Pearson correlation coefficient was employed to analyse the correlation between changes in ALD and other parameters. A p value of less than 0.05 was considered statistically significant.

RESULTS
A total of 104 eyes of 52 patients were followed up for 42±0.71 months. All surgeries were performed safely, and no complications occurred during the follow-up period. Table 1 shows the patients’ preoperative characteristics. Data loss during the follow-up period was within 10%.

Safety and efficacy
The safety index at 1 month postoperatively, 3 months postoperatively and at last follow-up was 1.25±0.28, 1.24±0.32 and 1.26±0.35 (p>0.05), respectively. The corresponding efficacy indexes were 1.05±0.31, 1.09±0.60 and 0.91±0.41 (3 months postoperatively vs at last follow-up, p<0.05), respectively. A total of 51.96%, 51.96% and 38.24% of eyes had a postoperative UDVA ≥20/20 at 1 month postoperatively, 3 months postoperatively and at last follow-up, respectively. Additionally, 92.16%, 91.18% and 89.22% of the eyes had a postoperative UDVA ≥20/40 at each follow-up, respectively. Moreover, the postoperative UDVA was the same or better than the preoperative CDVA in 63.81%, 63.81% and 52.38% of eyes at the three follow-up time points, respectively. None of the eyes showed decreased CDVA (figure 1A–C).

Predictability and stability
A scatter plot of attempted versus achieved SE is shown in figure 1D. At last follow-up, in the comparison of preoperative SE and the target refractive power, 61% of eyes were within ±0.50 D and 91% were within ±1.00 D, as shown in figure 1E. The average dioptre at last follow-up was −0.99±0.77 D (figure 1F).

Anterior segment parameters
The ACD, ACV, ACA and vault values at the three postoperative follow-up time points are summarised in table 2. The difference between preoperative ACD and at last follow-up was −0.23±0.43 mm. ACV decreased by 56.43±17.24 mm² at last follow-up in comparison with the preoperative level, while the difference of ACA was −14.15±8.66°. Compared with the preoperative

Table 1 Preoperative patient demographics

| Characteristics                  | Mean±SD          | Range         |
|----------------------------------|------------------|---------------|
| Age (years)                      | 54±4.73         | 40–54         |
| Gender (male/female)             | 14/38            |               |
| Axial length (mm)                | 28.9±2.06       | 25.13–32.96   |
| Refraction sphere (D)            | −12.88±3.71     | −21.00 to −4.00 |
| Refraction cylinder (D)          | −1.29±1.08      | −4.00 to 0    |
| Spherical equivalent (D)         | −13.52±3.78     | −22.88 to −5.63 |
| K-flat (D)                       | 43.43±1.76      | 39.5–47.40    |
| K-steepl (D)                     | 44.89±1.87      | 40.40–49.10   |
| CT (mm)                          | 0.52±0.31       | 0.460–0.590   |
| ATA, vertical (mm)               | 12.31±0.58      | 11.19–14.80   |
| ATA, horizontal (mm)             | 12.01±0.58      | 10.67–13.74   |
| WTW (mm)                         | 11.68±0.41      | 11–13         |

ATA, angle-to-angle distance; CT, corneal thickness; D, dioptre; WTW, white-to-white.
level, the vault at last follow-up decreased by 59.62±98.21 μm. At last follow-up, of all examined eyes, the vault values of 7.69% (8 of 104) were within 90–150 μm, 86.54% (90 of 104) within 150–750 μm, and 5.77% (6 of 104) over 750 μm.

**Corneal ECD**

Table 2 reveals a decrease in the number of ECDs. The average decrease in ECD at 3 months postoperatively was 201.53±309.96 cells/mm².

**Table 2** Clinical parameters and biometric values of the eyes before and after the implantable collamer lens V4c implantation

| Characteristics  | Preoperative | 1-month follow-up | 3-month follow-up | Last follow-up |
|------------------|--------------|-------------------|-------------------|----------------|
| UDVA (logMAR), range (min, max) | NA           | 0.09±0.22† (−0.18, 1.00) | 0.08±0.21† (−0.18, 1.00) | 0.18±0.25† (−0.18, 1.30) |
| CDVA (logMAR), range (min, max) | 0.09±0.17 (−0.08, 1.00) | 0.01±0.14* (−0.18, 0.82) | 0.00±0.16* (−0.18, 1.00) | 0.00±0.15* (−0.18, 1.00) |
| Spherical equivalent (D), range (min, max) | −13.52±3.78 (−22.88, −5.63) | −0.54±0.82† (−4.25, 0.88) | −0.62±0.84* (−4.50, 1.00) | −0.99±0.77† (−4.13, 0.00) |
| ACD (mm), range (min, max) | 3.11±0.32 (2.60, 3.97) | 2.90±0.37* (1.62, 3.86) | 2.93±0.33* (2.15, 3.81) | 2.88±0.34* (1.92, 3.81) |
| IOP (mm Hg), range (min, max) | 14.87±2.64 (8.40, 22.7) | 14.03±1.95* (10.10, 17.80) | 15.29±2.18* (9.4, 20.2) | 15.21±2.45 (9.90, 21.00) |
| ACV (μL), range (min, max) | 181.48±37.37 (62.80, 296.00) | 107.19±23.97* (46, 190) | 106.88±24.23† (62.00, 198.00) | 116.63±24.84† (65.00, 200.00) |
| ACA (°), range (min, max) | 37.03±6.15 (21.10, 47.70) | 21.50±5.05* (9.10, 33.70) | 20.89±5.46* (10.40, 36.10) | 22.35±4.70* (13.10, 37.30) |
| ECD (cells/mm²), range (min, max) | 2930.41±37.37 (2043.00, 4132.00) | NA | 2728.89±35.52* (2013.00, 3922.00) | 2521.91±201.53‡ (2088.00, 3198.00) |
| Vault (μm), range (min, max) | NA | 515.38±188.40 (180, 880) | 504.62±191.64 (120, 850) | 445.00±214.00 (90, 860) |

*Versus preoperative, p<0.05.
†1-month follow-up versus last follow-up, p<0.05.
‡3-month follow-up versus last follow-up, p<0.05.

ACA, anterior chamber angle; ACD, anterior chamber depth; ACV, anterior chamber volume; CDVA, corrected distance visual acuity; ECD, endothelium cell density; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; NA, not available; SE, spherical equivalent; UDVA, uncorrected distance visual acuity.
and the percentage decrease was 5.90±10.03% compared with the preoperative level, while the figures at last follow-up were 408.5±485.16 cells/mm² and 12.11%±13.94%, respectively. ECD in no eye decreased to <2000 cells/mm² at last follow-up.

### Anterior lens density

**Table 3** shows the average ALD values before and after ICL V4c implantation. No significant lens opacity was found on slit lamp examination, and the incidence of cataract and high IOP was 0%.

Compared with the preoperative value, the ALD increased at 1-month postoperatively at different depths (0.5, 1.0 and 1.5 mm) by 1.36%±3.25%, 1.88%±4.67% and 2.11%±5.94%, respectively. Corresponding data for 3-month follow-up were 2.16%±11.57%, 1.63%±11.54% and 2.41%±12.21%, respectively, and for the last follow-up visit the figures were 16.72%±9.85%, 16.52%±10.4% and 17.28%±11.93%, respectively. The results of the statistical analysis are shown in **figure 2**.

We found significant correlations between age and ALD values at postoperative 1-month, 3-month and last follow-up, as well as a significant correlation between SE and ALD values at 1-month and 3-month postoperatively. The results of the correlation analysis are summarised in **table 4**. There were no significant correlations between ALD or preoperative and postoperative ALD changes with changes in ACD, ACA, ACV or vault (p>0.05).

## DISCUSSION

The long-term safety and efficacy of ICL implantation have long been considered a central issue for its clinical application, which had been clearly established among the population aged 20–40 years. The results of the present study indicated a safety index of 1.26±0.35 and an efficacy index of 0.91±0.41 at 42-month postoperative follow-up in patients ≥40 years. Previous research findings from a 3-year follow-up of 184 eyes of 92 patients indicated indices of 1.03 and 0.90, respectively, while a recent study involving a 1-year follow-up after ICL V4c implantation in patients >40 years confirmed that the two indices were 1.09 and 1.17 in the current study, the safety indices at the three postoperative follow-up time points were not statistically different. Intriguingly, significant differences in efficacy index were found between 3 months postoperatively and at last follow-up. The slightly lower efficacy index may be related to the high proportion of super-high-degree myopes involved in this study, whose visual acuity could still have improved to a certain extent. Together, these results confirm that ICL V4c implantation is safe and efficacious for patients >40 years of age.

Improper operation during surgery is generally considered a factor strongly associated with decreased corneal endothelial cells. The results of this study did not reveal an unexpected decrease in ECD. A decrease in ECD of 12.11% was found in our study, with an average decline rate of 3.46%. Although previous research has shown a rate of decline of approximately 0.6% per year in the general population, it has been suggested that a level of 4% is normal in ICL V4c implantations. Therefore, these results suggest a safe range with a decline rate of 3.46% per year, indicating a reliable long-term ECD safety in patients ≥40 years of age after ICL V4c implantation. However, further research is required to establish the association between ECD and ICL V4c implantation in patients ≥40 years of age.

No significant difference in IOP was found between the preoperative level and the last follow-up, which supports previous research on IOP long-term stability after ICL V4c implantation. There was a significant difference in ACV, ACD or ACA between the preoperative level and the 1-month postoperative, 3-month postoperative or last follow-up level. No significant reduction in ACA or ACD was found at last follow-up compared with the 3-month postoperative follow-up, while interestingly ACV was observed to increase with a decreased vault. Therefore, a future study focused on long-term anterior segment structural changes
after ICL V4c is recommended. Collectively, the decrease in ACA, ACV, ACD and vault compared with preoperative levels is in accordance with earlier observations. In our study, eight eyes had a vault within 90–150 μm, but there was no cataract or high IOP in any of the cases. An intumescent lens due to increased age could be attributed to the low vault; thus, a proper vault is suggested to decrease the risk of complications. Further data collection to determine whether a larger vault is needed in patients with myopia ≥40 years of age are warranted.

The increase in lens density is closely related to the formation of cataracts. ICL implantation is generally considered to contribute to an increase in lens density. So far, three factors have been identified as potential inducements: improper operation during surgery (lens contact), lower vault and changes in aqueous humour circulation. Forty years is the turning point for lens density changes: in people <40 years old, the lens density has no obvious change or only slightly increases, but in those ≥40 years old the lens density shows a linear correlation with age. We consider that this research on the changes in ALD in patients >40 years of age undergoing ICL V4c implantation will serve as a basis for future studies.

The first serious discussion and analysis of ALD took place in 2020 and reported a 4-year follow-up for ALD in ICL V4c implanted patients ≤40 years of age, revealing an increase in ALD at different depth zones: the increase at depths of 1 and 1.5 mm was relatively close (17.1%±11.09% and 16.76%±10.4%) and greater than at a depth of 0.5 mm (10.41%±11.5%). The results of this study are partially similar to our findings: the increase in ALD at depths of 0.5, 1 and 1.5 mm zones were 16.52%±10.46%, 16.72%±9.85% and 17.28%±11.93%, respectively. Interestingly, the ALD increase at a depth of 0.5 mm was greater in older age group than that in the younger age group. We suppose that at a depth of 0.5 mm, the greater increased ALD may be related to cortical turbidity contributed by the older age group compared with that in the younger age group. At a depth of 1.5 mm, the increased ALD may be related to the faster progression of nuclear turbidity due to super-high myopia. Therefore, more research on this topic needs to be undertaken for the association between these factors and change in ALD to be more clearly understood.

This is the first study reporting an observation of ALD with Pentacam HR in ICL V4c implantation patients ≥40 years of age for myopia correction. The results of the correlation analysis suggest similar conclusions of linear regression between ALD and age as the findings of previous studies. Further analysis showed that the SE was negatively correlated with ALD preoperatively and at 3 months postoperatively. This result may be explained by the fact that a higher incidence of nuclear cataracts could be found in high-degree myopes. There was no significant correlation between ALD changes at last follow-up and SE. This result may be explained by the increased cortical turbidity due to an increased age and the disturbed circulation of aqueous humour after ICL V4c implantation, which may play a more important role in the increase of ALD in long-term follow-up. No correlation was found between ALD and vault, ACD, ACV, ACA or changes in these parameters. In addition, there was a statistically significant increase in ALD at postoperative 3-month and last follow-up compared with that at preoperative levels, but the increased ALD value was minor when compared with that in the previous report regarding patients <40 years old after ICL V4c implantation in the long term. However, the precise mechanism remains to be elucidated. It is unclear if the affected aqueous humour circulation participates in the increase in ALD.

Previous studies have demonstrated that the increase in ALD may be related to age-related oxidative changes in the lens cortex. The loss of soluble α lens leads to the accumulation and combination of crystallins in the membrane of fibre cells, resulting in an increase in ALD. Interestingly, the participants in this study had a greater average age and a relatively lower mean average ALD value than those in previous studies, a finding which may be related to the different measurement methods. A 3 mm diameter around the centre of the pupil was selected in this study, while the previous study chose a 4 mm diameter. Some authors have speculated that subcortical areas correspond to the main opacity areas of most eyes. A larger subcortical zone was included in the 4 mm diameter, which was attributed to the discrepancy on the surface. A further study with more focus on the influence of different zone diameters around the pupil on ALD after ICL V4c implantation is necessary.

In conclusion, ICL V4c implantation provides long-term safety and effectiveness for myopia correction in the population over 40 years of age. At long-term follow-up, there was an increase in ALD, which may be related to age and SE. This research will serve as a basis for further progress in determining the factors and precise mechanisms related to these changes.

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Patient consent for publication Not required.

Ethics approval This study followed the tenets of the Declaration of Helsinki and was approved by the ethics committee of the Eye and ENT Hospital of Fudan University. All procedures and the nature and possible consequences of the study were explained to the patients fully in accordance with the Declaration of Helsinki.

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