• Clinical Research •

Long-term observation of the endothelium morphology and corneal thickness in myopic adolescents treated with orthokeratology: a 10-year retrospective study

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Abstract

● **AIM:** To assess the long-term safety of orthokeratology (ortho-k) in myopic children by evaluating changes in corneal endothelial morphology and central corneal thickness (CCT) after prolonged ortho-k lens wear.

● **METHODS:** This study included 65 myopic children (130 eyes). The ortho-k group comprised 39 children who had worn ortho-k lenses for more than 10y. The control group included 26 children who wore single-vision spectacles for myopia correction. Clinical data and adverse events were documented throughout the follow-up period. Endothelial cell density (ECD), coefficient of variation (CV) of cell area, percentage of hexagonal cells (%SIX), and CCT were measured at baseline and at the final follow-up visit.

● **RESULTS:** The 39 participants (18 males, 21 females) enrolled in the ortho-k group completed the 10-year follow-up examinations successfully. The ages ranged from 7 to 12 (9.24±1.26)y. In the control group, 26 participants (13 males, 13 females) were successfully recalled and completed their 10th year examinations. The ages ranged from 7 to 12 (9.62±1.68)y. In the ortho-k group, ECD was 3119.86±202.07 cells/mm^2 at baseline and 3057.42±264.52 cells/mm^2 at the 10-year follow-up (*P*=0.058). CV was 30.78%±6.70% and 32.45%±7.87% (*P*=0.053). %SIX was 62.23%±13.07% and 60.31%±11.59% (*P*=0.234). CCT decreased by 8±4 μm at the 6-month visit and remained stable thereafter (538.85±43.61 μm at 6mo *vs* 540.78±41.44 μm at 10y, *P*=0.528). At the 10-year follow-up, no significant between-group differences were observed in ECD, CV, %SIX, or CCT (all *P*>0.05).

● **CONCLUSION:** This 10-year retrospective study demonstrates that long-term ortho-k lens wear has no significant adverse effects on corneal endothelial morphology or CCT compared with spectacle wear. Ortho-k shows excellent long-term safety with regard to corneal endothelial parameters and CCT, comparable to that of conventional spectacle correction in myopic children.

● **KEYWORDS:** myopia; orthokeratology; corneal endothelium morphology; central corneal thickness; percentage of hexagonal cells; long-term safety

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INTRODUCTION

Myopia has now become a major public health disease worldwide, with a heavy economic burden on all countries[1-2]. By 2050, approximately 50 percent of the world's population will have myopia, and 10 percent of them will have high myopia, and this trend is growing[3]. In China, a study has shown that the prevalence of myopia is estimated to be approximately 80% in 18-year-old[4]. The prevalence of myopia among students aged 6-18y may keep increasing in the next ten years and controlling that progression is vital to prevent higher myopia as well as many other ocular complications[5]. As the epidemiological and mechanistic studies of myopia intensify, the age of first onset of myopia and early intervention in the

treatment and prevention of myopia are important factors in preventing progression to high myopia or even pathological myopia[6]. Meanwhile, in recent years, there are more and more emerging means of myopia prevention and control[7-8]. In addition to frames, the effectiveness of myopia prevention and control, such as low-level red-light therapy, low-concentration atropine, outdoor exercise, defocus incorporated soft contact, and orthokeratology (ortho-k), has also been revealed gradually[9-12]. Ortho-k, is a rigid gas-permeable contact lens in reverse geometry design that when worn overnight, has been shown to temporarily reduce or eliminate daytime myopia blur. Over the past decade, multiple researches have verified that ortho-k therapy is effective and relatively safe (if managed correctly) in slowing the progression of myopia in children[13-15]. Due to the significant correlation between axial elongation and myopia progression, many studies have also presented the effectiveness of ortho-k in the reduction in myopic axial elongation[16]. However, with ortho-k use growing rapidly worldwide, potential ocular issues associated with longtime overnight wear have become a worthy focus of concern.

To date, a number of studies have been conducted on the safety of ortho-k treatment. These studies have focused on potential adverse effects, including corneal staining, secondary infection, corneal nerve damage, and dry eye[17-20]. Corneal endothelial morphology and corneal thickness, as important indicators for the safety of ortho-k lens wear, are a matter of concern. In particular, the changes in corneal thickness and endothelial morphology should be observed regularly to evaluate the impact of long-term wear on the cornea. The quantity of corneal endothelium has a non-renewable character, while the shape of the corneal endothelium affects the quality of vision. Studies have shown that long-term alignment of a contact lens and the cornea will produce a constant mechanical pressure. This pressure may have an impact on the cornea, such as reduced corneal thickness[21]. In recent years, there is no entirely clear conclusion on whether long-term wear produces significant changes in central corneal thickness (CCT). Meanwhile, there have been few studies to evaluate the long-term effects of ortho-k on the corneal endothelium by relevant parameters, such as endothelial cell density (ECD), coefficient of variation (CV) in cell size, and percentage of hexagonal cells (%SIX).

Given that more and more myopic children use ortho-k lenses for long periods of time during their growth years, it is vital to observe changes in corneal endothelium morphology and CCT before and after long-term wear of ortho-k. Therefore, this retrospective study aims to assess whether ten years of ortho-k treatment has a sustained effect on corneal endothelial morphology and CCT in myopic children, and to evaluate the long-term safety of ortho-k treatment on corneal structures.

PARTICIPANTS AND METHODS

Ethical Approval This study was approved by the Ethics Committee of the Tianjin Medical University Eye Hospital (No.2024KY-67). All study procedures adhered to the tenets of the Declaration of Helsinki. All children and guardians have provided informed consent.

Study Design We conducted a retrospective data review of patients seen between July 2012 and August 2023 at Tianjin Medical University Eye Hospital. Clinical data, including sex, age, refraction, corrected visual acuity, intraocular pressure, axial lengths, ECD, CV, %SIX, CCT, and adverse events (AE), were recorded.

Participants Medical records of patients who continued ortho-k treatment or spectacles for myopia correction for more than 10y were reviewed. Finally, a total of 130 eyes, 65 participants (31 males and 34 females) were included, with an age range of 7 to 12y and an average age of 9.39±1.45y (at baseline). The inclusion criteria were children with an ocular refraction of -0.50 to -6.00 diopters (D) of myopia, with or without refractive astigmatism not greater than 1.50 D, with or without anisometropia not greater than 1.50 D, and a best-corrected visual acuity at least 0.00 logMAR units (Snellen equivalent to 20/20). The exclusion criteria included any contraindications for wearing contact lenses, any history of inflammatory ocular disease or surgery, failure to complete follow-up and failure to follow doctor's orders.

Orthokeratology Lens Ortho-k lenses [Emerald Lenses; Euclid Systems Corp., Sterling VA, oxygen permeability 95×10^{-11} $cm^2/s\cdot mL$ $O_2/(mL\cdot hPa)$ @35°C, geometric reverse four-arc surface] were used in this study. Participants in the ortho-k group were informed of instructions on lens handling and care before receiving their lenses and were advised to wear their ortho-k lenses for 6-10h a night. Ortho-k lenses were replaced during the follow-up period, with the average replacement period less than a year and a half. For the control group, participants wore single-vision spectacles and continued to use them for 10y or more without accepting any other treatments. Given diurnal variations in some values, participants were required to undergo all tests approximately 2h after their lens removal.

Examinations Endothelial images were captured using a corneal endothelial cell counter (CEM-530. Beckman Coulter, USA). The CCT were evaluated by Lenstar (LS900. Haag-Streit, Swiss). At least three consecutive measurements were taken for each visit, and their average was used as a representative value. All examinations, meanwhile, were performed by a skilled clinician to ensure the reliability of the data (Figure 1).

Statistical Analysis All data are presented as mean±standard deviation (SD). The statistical software, SPSS 26.0 (USA),

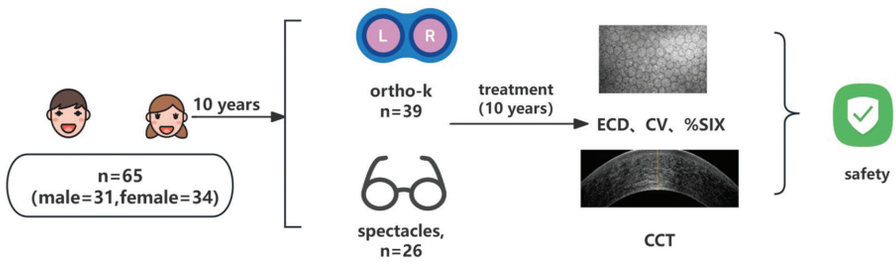

Figure 1 The design of this 10-year study The figure includes a visualization of the included population, subgroup information, observational indicators with assessment of outcomes. ECD: Endothelial cell density; CV: Coefficient of variation; %SIX: Percentage of hexagonal cells; CCT: Central corneal thickness.

Table 1 Demographic data and baseline central corneal thickness and corneal endothelial parameters of the subjects mean±SD

Parameters	All (*n*=65)	Ortho-k (*n*=39)	Control (*n*=26)	*P*
Age (y)	9.39±1.45	9.24±1.26	9.62±1.68	0.22[b]
Gender				0.83[c]
Male	31	18	13	
Female	34	21	13	
Spherical equivalent refractive error (D)	-2.58±1.28	-2.71±1.34	-2.38±1.18	0.158[b]
Intraocular pressure (mm Hg)	14.34±2.88	14.40±2.95	14.26±2.80	0.904[b]
Axial length (mm)	24.61±0.95	24.70±0.97	24.46±0.92	0.168[b]
Endothelial cell density (cells/mm^2)	3120.52±219.19	3119.86±202.07	3121.52±244.69	0.063[a]
Coefficient of variation in cell size (%)	30.02±6.13	30.78±6.70	28.87±4.33	0.346[a]
Hexagonality (%)	62.65±11.76	62.23±13.07	63.27±9.56	0.206[a]
Central corneal thickness (μm)	546.07±39.90	547.24±41.26	544.31±38.10	0.683[a]

[a]Unpaired *t*-tests (unless otherwise specified); [b]Mann-Whitney *U* tests; [c]Pearson Chi-square. SD: Standard deviation.

was used for statistical analyses, which considered $P<0.05$ to be statistically significant. Unpaired *t*-tests, Mann-Whitney *U* tests, or Pearson Chi-squares, were used to compare the baseline characteristics in the two groups, depending on the type of the data and the normality of the distribution of data. Data obtained after 10-years of ortho-k lens therapy were compared with data gathered before the treatment using a paired *t*-test. Repeated measures Analysis of Variance/Analysis of Covariance (ANOVA/ANCOVA) were used to compare CCT, HEX, CV, and %SIX at the baseline and the 10-year visits in the two groups.

RESULTS

A total of 65 participants were included in the study (31 males, 34 females). The 39 participants (18 males, 21 females) enrolled in the ortho-k group completed the 10-year follow-up examinations successfully. Their ages ranged from 7 to 12 (9.24±1.26)y. In the control group, 26 participants (13 males, 13 females) were successfully recalled and completed their 10th year examinations. Their ages ranged from 7 to 12 (9.62±1.68)y. There were no significant inter-group differences or variations in age, gender, spherical equivalent refractive error, intraocular pressure, axial length, ECD, CV, %SIX, or CCT among two groups at the baseline ($P>0.05$; Table 1).

Baseline Corneal Endothelial Morphology and Central Corneal Thickness In the Ortho-k group, their ECD ranged from 2732 to 3671 (3119.86±202.07) cells/mm^2, their CV ranged from 14% to 46% (30.78%±6.70%), their %SIX ranged from 35% to 88% (62.23%±13.07%), and their CCT ranged from 436 to 682 (547.24±41.26) μm. In the spectacle control group, their ECD ranged from 2509 to 3586 (3121.52±244.69) cells/mm^2, their CV ranged from 19% to 43% (28.87%±4.33%), their %SIX ranged from 40% to 85% (63.27%±9.56%), and their CCT ranged from 434 to 623 (544.31±38.10) μm (Table 1).

Effect of Time and use of Ortho-k on the Corneal Endothelial Morphology and the Central Corneal Thickness Changes in the endothelial morphology and the CCT over ten years in the two groups are shown in Table 2. We found that time was shown to have a significant effect on CV ($P=0.011$, $P<0.05$), %SIX ($P=0.04$, $P<0.05$), and CCT ($P=0.003$, $P<0.05$). All four parameters were significantly changed over time. Meanwhile, there were no significant interactions found between time and study groups in the four parameters ($P>0.05$). Meanwhile, the change in endothelial morphology and CCT was not significantly different between the two groups ($P>0.05$).

Corneal Endothelial Morphology and Central Corneal Thickness After Ortho-k Treatment Table 3 and Figure 2 show that the ECD did not change significantly before (3119.86±202.07) cells/mm^2 and after treatment

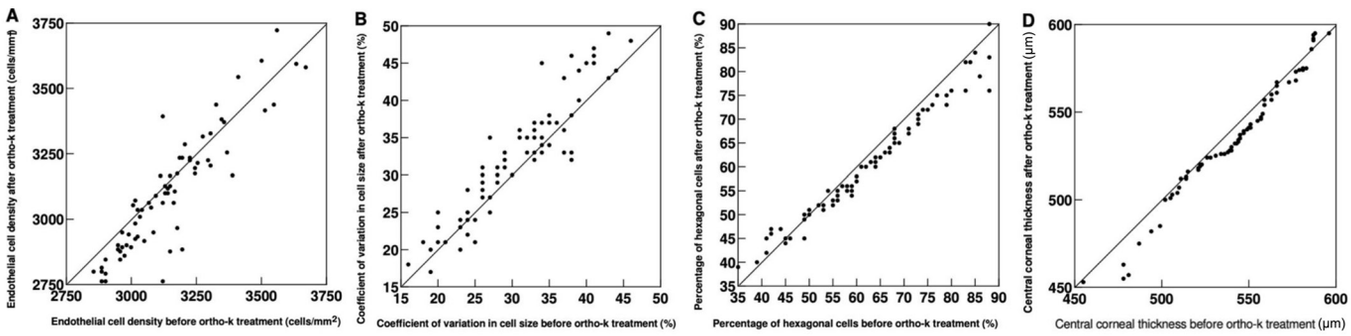

Figure 2 Scatter plots of ECD (A), CV (B), %SIX (C), and CCT (D) 10y after ortho-k treatment compared with baseline No significant changes were found in ECD, CV, and %SIX (*P*=0.058, 0.053, 0.234, respectively). CCT was reduced (*P*=0.005, *P*<0.01). ECD: Endothelial cell density; CV: Coefficient of variation; %SIX: Percentage of hexagonal cells; CCT: Central corneal thickness; Ortho-k: Orthokeratology.

Table 2 Mean changes in the central corneal thickness and endothelial morphology over ten years in the two groups of subjects

Parameters	Effect of time[b]	Time×Group[b]	Ortho-k (*n*=39)	Control (*n*=29)	Between groups *P*
ECD (cells/mm^2)	0.022	0.567	-62.44±286.14	-37.65±149.38	0.705
CV (%)	0.011	0.992	1.67±7.50	1.65±6.79	0.053
%SIX (%)	0.040	0.678	-1.92±14.14	-2.88±10.79	0.743
CCT (μm)	0.003	0.643	-6.46±19.55	-1.77±21.49	0.769

ECD: Endothelial cell density; CV: Coefficient of variation in cell size; %SIX: Percentage of hexagonal cells; CCT: Central corneal thickness; Ortho-k: Orthokeratology; ANOVA: Analysis of variance; ANCOVA: Analysis of covariance. [b]Repeated measures ANOVA/ANCOVA within subject effect and interaction.

Table 3 Changes in the central corneal thickness and endothelial morphology in ortho-k group post lens wear mean±SD

Change	Pre lens wear	Post lens wear (6mo)	Post lens wear (10y)	*P*[a] (Pre *vs* 6mo, Pre *vs* 10y, 6mo *vs* 10y)
ECD (cells/mm^2)	3119.86±202.07	3116.42±191.37	3057.42±264.52	0.892, 0.058, 0.061
CV (%)	30.78±6.70	31.99±7.30	32.45±7.87	0.213, 0.053, 0.608
%SIX (%)	62.23±13.07	62.05±11.85	60.31±11.59	0.909, 0.234, 0.308
CCT (μm)	547.24±41.26	538.85±43.61	540.78±41.44	0.014[c], 0.005[c], 0.528

ECD: Endothelial cell density; CV: Coefficient of variation in cell size; %SIX: Percentage of hexagonal cells; CCT: Central corneal thickness; SD: Standard deviation; Ortho-k: Orthokeratology. [a]Paired *t*-tests. [c]Significantly different.

(3057.42±264.52) cells/mm^2; *P*=0.058. The CV was 30.78%±6.70% and 32.45%±7.87% at baseline and after 10-year ortho-k treatment, respectively. There were no statistical differences between baseline and after 10-year ortho-k treatment (*P*=0.053). The %SIX did not change significantly [(62.23%±13.07%) pre-treatment and (60.31%±11.59%) post-treatment (*P*=0.234)]. CCT reduced by an average of 8.39 μm (*P*=0.014) at the 6-month visit and remained unchanged during the ten years (538.85±43.6 μm at the 6-month visit and 540.78±41.44 μm at the 10-year visit; *P*=0.528).

Other Adverse Events During the 10-year study period, only 5 of 78 eyes (6.41%) in the ortho-k group reported observed adverse events (3 eyes with allergic conjunctivitis; 2 eyes with hordeolum). Participants who were affected by complications resumed wearing ortho-k after 1-2wk of treatment. No other severe complications, such as corneal ulcers, were noted in all participants.

DISCUSSION

We concluded from a 10-year retrospective study that there were no statistically significant differences in corneal endothelial by ECD, CV, and %SIX between patients before and after ortho-k therapy. To our knowledge, this is the first study with the longest time span to evaluate the safety of corneal structure after long-term ortho-k treatment.

Ortho-k, a non-surgical vision correction modality, uses rigid gas-permeable lens material and a highly specific, reverse geometry design to correct refractive errors quickly and temporarily by changing the curvature of the anterior cornea surface[13]. There are more studies on the evaluation of corneal endothelium for ortho-k treatment, but corneal endothelium is very rare[16,22]. Moreover, decreased corneal ECD owing to the reasons mentioned above results in blurred vision or impaired visual acuity, which requires corneal transplantation for function recovery[23]. Therefore, it is clinically essential to observe the status of corneal endothelial cells.

Correlation analysis in our study suggests that the change of ECD, CV and %SIX was not significant. The changes in ECD of all participants showed a fluctuating, but downward trend, accompanied by a 1.92% reduction in %SIX and a 1.67%

increase in CV after ten-years of ortho-k treatment. And in the control group, a greater reduction (2.88%) in %SIX and a 1.65% increase in CV were recorded. Yuan *et al*[24] found a similar conclusion that no changes occurred in ECD, CV, and %SIX before and after one year of ortho-k lens wear in 106 eyes of 53 patients aged 8-15y. In another retrospective study conducted by Guo and Xie[25] there were no significant changes found in ECD, %SIX, and CV after seven years of ortho-k lens wear in 30 participants aged 8-20y. These are consistent with our findings.

Besides, it is known that ECD reduces from birth as age increases. ECD reduces rapidly in the first five years of age, then the rate of reduction slows down during childhood period, and finally becomes stable at 3000 cells/mm^2 by age 20[26]. We found that the ECD reduced by about 2% in ortho-k group and 1.2% in the control group in ten years. Previous studies have presented that age-related reduction in ECD is accompanied with a reduction in %SIX and an increase in CV in normal eyes[18]. Cheung and Cho[27] reported a significant reduction in %SIX and an increase in CV at the central endothelial layer after two years of ortho-k treatment among children aged 6-12 years old. They acknowledged that the reduction of the central ECD was a process of aging, and the process was not due to the mechanical stress caused by wearing the ortho-k lens. A systematic review reported that the rate of cell loss in central endothelium is 0.13%±0.25% per year in healthy groups aged 10-89 years old, and the loss of cells is higher in younger groups[22]. In this study, the change in ECD in our data was similar to those observed in the healthy groups, but the changes in ECD did not reach statistical significance. The reason for cell loss is not clear, and this may be a natural aging process not influenced by external factors. In the current study, ECD, CV, and %SIX changed with time in both groups. We found a correlation between the three parameters with time, while the association between these parameters and other parameters, such as gender, refractive error, or axial length was not considered.

Furthermore, we observed that CCT reduced by about 8.39 μm at the 6-month visit. Cheung and Cho[28] reported a similar conclusion that CCT significantly reduced by 9±9 μm after 6mo of lens wear. In a one-month longitudinal study, Nieto-Bona *et al*[29] found that CCT significantly reduced by 6.5±8 μm (confocal microscope determined) and 6.4±7 μm (optical coherence tomography determined) 1mo after ortho-k lens wear. Other studies reported that significant central thinning of the cornea occurred 24h after lens wear and usually peaks at 1wk[30]. The redistribution of corneal tissue and the rearrangement of cells, caused by the specific lens design, is the rationale for the slight thinning of CCT. We found that after a very slight thinning, the CCT reached relatively stabilization during 6mo to 10y. These studies all demonstrated the minimal effect of ortho-k on CCT in children. Some studies have shown that the effect of ortho-k lens on CCT is reversible. A study showed that the CCT was almost restored to baseline after 3mo of discontinuation[31]. The change of CCT after discontinuation was not measured in this study, and further research is needed, especially for those who have accepted long-term ortho-k treatment.

Inevitably, our study has some limitations. First, this is a retrospective study and although it spans a long period of time, it is not a longitudinally observable study and can be observed in the future with prospective studies. Moreover, our study included a small sample size due to the time span, and more observational samples need to be added to further evaluate safety. Finally, we looked at the safety of single ortho-k treatment, and the next step could be a long-term, safety study of combination therapy. This study focuses on safety during treatment; we have discussed effective predictive indicators for treatment in efficacy studies and long-term studies in our other research[32].

In general, ortho-k is a relatively safe procedure for children who need long-term myopia management therapy. Considering the variability of clinical research, the limited sample size could influence the stability of the results, so more work needs to be done in future studies.

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Authors' Contributions: Liu L and Wei RH conceived and supervised the experiment. Zhao LQ and Wang ZX performed the study. Li Y and Wang BY collected the data. Du B analyzed the data. Beeman J helped perform the analysis with constructive discussions. Zhao LQ and Wang ZX wrote the manuscript. Zhao LQ and Wang ZX contributed equally to this work and were both considered first authors. Liu L and Wei RH contributed equally to this work and were both considered corresponding authors. All authors read and approved the final manuscript.

Data Availability Statements: The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Conflicts of Interest: Zhao LQ, None; **Wang ZX,** None; **Li Y,** None; **Wang BY,** None; **Du B,** None; **Beeman J,** None; **Wei RH,** None; **Liu L,** None.

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