Full title: Short- and long-term changes in corneal aberrations and axial length induced by orthokeratology in children are not correlated.

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ABSTRACT

Purpose: To assess the correlation between changes in corneal aberrations and the 2-year change in axial length in children fitted with orthokeratology contact lenses (OK).

Methods: Thirty-one subjects 6-12 years of age and with myopia -0.75 to -4.00DS and astigmatism ≤1.00DC were fitted with OK. Measurements of axial length and corneal topography were taken at regular intervals over a 2-year period. Corneal topography at baseline and following 3- and 24-months of OK lens wear was used to derive higher order corneal aberrations which were correlated with OK-induced axial length changes at 2-years.

Results: Significant changes in C_3^{-1}, C_4^0, C_4^4, RMS secondary astigmatism and fourth and total HOA were found with both 3- and 24-months of OK lens wear in comparison to baseline (all $p<0.05$). Additionally, significant changes in C_3^3 and RMS tetrafoil were found at 3-months and in second order RMS at 24-months of OK lens wear in comparison to baseline (all $p<0.05$). However, none of the changes in corneal aberrations were significantly correlated with the 2-year change in axial elongation (all $p>0.05$). Coma angle of orientation changed significantly pre- in comparison to 3- and 24-months post-OK as well as secondary astigmatism angle of orientation pre- in comparison to 24-months post-OK (all $p<0.05$). However, coma, trefoil, secondary astigmatism and tetrafoil angles of orientation pre- or post-OK were not significantly correlated with the 2-year change in axial elongation (all $p>0.05$).

Discussion: Short- and long-term OK lens wear induces significant changes in corneal aberrations that are not significantly correlated with changes in axial elongation after 2-years.

Key words: cornea; aberrations; topography; myopia progression; orthokeratology; contact lenses; axial length

INTRODUCTION

The prevalence of myopia has increased substantially in recent decades and has been estimated to currently affect approximately 25% of the world population.[1-3] Myopia has become an important health concern as it is strongly associated with different ocular pathologies, such as vitreous and retinal detachment, macular degeneration, and glaucoma.[4-7] As a result, myopia can incur significant ocular-related morbidity and healthcare costs.[8-10]

It has been suggested that higher-order aberrations may play a role in the development of refractive errors by reducing retinal image quality.[11] In young adults, Marcos et al. observed an increase in myopia to be associated with a significant positive increase in corneal spherical aberration and a negative increase in internal spherical aberration.[12] Llorente et al. found ocular third-order total root-mean-square (RMS) aberration (i.e. coma-like), ocular spherical aberration and corneal spherical aberration to be significantly greater in young hyperopic eyes than in young myopic eyes whereas internal spherical aberration did not differ significantly between the two groups.[13] Philip et al. found no differences in ocular or corneal horizontal, vertical or RMS coma aberrations and coma-like aberrations between hyperopic, emmetropic and myopic adolescent eyes, although ocular spherical aberration was significantly less positive in low myopic, moderate myopic and emmetropic eyes compared to low hyperopic eyes.[14] More recently, Philip et al. monitored ocular aberrations in emmetropic children over a 5-years period and found that children who became myopic underwent an increase in negative spherical aberration or a decrease in positive spherical aberration together with an increase in RMS coma and coma-like aberrations, whereas eyes that remained emmetropic exhibited an increase in positive spherical aberration and a decrease in vertical coma.[15] Furthermore, third-order RMS and coma RMS at baseline were found to be greater in the group that remained emmetropic in comparison to the group that became myopic.[15]

Orthokeratology (OK) contact lens wear has consistently shown to be effective in reducing myopia progression by 30 to 50% in comparison with conventional spectacle and soft contact lens wear in children.[16-21] It is well established that OK induces central corneal flattening and an increase in mid-peripheral corneal thickness,[22] which significantly affect corneal and ocular aberrations.[23-27] Of special interest is a recent report by Hiraoka et al. performed in Japanese children over a 1-year period that found changes in spherical defocus, second-order aberration, coma-like aberration, spherical-like aberration and total higher-order aberrations to be significantly correlated with changes in axial length.[28] This study evaluated whether changes in corneal aberrations are correlated with axial elongation in children wearing OK with reference to data from the Myopia Control with Orthokeratology contact lenses in Spain (MCOS) study.[20] The MCOS study found a statistically significant difference in axial length elongation relative to baseline over a 2-year period between white European children with myopia wearing OK (N=31) and distance single-vision spectacles (N=30).[20]

METHODS

This study was part of a larger study designed to assess different aspects of OK lens wear specifically prescribed for the control of myopia progression in children.[20, 29-35] The methods employed in MCOS have been described in detail elsewhere.[20, 29-35] In brief, normal, healthy white European subjects 6 to 12 years of age with moderate levels of mean spherical myopia (-0.75 to -4.00D) and astigmatism (≤1.00D) and free of systemic or ocular disease were fitted with Menicon Z Night contact lenses for overnight use (Menicon Co., Ltd, Nagoya, Japan). An OK fit was considered to be successful if the subject showed a CCLRU score regarding anterior eye segment signs ≤ 1 unit, a “bull’s eye” corneal topography pattern and monocular and binocular visual acuities within ±1 line of the best-correct spectacle visual acuity. All patients underwent ocular examinations including slit-lamp examination, manifest refraction, and corneal topography at baseline and after 1 day, 2 weeks, 3 months and at 6-month intervals over a 2-year period. Axial length was measured at the time of enrolment and 6, 12, 18, and 24 months after the initiation of the treatment. Follow-up visits were scheduled to fall within 2 hours of awakening. A decrease in one line of visual acuity accompanied by a change in subjective refraction at any of the follow-up visits was considered clinically significant and was remedied by supplying new contact lenses. Full informed consent and child assent was obtained from the parents/guardians prior to the start of all experimental work and data collection. Patient participation in the study could be discontinued at the examiner’s discretion should significant symptoms or slit-lamp findings occur. Subjects were instructed they could withdraw from the study at anytime. The study was conducted in accordance with the Tenets of the Declaration of Helsinki and approved by the Institutional Ethical Committee Review Board of Novovision Ophthalmology Clinic.

Measurements of axial length were taken with the Zeiss *IOLMaster* (Carl Zeiss Jena GmbH).[36] Three separate measurements of axial length were recorded and a mean obtained. The 2-year change in axial length relative to baseline was calculated as a percentage to normalize between-subjects differences in changes in axial length relative to the baseline axial length ([2-years change in axial length/baseline axial length]*100).

Corneal topography measurements were performed with the Wavelight Allegro Topolyzer (WaveLight Laser Technologies AG, Erlangen, Germany). The instrument incorporates a high resolution placido-ring corneal topographer which detects 22,000 elevated data points of measurement from 22 ring edges with a claimed accuracy and reproducibility of ± 0.10D according to the manufacturer. The first measurement taken for each eye, which provided an optimum index value according to the manufacturer's recommendations, was used for the study. Baseline and 3- and 24-months topographic outputs were taken as representative of the pre- and the short and long-term post-OK treatment status, respectively. Corneal topographies were analyzed using Oculus Keratograph software (Version 1.76, Oculus Optikgeräte GmbH, Germany). Corneal aberrations of the anterior cornea were derived from anterior cornea elevation data following previously reported methodology.[26, 34] Corneal height data were calculated with reference to a spherical surface with a radius of curvature equal to the subject's central corneal radius and for a 8mm diameter. Subsequently, data were divided by the appropriate normalization factor *Fnm*, where *n* is the order of the Zernike monomial and *m* is the frequency of the term, and multiplied by the pupil radius as recommended by the Optical Society of America[37] and ANSI.[38] The normalization factors were determined as follows:

- If n-2m $\neq$ 0 then Fnm = square root (2[n+1])
- If n-2m = 0 then Fnm = square root (n+1)

Normalized height data were imported to an analysis software program (Zemax, Redmond, WA, USA) to reconstruct the corneal surface for the entrance pupil and ray tracing was performed to establish the Zernike aberration coefficients for a 5 mm entrance pupil. To calculate corneal aberrations for the entrance pupil center, the cornea's location and tilt for the entrance pupil relative to the coaxially-sighted corneal light reflex (CSCLR) was input into Zemax software. Pupil centration was automatically provided by the corneal topographer whereas tilts around the x and y axes were calculated as the angles of the horizontal and vertical location of the entrance relative to the CSCLR divided by a set distance of 148.3 mm representative of the distance between the cornea and the fixation target.[26] The entrance pupil was positioned at a distance of 3.60 mm from the anterior corneal surface.[39] A wavelength of 546 nm was used to match the wavelength used by the Wavelight Allegro Topolyzer instrument for ocular aberrations. Corneal aberrations were expressed by Zernike expansion (i.e. C_2^{-2} up to C_4^{4}) and the RMS of coma aberration (i.e. $\surd\ [(C_3^{-1})^2 + (C_3^{1})^2]$), trefoil (i.e. $\surd\ [(C_3^{-3})^2 + (C_3^{3})^2]$), secondary astigmatism (i.e. $\surd\ [(C_4^{-2})^2 + (C_4^{2})^2]$)

and tetrafoil (i.e. $\sqrt{[(C_4^{-4})^2 + (C_4^{4})^2]}$), as well as RMS of the second, third (i.e. coma-like), fourth (i.e. spherical-like) and total higher-order corneal aberrations (HOA) (i.e. third to fourth order) were calculated. Additionally, the angles of orientation of coma, trefoil, secondary astigmatism and tetrafoil vectors of the combined Zernike terms were calculated using the formula shown below as described by Kosaki et al.,[40] where *n* is the order of the Zernike monomial and *m* is the frequency of the term (i.e. coma: n=3 and m=1; trefoil: n=3 and m=3; secondary astigmatism: n=4 and m=2; and tetrafoil: n=4 and m=4)

If $C_n^m \neq 0$

$$axis = \tan^{-1}\left(\frac{c_n^{-m}}{c_n^{m}}\right)\left(c_n^{m} < 0\right)$$
$$axis = \tan^{-1}\left(\frac{c_n^{-m}}{c_n^{m}}\right) + 180\left(c_n^{m} > 0\right)$$

If $C_n^m = 0$

$$angle = 90\left(c_n^{-m} < 0\right)$$
$$angle = 270\left(c_n^{-m} > 0\right)$$

The changes in corneal aberrations and angles of orientation (i.e. post-OK – pre-OK) at the entrance pupil were correlated with changes in axial length over 2 years.

Statistical analysis

Differences between visits (i.e. pre- *vs*. post-OK) were tested using a paired t-test or Wilcoxon signed rank test depending on normality of data distribution. Similarly, correlations between the 2-year change in axial length and changes in corneal aberrations and the orientation of combined asymmetric aberration components were determined with the Pearson product moment correlation or Spearman Rho tests depending on normality of data distribution. Data from right eyes only were used for analysis. Statistical analyses and graphing were performed with *SigmaPlot* (Systat software Inc, California, USA). The level of statistical significance was set at 5%.

RESULTS

Thirty-one children were prospectively fitted with OK contact lenses, but two children discontinued the study; one due to discomfort with contact lens wear and another one due to unknown reasons.[30] The remaining subjects engaged enthusiastically in the study and were compliant with contact lens wear for the entire duration of the study. Subjects who discontinued the study were not included in the data analysis. The subjects' demographic and baseline data have been reported elsewhere.[20, 30] At the start of the study, subjects had a mean age of 9.6 ± 1.6 years; 15 were male and 16 were female. Over two years of OK lens wear, axial length increased from 24.49 ± 0.78 mm to 24.96 ± 0.86 mm ($p < 0.001$).[20]

Three months of orthokeratology lens wear induced statistically significant changes in vertical coma (i.e. C_3^{-1}), oblique trefoil (i.e. C_3^3), spherical aberration (i.e. C_4^0), vertical tetrafoil (i.e. C_4^4), RMS secondary astigmatism, RMS tetrafoil, spherical-like and total HOA (Figure 1) (all $p<0.05$). Similarly, 24-months of OK lens wear induced statistically significant changes in vertical coma (i.e. C_3^{-1}), spherical aberration (i.e. C_4^0), vertical tetrafoil (i.e. C_4^4), RMS secondary astigmatism, second-order RMS, spherical-like and total HOA (Figure 1) (all $p<0.05$). Of special interest is, however, that neither short- nor long-term changes in corneal aberrations were significantly correlated with the 2-year change in axial elongation (Table 1) (all $p>0.05$).

Coma angle of orientation changed significantly pre- (mean axis: 194º; range: 4 to 295º) in comparison to 3- (mean axis: 246º; range: 55 to 346º) ($p=0.006$) and

24-months post-OK (mean axis: 232º; range: 29 to 288º) (p=0.014) (Figure 2). Trefoil angle of orientation did not change significantly pre- (mean axis: 61º; range: 2 to 109º) in comparison to 3- (mean axis: 88º; range: 1 to 115º) (p=0.383) or 24-months post-OK (mean axis: 75º; range: 6 to 116º) (p=0.645) (Figure 3). Secondary astigmatism angle of orientation did not change significantly pre- (mean axis: 156º; range: 4 to 176º) in comparison to 3-months post-OK (mean axis: 112º; range: 14 to 175º) (p=0.259), but a statistically significant change was found pre- in comparison to 24-months post-OK (mean axis: 139º; range: 20 to 170º) (p=0.009) (Figure 4). Tetrafoil angle of orientation did not change significantly pre- (mean axis: 7º; range: 1 to 89º) in comparison to 3- (mean axis: 1º; range: 1 to 90º) (p=0.248) or 24-months post-OK (mean axis: 20º; range: 5 to 82º) (p=0.290) (Figure 5). Coma, trefoil, secondary astigmatism and tetrafoil angles of orientation pre- or post-OK were not significantly correlated with the 2-year change in axial elongation (all p>0.05).

DISCUSSION

Short- and long-term OK lens wear induced significant changes in vertical coma, spherical aberration, vertical tetrafoil, RMS secondary astigmatism and fourth and total HOA RMS. Additionally, significant changes in oblique trefoil and RMS tetrafoil at 3-months and in second order RMS at 24-months of OK lens wear were found in comparison to baseline (Figure 1). However, neither short- nor long-term changes in corneal aberrations were significantly correlated with the 2-year change in axial elongation.

Philip et al. reported that children who remain emmetropic exhibit an increase in ocular positive spherical aberration and a decrease in vertical coma.[15] This finding is consistent with the present study as an increase in corneal positive spherical aberration with OK lens wear was observed which might partly account for the significant reduction in axial elongation found over the 2-years of follow-up; albeit the increase in corneal positive spherical aberration was not significantly correlated with the 2-year change in axial elongation. In contrast to the study of Hiraoka et al.,[28] the present study could not demonstrate significant associations between the 3- and 24-months induced change in any of the corneal aberration components examined and the 2-year change in axial elongation following OK lens wear. Our data are consistent with those reported by Hiraoka et al. in that coma-like, spherical-like and total HOA increased with OK lens wear, although the increase in coma-like aberration was not statistically significant. It should be noted, however, that differences between Hiraoka et al. study and this study might account for the discrepancy in the results of the correlations between changes in aberrations and changes in axial length found between the two studies. Hiraoka et al. opted to analyze ocular aberrations in Japanese subjects using one particular OK lens design (i.e. αOrtho-K; Alpha Corp., Nagoya, Japan), whereas in our study we measured only corneal aberrations in white European subjects using a different lens design (i.e. Menicon Z Night, Menicon Co., Ltd, Nagoya, Japan). In the present study, the effect of orientation of combined asymmetric corneal aberration components on axial elongation was also assessed. However, coma, trefoil, secondary astigmatism and tetrafoil angles of orientation pre- or post-OK were not significantly correlated with the 2-year change in axial elongation.

A limitation of this study was that anterior corneal rather total ocular aberrations were measured. However, corneal changes induced by OK lens wear are limited to the anterior cornea.[22] Anterior corneal aberration components have been reported to be generally higher than the overall ocular aberrations but balanced to a considerable degree by internal ocular aberrations.[41] Although one previous study found the change in corneal aberrations to be partially neutralized by the internal aberrations of the eye with 7 days of OK lens wear,[26] a more recent study found almost identical anterior corneal and ocular aberrations at baseline and following 1 year of OK lens wear.[28]

In summary, short- and long-term OK lens wear induced significant changes in corneal aberrations measured at the entrance pupil that are not significantly correlated with the 2-year change in axial length. Furthermore, as far as we are aware, this is the first study to report the lack of a significant correlation between the orientation of the combined asymmetric aberration components and change in axial elongation induced by OK. Nevertheless, OK has consistently shown to be effective in reducing myopia progression across different ethnic groups.[16-21] However, further research should be undertaken to understand the etiological basis for the efficacy of OK in the control of myopia progression. We envisage that the findings of this study will contribute to the debate on the uncertainty concerning the role of changes in corneal aberrations induced by OK in the etiology of human myopia.[28]

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FIGURE LEGENDS

Figure 1. Pre- (black bars) and 3- (white bars) and 24-months (grey bars) post-OK lens wear corneal aberrations. *denotes statistically significant differences pre- in comparison to post-OK at $p<0.05$. OK, orthokeratology; RMS, root-mean-square; Astig, astigmatism; HOA, higher-order aberrations. Error bars represent one standard deviation of the mean.

Figure 2. Magnitude (i.e. $\sqrt{\ }[(C_3^{-3})^2 + (C_3^{3})^2]$) in µm) and orientation (i.e. angle in degrees) of the combined horizontal and vertical coma components (i.e. C_3^{-3} and C_3^{3}) before pre- (black circles) and 3- (white circles) and 24-months (grey circles) post-OK lens wear. OK, orthokeratology.

Figure 3. Magnitude (i.e. $\sqrt{\ }[(C_3^{-3})^2 + (C_3^{3})^2]$) in µm) and orientation (i.e. angle in degrees) of the combined vertical and oblique trefoil components (i.e. C_3^{-3} and C_3^{3}) before pre- (black circles) and 3- (white circles) and 24-months (grey circles) post-OK lens wear. OK, orthokeratology.

Figure 4. Magnitude (i.e. $\sqrt{\ }[(C_4^{-2})^2 + (C_4^{2})^2]$) in µm) and orientation (i.e. angle in degrees) of the combined oblique and vertical secondary astigmatic components (i.e. C_4^{-2} and C_4^{2}) pre- (black circles) and 3- (white circles) and 24-months (grey circles) post-OK lens wear. OK, orthokeratology

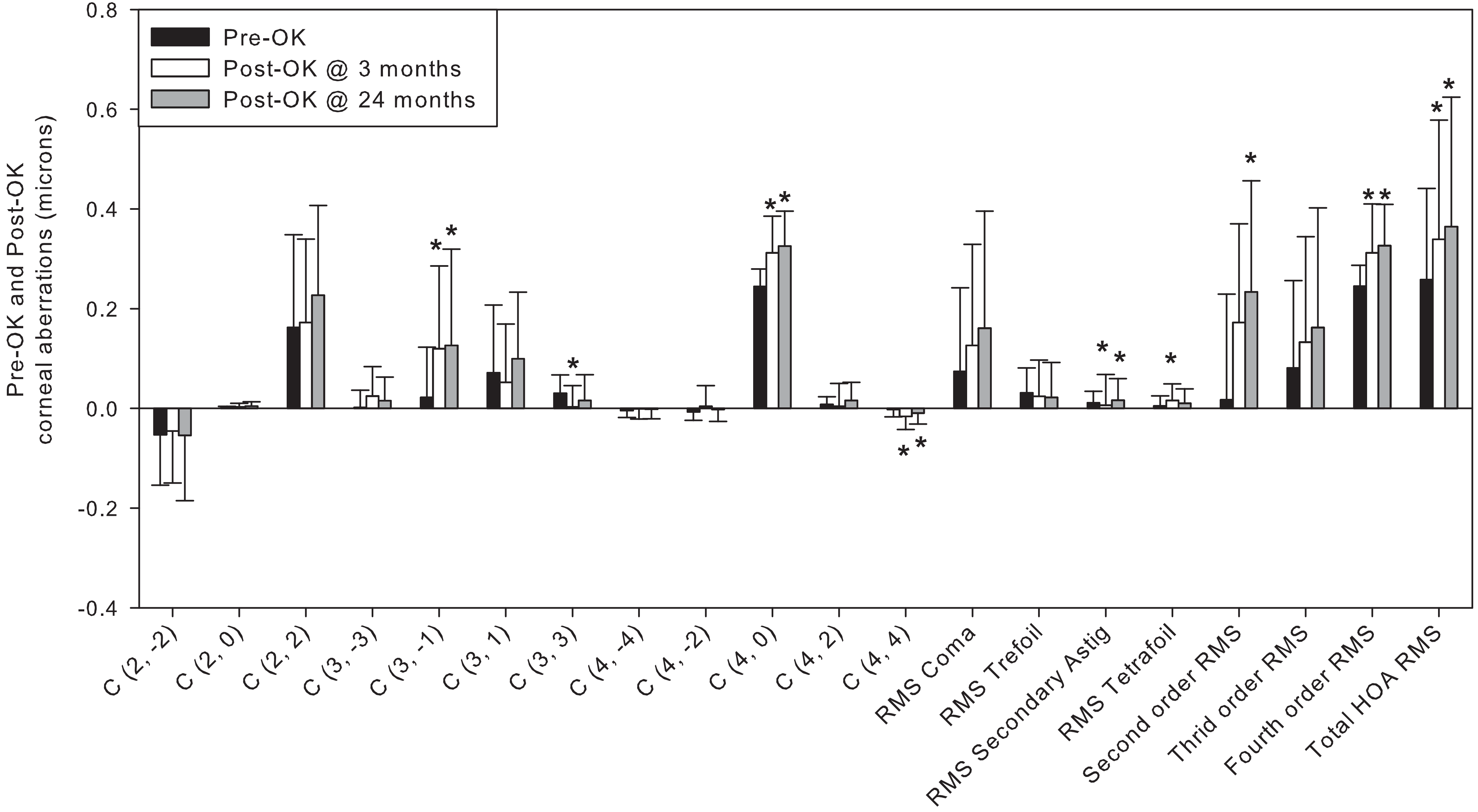
Figure 5. Magnitude (i.e. $\sqrt{\ }[(C_4^{-4})^2 + (C_4^{4})^2]$) in µm) and orientation (i.e. angle in degrees) of the combined oblique and vertical tetrafoil components (i.e. C_4^{-4}

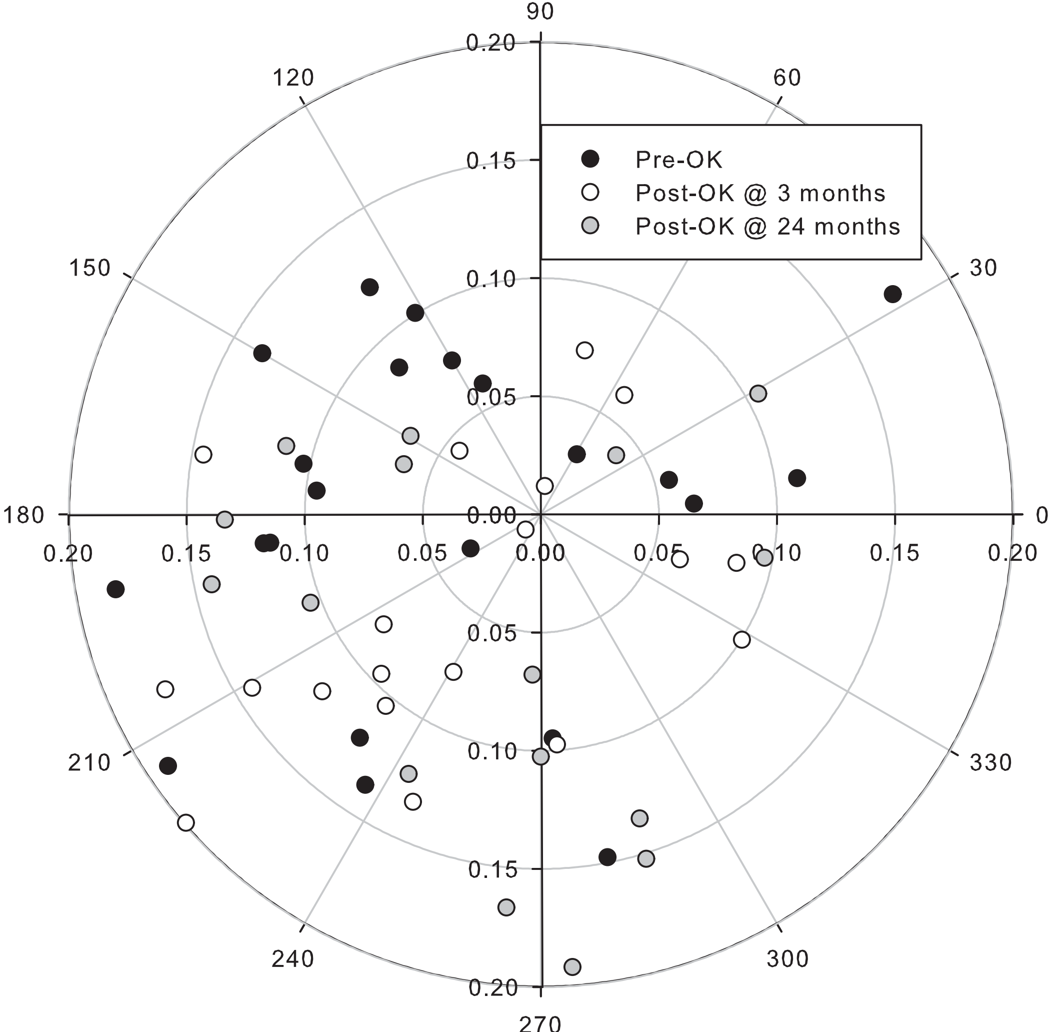
and C_4^4) pre- (black circles) and 3- (white circles) and 24-months (grey circles) post-OK lens wear. OK, orthokeratology

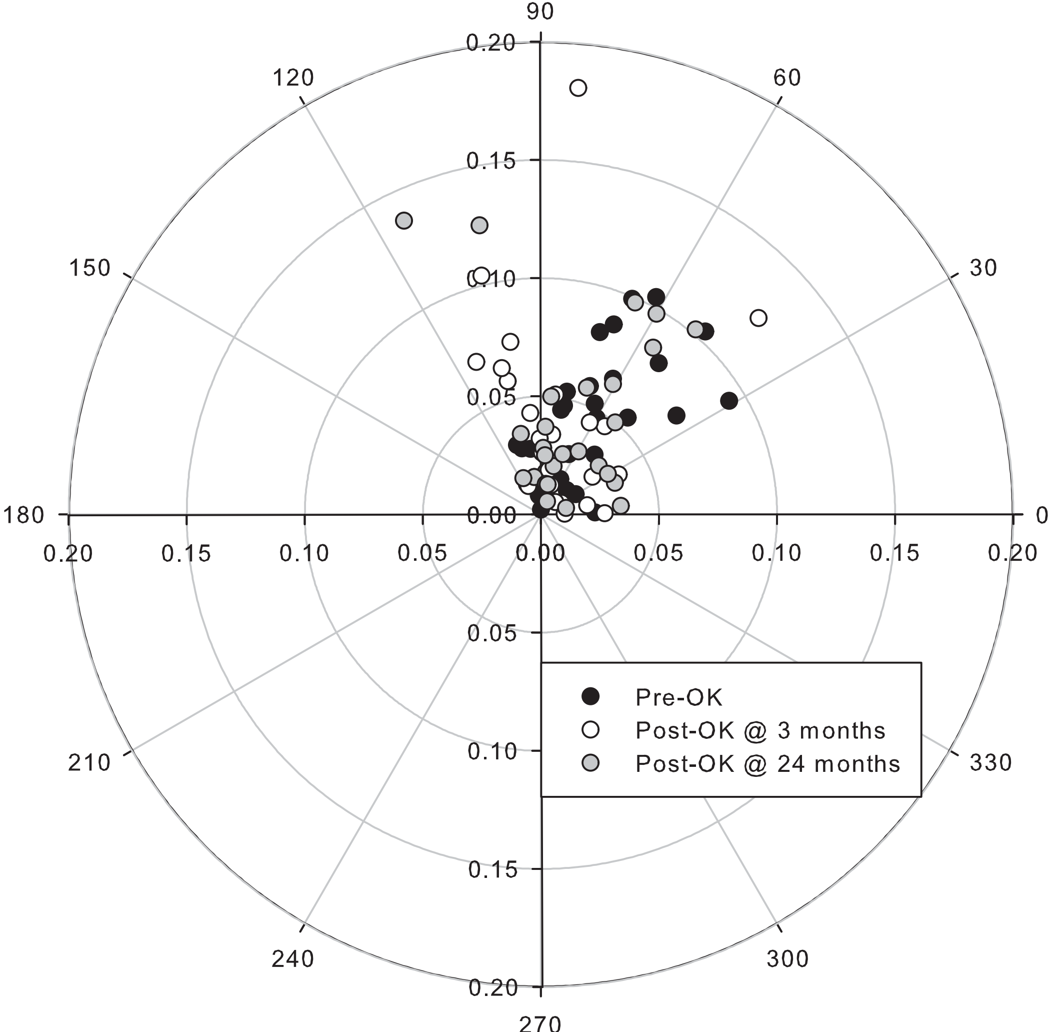
TABLE LEGENDS

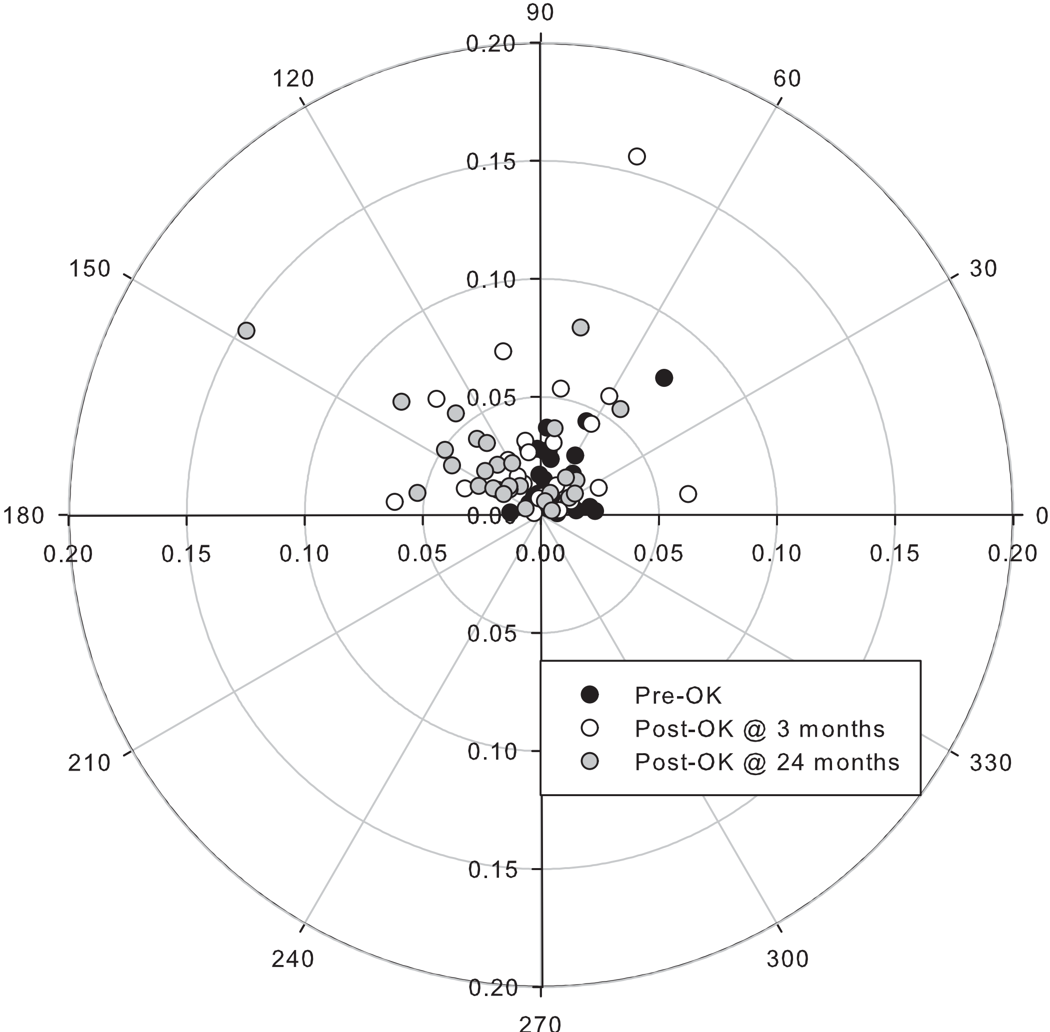
Table 1. Statistical results (i.e. r and p-vales) for the simple correlations between the 2-year changes in axial elongation and the 3- and 24-month changes in corneal aberrations following orthokeratology lens wear. RMS, root-mean-square; HOA, higher-order aberrations

	@ 3 months		**@ 24 months**	
Zernike Coefficients	**Correlation Coefficient (r)**	**p-value**	**Correlation Coefficient (r)**	**p-value**
C (2, -2)	-0.019	0.925	-0.235	0.226
C (2, 0)	0.133	0.499	0.112	0.566
C (2, 2)	0.046	0.817	0.139	0.477
C (3, -3)	0.130	0.511	0.022	0.910
C (3, -1)	0.180	0.359	0.067	0.731
C (3, 1)	-0.293	0.131	-0.147	0.451
C (3, 3)	-0.045	0.821	-0.126	0.518
C (4, -4)	-0.085	0.667	-0.340	0.076
C (4, -2)	0.073	0.711	-0.099	0.615
C (4, 0)	0.188	0.338	0.150	0.443
C (4, 2)	0.030	0.881	0.082	0.675
C (4, 4)	-0.182	0.354	-0.273	0.159
RMS Coma	0.309	0.110	0.151	0.438
RMS Trefoil	0.046	0.817	0.225	0.247
RMS Tetrafoil	0.061	0.758	-0.078	0.689
RMS Secondary Astigmatism	0.018	0.929	0.066	0.737
Second order RMS	0.211	0.281	0.058	0.767
Third order RMS	0.302	0.118	0.194	0.320
Fourth order RMS	0.102	0.607	0.156	0.424
Total HOA RMS	0.316	0.102	0.215	0.269


Pre-OK and Post-OK corneal aberrations (microns)
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
Pre-OK
Post-OK @ 3 months
Post-OK @ 24 months
C (2, -2)
C (2, 0)
C (2, 2)
C (3, -3)
C (3, -1)
C (3, 1)
C (3, 3)
C (4, -4)
C (4, -2)
C (4, 0)
C (4, 2)
C (4, 4)
RMS Coma
RMS Trefoil
RMS Secondary Astig
RMS Tetrafoil
Second order RMS
Thrid order RMS
Fourth order RMS
Total HOA RMS


90
60
30
0
330
300
270
240
210
180
150
120
0.20
0.15
0.10
0.05
0.00
0.05
0.10
0.15
0.20
● Pre-OK
○ Post-OK @ 3 months
● Post-OK @ 24 months


90
120
60
150
30
180
0
210
330
240
300
270
0.20
0.15
0.10
0.05
0.00
0.05
0.10
0.15
0.20
0.20
0.15
0.10
0.05
0.00
0.05
0.10
0.15
0.20
● Pre-OK
○ Post-OK @ 3 months
● Post-OK @ 24 months


90
120
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30
180
0
210
330
240
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270
0.20
0.15
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0.05
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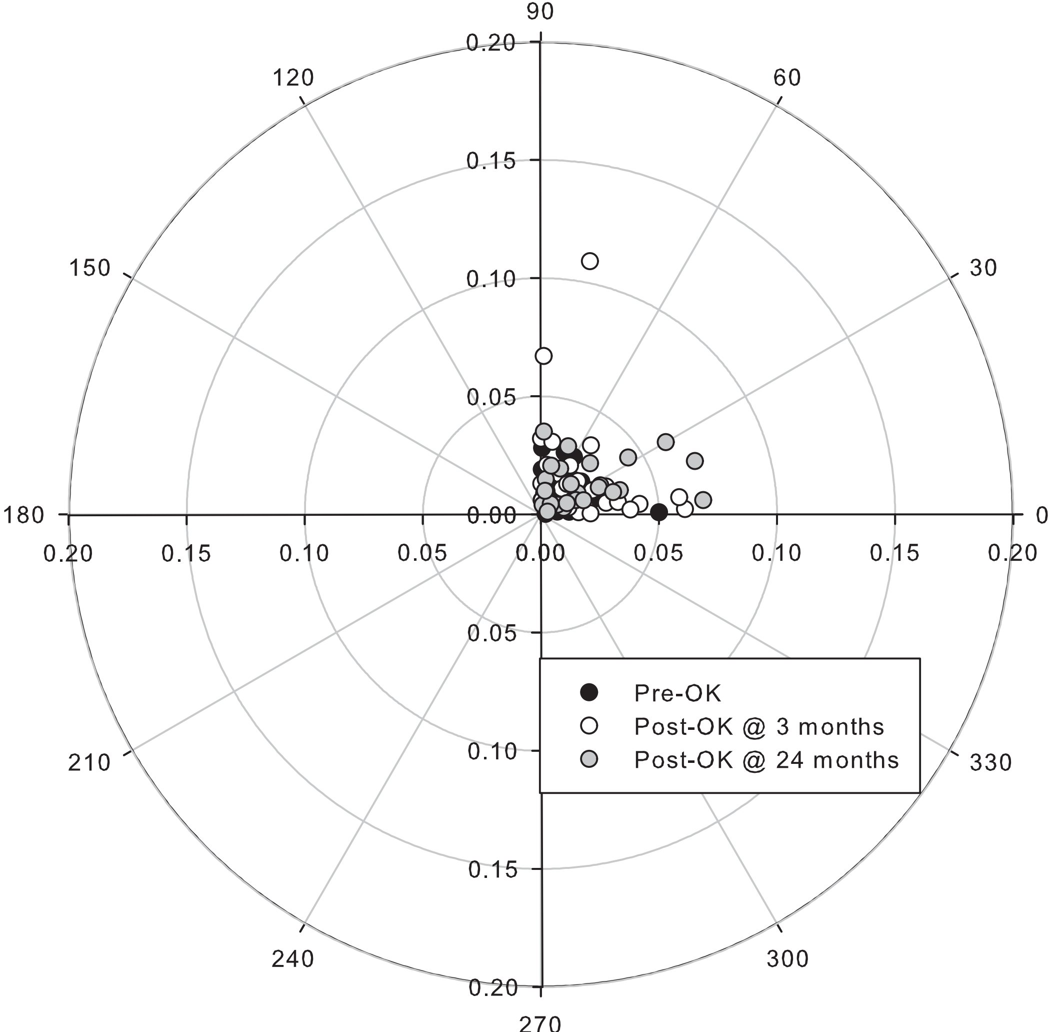
0.15
0.20
0.20
0.15
0.10
0.05
0.00
0.05
0.10
0.15
0.20
● Pre-OK
○ Post-OK @ 3 months
● Post-OK @ 24 months



90
120
60
150
30
180
0
210
330
240
300
270
0.20
0.15
0.10
0.05
0.00
● Pre-OK
○ Post-OK @ 3 months
● Post-OK @ 24 months