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Internal Astigmatism in Myopes and Non-myopes: Compensation or Constant?

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Abstract

Purpose—To examine internal astigmatism (IA) in myopes and non-myopes using a new method to assess compensation of corneal astigmatism (CA) by IA, to look for predictors of high IA in young adult myopes and determine if as CA changes IA changes to reduce refractive astigmatism (RA) in an active compensatory process in myopes.

Methods—Right eye keratometry and cycloplegic autorefraction were measured annually over 14 years in 367 myopes and once in 204 non-myopes age- (mean 21.91 years $\pm$ 1.47), gender-, and ethnicity-matched to myopes at year 12. CA and RA at the corneal plane were expressed as J0, J45. IA = RA - CA. Inverse power transformation provided cylinder power and axis of IA for the compensation factor (IA/CA). Analyses included: 1) paired and unpaired t-tests (refractive data), 2) chi-square tests (distributions of compensation factor), 3) logistic regression analysis (predictors of high IA), and 4) linear mixed models (time effect on RA, CA and IA).

Results—The magnitude of IAJ0 varied by refractive error (myopes -0.25 ± 0.24 vs non-myopes -0.32 ± 0.21 , $p < 0.001$). Compensation of CA by IA was poorer in myopes than non-myopes (χ^2 $p < 0.001$). When matched by CA, compensation remained poorer in myopes than non-myopes (χ^2 all $p < 0.04$). Within each refractive group compensation was better when CA was low than high (χ^2 $p < 0.001$). When CA was low in myopes, high IA ($> 1.00D$) was less likely ($p = 0.01$). Longitudinal follow-up of myopes found no evidence for an active compensatory role for IA as CA increased over time. There were differences in IAJ0 by ethnicity over time ($p < 0.0001$).

Conclusions—In myopic and non-myopic eyes with low amounts of CA, IA may reduce CA's contribution to RA, but IA is not a constant. However, there is no evidence for an active compensatory role for IA reducing CA in myopes.

Keywords

internal astigmatism; corneal astigmatism; myopia; compensation; residual astigmatism

To focus objects clearly in a single plane, an eye with regular astigmatism requires an optical correction with two different powers oriented perpendicular to each other¹. The amount of astigmatic correction required to correct the eye's astigmatism is often referred to as refractive astigmatism (RA). The primary source of RA is the anterior cornea.^{1,2} Although the correlation between RA and corneal astigmatism (CA) is high (0.88 to 0.91)^{3,4}; most eyes have larger amounts of CA than RA. The difference between RA and CA has been termed internal astigmatism (IA) and has been attributed to the refracting power of the lens² (Javal 1890 as cited Kratz and Walton⁵), posterior cornea^{2,6} and errors in optical centration⁷

(Young 1801 as cited by Bannan and Walsh⁸). While the posterior cornea may contribute to IA by not neutralizing the anterior corneal toricity, it has been reported that a greater portion of the anterior corneal toricity is reduced by the posterior cornea than would be predicted if the posterior corneal curvature were simply mirroring the toricity of the anterior cornea⁹. Other terms for IA, reflecting the uncertainty of its origin, include: physiological astigmatism (see⁵ for the evolution of this terminology), residual astigmatism², ocular residual astigmatism⁷, intraocular, lenticular or non-corneal astigmatism¹⁰. Although originally regarded as a mathematical constant of -0.50 to -0.75D axis 90 (Javal 1890 as cited by Kratz and Walton⁵), investigators have questioned if IA plays an active compensatory role in reducing RA^{11,12} or is influenced by refractive error^{7, 13, 14}. Internal astigmatism has also been of interest to refractive and cataract surgeons desiring to minimize astigmatism derived from intraocular components that may manifest following alteration of the cornea or removal of the lens.^{7, 10, 14, 15}

The application of vector analysis¹⁶, which expresses a refractive error in terms of M (spherical equivalent), J0 (power of Jackson cross cylinder at 90 and 180 degrees) and J45 (power of Jackson cross cylinder at 45 and 135 degrees), has expanded the ability to calculate IA by including any orientation of corneal and refractive astigmatism rather than confining the analysis to those axes that are within 20 to 30 degrees (degrees) on either side of axis 180, (termed with the rule (WTR) in negative cylinder format) or within 20 to 30 degrees on either side of axis 90, (termed against the rule (ATR) in negative cylinder format).^{17,18}

A recent study by Park and colleagues⁷ applied vector analysis to investigate IA in a sample of myopic eyes presenting for refractive surgery. Drawing on the work of others^{19,20,21}, Park and coworkers calculated the compensation factor (CF) $(CA - RA) / CA$ for J0 and J45 to investigate how IA combines with CA to produce the resultant RA. Based on the ratio, they classified compensation for both J0 and J45 into 6 different categories: full compensation (CF=0.9 to 1.1), under compensation (CF=0.1 to 0.9), no compensation (CF=-0.1 to 0.1), over compensation (CF=1.1 to 2), same axis augmentation (CF<-0.1) and opposite axis augmentation (CF>2). They plotted the percentages of eyes in each of the CF categories for J0 and J45 separately and found full compensation was rare for the J0 component at 4%, but greater for the J45 component (12%). Under compensation was greatest for the J0 component (68%) while augmentation (same axis plus opposite axis) was greatest for the J45 component (36%) followed closely by under compensation at 35%. While these results describe the relationship between internal and corneal astigmatism in the 180 deg and 45 deg meridians of the sample, without linking J0 and J45 at the subject level, only a partial picture emerges of how CA combines with IA to produce the eyes' RA. For example, the CF for J0 could be under compensation while for J45 could be augmentation, making it difficult to understand what is occurring in the eye as a whole.

Park et al⁷ did confirm the general compensatory role of IA in reducing the corneal contribution to RA and explored factors that might predict high IA in a group of myopic patients, a useful tool that would assist the surgeon in determining the optimal power for intra-ocular lenses^{15,22} or better predict outcomes from corneal refractive surgery^{7,10,14}. They reported a significant correlation between IA and the mean spherical equivalent and

between IA and RA. However, they were unable to consider axial length in their investigation and suggested that longer eyes could be more susceptible to IA induced by lens tilt or optical centration errors.

In this report, IA is examined in myopes and non-myopes to address many of these lingering questions. Comparing a cohort of myopic individuals to age-, gender-, and ethnically-matched non-myopic adults allows IA to be evaluated between two different refractive error groups. Differences in compensation by refractive error and by magnitude of CA were also explored using a new analysis method that addresses some of the limitations of previously used approaches^{7,20,21}. Longitudinal data from the myopic cohort provide an opportunity to evaluate whether IA plays an active compensatory role in reducing RA as CA changes over time. During the long term follow-up, myopia progressed and had stabilized by 24 years of age in 96% of the COMET cohort based on estimates from Gompertz functions²³. At the final 14-year follow-up visit, participants were on average 24.08 (SD $\pm$ 1.30) years of age with a mean myopic refractive error of -5.15D (SD $\pm$ 2.00D), characteristics that lend themselves to consider refractive surgery as a viable treatment option. Additional analyses were explored for associations between high IA and its risk factors, including demographic and ocular factors such as axial length that could result in unanticipated astigmatism following refractive surgical correction.

METHODS

Because data were similar in both eyes²⁴, only data from the right eye are reported. Cylinder is expressed in negative cylinder format. All refractive error values reported in this paper are referenced to the corneal plane as described below.

Subjects

Two different groups contributed to the analyses reported here. The Correction of Myopia Evaluation Trial (COMET) ethnically diverse cohort consists of 469 myopic subjects 6 to less than 12 years of age at enrollment recruited by four schools/colleges of optometry located at Birmingham, AL, Boston, MA, Houston, TX, and Philadelphia, PA. Entrance criteria included myopia between -1.25 and -4.50D inclusive spherical equivalent (SE) in each eye, with no more than 1.50D of astigmatism in either eye and 1.00D or less of anisometropia (SE) based on cycloplegic autorefraction as described below²⁴. Subjects were randomized to single vision lenses (SVLs) or +2.00 progressive addition lenses (PALs) and examined yearly with cycloplegic autorefraction. After 5 years the randomized clinical trial ended, and subjects, in consultation with their study optometrist, were corrected with SVLs, PALs or contact lenses and were examined yearly for an additional 9 years as an observational study of myopia progression and stabilization. As no clinically significant benefit to wearing PALS compared to SVLs was observed²⁵, the two lens groups were combined for future analyses. Seven subjects enrolled in COMET were excluded from longitudinal analysis because they had less than 3 years of follow-up.²⁵

Two hundred and six non-myopic subjects, age, ethnic/racial- and gender-matched to the COMET cohort, were recruited by the same four schools/colleges of optometry to serve as a comparison group for the COMET cohort at the 12- year follow-up (n=367). Participants in

this non-myopic group were 18-24 years of age at enrollment with SE refractive error between -0.25D and $+2.00$ in each eye, with no more than 1.50D of astigmatism in either eye and less than 1.00D of anisometropia by SE. Two subjects without corneal astigmatism measures were excluded from the analysis.

This research complied with the tenets of the Declaration of Helsinki and the protocols of each study were reviewed by the institutional review boards at each recruitment site. Written informed consent was obtained from the parents, and assent from the children prior to enrollment in the COMET study. COMET participants were consented as adults when they turned 18 years old. Non-myopic participants also provided written informed consent prior to enrollment.

Procedures

Refractive error and keratometry were measured in each eye with the Nidek ARK 700A autorefractor by experienced examiners, trained and certified in the procedures. The Nidek autorefractor target was a hot air balloon pictured on a horizon at the end of a highway. Prior to drop instillation, at least three autokeratometry measurements were made over a 3.3mm diameter of the cornea corresponding to the mires of the instrument. The instrument averaged the measures and provided the corneal radii and orientation of the steepest and flattest principal meridians, the corneal power in diopters in each principal meridian based on a refractive index of 1.3375 , and the corneal astigmatism (difference in power between the two principal meridians) with the corresponding axis of correction in minus cylinder notation.

Cycloplegic autorefraction was measured 30 minutes after the last of 2 drops of 1% tropicamide separated by 4 to 6 minutes. The tropicamide was preceded by 1 drop of proparacaine or benoxinate. At least four reliable measurements of refractive error were obtained in each eye with a vertex distance of the autorefractor set to 12mm and a step size of 0.25D . Residual accommodation in this myopic cohort measured while fixating a target at 33 cm using this cycloplegic paradigm has been reported to be $0.38\text{ D} \pm 0.41\text{D}^{26}$ and would be expected to be less when fixating the distant target used to determine the refractive errors reported here²⁶. These measurements were obtained annually from the COMET participants over 14 years of follow-up and once from the non-myopic participants at their single visit coinciding with study year 12 of the COMET subjects' participation.

Outcome Variables

Refractive Astigmatism (RA)—For each participant, the sphere, cylinder and axis for each reliable autorefraction measurement were used to calculate M, J0 and J45¹⁶. These individual vectors were averaged to obtain a single M, J0 and J45 for RA at each study visit. The inverse power transformation of the averaged M, J0 and J45 yielded the power to correct the least myopic meridian (LMM), the power to correct the most myopic meridian (MMM), cylinder power and axis of RA. Next, the power to correct the LMM and MMM were transformed to the corneal plane with approximate vertex distance of 12mm as described in equation 1 in a paper by Holladay and colleagues²⁷, and the adjusted RA cylinder power was calculated as the difference between the vertex adjusted LMM and MMM values. The final

RAJ0 and RAJ45 were computed using forward power transformation¹⁶ again by using the cornea vertex plane adjusted cylinder power and the RA axis.

Corneal Astigmatism (CA)—Similarly, CA was determined from the keratometer readings and used to calculate CAJ0 and CAJ45 where CAJ0 is the corneal astigmatism at J0 and CAJ45 is the corneal astigmatism at J45.

Internal Astigmatism (IA)—IA was calculated for J0 and J45 as the difference between the RA at the corneal plane and the CA ($IAJ0 = RAJ0 - CAJ0$; $IAJ45 = RAJ45 - CAJ45$). The inverse power transformation gave the cylinder power and axis of IA.

Compensation Factor—To examine the role IA plays in reducing the contribution of CA to RA, a new analysis method was developed. The ratio: IA cylinder power/CA cylinder power was calculated for each subject, with CA ≥ 0.25 D and plotted at the difference between the CA axis and the IA axis beginning at the CA axis moving counterclockwise until reaching the IA axis. For example, if the axis of CA is 30 deg and the IA axis is 45 deg, then the IA/CA ratio would be plotted at 15 deg and if the axis of CA is 45 deg and the IA axis is 30 deg then the IA/CA ratio would be plotted at 165 deg. Perfect compensation occurs when the ratio equals 1 (IA cylinder power equals CA cylinder power) and the axes are 90 degrees apart. The level of compensation was grouped into 6 categories: 1) near perfect compensation = IA/CA ratio is 0.75 to 1.25, axes separated by near 90 degrees (75 to 105 degrees); 2) over compensation = ratio 1.25 to 1.75, axes are separated by near 90 degrees; 3) under compensation = ratio 0.25 to 0.75, axes are separated by 90 degrees, 4) incomplete compensation by axis = ratio is 0.75 to 1.25, axes separated by 45 to 75 or 105 to 135 degrees; 5) incomplete compensation by ratio and axis = ratio is over or under compensation and axis separated by 45 to 75 or 105 to 135 degrees; 6) all other values of ratio and axis.

Statistical Analysis

Prior to analysis, the data were checked for outliers. Thirty observations (26 participants each contributing one time point and 2 participants each contributing 2 time points) were identified using the exclusion criteria detailed in the Appendix (available at [LWW insert link]). These outliers were also verified by inspection of scatterplots and were omitted from analysis (observations removed, not participants).

For the analyses based on the baseline and 12-year visit, three samples were used. Two of the samples are from the COMET cohort at two visits- baseline (COMET BL), and the 12-year (COMET 12-year); the third is the cohort of non-myopes. Two sets of comparisons were made: 1) within-group comparisons between COMET BL and COMET 12-year, and 2) between-group comparisons between COMET 12-year and non-myopes. For all the compensation factor distribution comparisons, 6 major categories of compensation level were used as previously defined.

For the within-group comparisons (COMET BL vs. COMET 12-year), the following statistical tests were applied. Paired t-tests were used for comparisons of refractive data. To compare compensation level distributions the overall within-group comparison was done by

the Bhapkar test, which is suitable for comparison of paired data with categorical outcomes. Within-group compensation level distributions were also compared by level of CA (all data were stratified by four CA levels: CA 0.25D to 0.50D, 0.75D to 1.00D, 1.25D to 1.50D and greater than 1.50D). Within each CA stratum, compensation levels were compared via the Generalized Estimating Equations (GEE) method, which has the capacity to adjust for partially repeated measures.

For the between-group comparisons (COMET 12-year vs. non-myope), the following statistical tests were applied. Unpaired t-tests were used for between-group comparisons of refractive data, and the Chi-square test was used for comparison of gender and ethnicity distributions. Chi-square tests were also applied for the following between-group comparisons of the compensation factor distribution: 1) the overall compensation factor distributions between COMET 12-year and non-myopes; 2) the compensation factor distribution between COMET 12-year and non-myopes stratified by CA level as defined above; and 3) the compensation factor distributions across 5 spherical refractive error groups (-0.25D to $+2.25\text{D}$, -0.50D to -3.00D , -3.00D to -4.00D , -4.00D to -5.25D and -5.25D to -10.00D).

To further evaluate the compensation by CA level, the compensation factor distribution was compared across the 4 CA levels within each of the samples (COMET BL, COMET 12-year and non-myopes) using the Chi-square test.

For the myopic COMET cohort, the associations between the change in axial length and changes in RA, CA and IA cylinder (calculated as described above from the inverse power transformation of IAJ0 and IAJ45) from baseline to the 12 year follow-up were examined using scatter plots and Spearman correlation coefficients (SCC) to measure the strength of correlations. SCC was selected because it produces more robust results in the presence of non-normality.

Univariate and multivariate logistic regression analyses were applied to identify demographic factors from baseline and ocular factors measured at study year 14 significantly associated with high internal astigmatism ($> 1.00\text{D}$ at study year 14). Univariate logistic regression considered each factor individually and multivariate considered all factors simultaneously except RA, which was excluded because of its relationship to CA and IA, and refractive sphere, because of its correlation with axial length.

For the longitudinal data set, linear mixed models were used to examine the time effect on refractive, corneal and internal astigmatism by demographic variables (e.g. gender, baseline age and ethnicity) and treatment (lens type) for two observation periods (from baseline to the 5-year visit and from the 5-year to the 14-year visit). The slopes were compared between gender, ethnicity, treatment, and baseline age groups by testing the interaction terms between time and these factors first. As none of the interaction terms was significant, a common slope was assumed in the final linear mixed model. Only the intercept difference between groups was reported in the results. P-values < 0.05 are considered significant.

RESULTS

COMET BL, COMET 12-year and Non-myopes

Table 1 displays the demographic data of the COMET BL who were also examined at the 12-year follow-up visit (n=363), COMET 12-year (n=363), and the non-myopes (n=204). The COMET and non-myope groups are ethnically diverse, with Caucasians (44% to 45%), African-Americans (26.5% to 26.7%) and Hispanics (13.7% to 15.7%) the most predominant, and females comprise about 54% of each group. There were no gender or ethnic differences between the groups, and by study design, age (21.9 years) was not different between the COMET 12-year group and the non-myopes. As expected, the mean spherical equivalent showed statistically significant differences between groups with non-myopes averaging slightly hyperopic, $+0.62\text{D} \pm 0.41\text{D}$, and the COMET BL group showing less SE myopia, $-2.28\text{D} \pm 0.75\text{D}$, compared to the COMET 12-year group ($-4.64\text{D} \pm 1.65\text{D}$).

As shown in Table 1 the mean CAJ0 was greater than the mean RAJ0 in all three samples (COMET BL CAJ0 = 0.31D, RAJ0 = 0.04D; COMET 12-year CAJ0 = 0.49D, RAJ0 = 0.24D, non-myopes CAJ0 = 0.33D, RAJ0 = 0.02D), illustrating that although the anterior cornea contributes the largest amount of the eye's refractive power, not all of the CA is manifested in the RA. All corneal and refractive J45 values are small and, in general, do not differ between samples.

Internal Astigmatism

Table 1 also shows that IAJ0 was greatest in the non-myopes ($-0.32\text{D} \pm 0.21\text{D}$), followed by COMET BL ($-0.27\text{D} \pm 0.21\text{D}$), with COMET 12-year having the least amount of IAJ0 ($-0.25\text{D} \pm 0.24\text{D}$). When expressed in terms of cylinder power ($2 \times \text{IAJ0}$), these values are similar to the common clinical notion that IA is about $-0.50\text{D} \times 090$ (Javal 1890 as cited by Kratz and Walton⁵, modified by Grosvenor et al.²⁸). The differences in IAJ0 between the non-myopes and the COMET 12-year ($p < 0.03$) and between the COMET BL compared to COMET 12-year ($p < 0.001$), although small, were both statistically significant. The mean IAJ45 was small and not different between samples ($-0.06\text{D} \pm 0.18\text{D}$ for COMET BL or $-0.07\text{D} \pm 0.18\text{D}$ for COMET 12-year and non-myopes).

Compensation of Corneal Astigmatism by Internal Astigmatism

Figure 1 illustrates the reduction of CA by IA or compensation for the COMET BL (Figure 1A, n=347), COMET 12-year (Figure 1B, n=347), and non-myopes (Figure 1C, n=196). Subjects were binned into categories based on their IA/CA ratio and the angle or separation in degrees between their IA and CA axis. The percentage of subjects in these categories is plotted on the z-axis for each sample. The number of subjects (n=347) differ from those shown in Table 1 (n=363), because those without any CA were excluded as a ratio could not be calculated. Near perfect compensation (shown by the black bar) occurs when the IA/CA ratio is about 1 (0.75 to 1.25) and the axes are separated by about 90 degrees (75 to 105 degrees). Over compensation occurs when the axes are separated by about 90 degrees but IA is greater than CA, (ratio greater than 1.25) shown by the purple bar. Under compensation occurs when IA is less than CA (ratios less than 0.75) for axes separated by about 90 degrees

(i.e. orange bar). If the ratio is close to 1 but the axes are not separated by about 90 degrees, compensation is also incomplete (i.e. yellow bars). Compensation decreases more as the angle between axes deviates farther from 90 degrees and the ratio differs farther from one (i.e. blue and red bars).

For the COMET BL sample, near perfect compensation occurred in 28.24% and over compensation occurred in 8.36%. For the COMET 12-year, near perfect compensation was 14.41% and over compensation was only 1.73%. For the non-myopes, both full compensation (34.18%) and over compensation (13.27%) exceeded that of either myopic COMET sample. Comparisons using the 6 different colored categories shown in Figure 1 found a significant difference between the COMET 12-year and the non-myopes (Chi-square test $p<0.001$). Also the comparison between COMET BL and COMET 12-year using the 6 grouped categories showed a significant difference (Bhapkar test $p<0.0001$).

Figure 2 displays the distribution of compensation for the three samples (COMET BL, COMET 12-year and non-myopes) by level of corneal astigmatism. Figure 2A shows compensation by IA for lower amounts of CA (0.75D to 1.00D) and Figure 2B plots the compensation when higher amounts of CA (1.25D to 1.50D) are present. The compensation was poorer in the COMET 12-year sample compared to the non-myopes at both the lower (Figure 2A) and higher CA (Figure 2B) levels (Chi-square $p<0.001$ for CA 0.75D to 1.00D and CA 1.25 to 1.50D). This is also true for the other two CA categories not shown, CA 0.25D to 0.50D ($p=0.002$) and CA greater than 1.50D ($p=0.04$). When comparing the compensation factor between COMET BL and COMET 12-year stratified by CA level, the compensation level distribution shifted toward poorer compensation from COMET BL to COMET 12-year in all four CA categories (all $p<0.002$).

Comparison within a study sample across 4 different CA levels shown in Figure 2 (comparing Figure 2A to Figure 2B in the same sample) shows greater amounts of under compensation (orange bars) and less over compensation (purple bars) for higher amounts of CA. Chi-square analysis found that within each sample, compensation differed significantly by CA level (all p 's <0.001 , for data shown in Figure 2 as well as for that not shown for the two other CA levels, 0.25D to 0.50D and >1.50 D).

Compensation of CA by IA was evaluated further by comparing the non-myopes (sphere -0.25 D to $+2.25$ D) to COMET 12 year stratified by different levels of spherical refractive error (split into quartiles by spherical refractive error: -0.50 D to -3.00 D, -3.00 D to -4.00 D, -4.00 D to -5.25 D and -5.25 D to -10.00 D) as shown in Figure 3. Compensation in the non-myopes was significantly different from each of the 4 COMET 12-year groups (Chi-square all p 's <0.01), with non-myopes showing a large percentage of near perfect compensation. There was no difference in the distribution of compensation levels across the myopic COMET 12-year quartiles (Chi-square $p=0.80$).

Associations between Axial Length and RA, CA and IA in Myopes

Figure 4 shows the association between the change in RA (left panel), CA (middle panel) and IA (right panel) cylinder from COMET BL to COMET 12-year and the change in axial length over the same time period. There was no association between axial length and either

IA cylinder (SCC = -0.04 , $p=0.04$) or RA cylinder (SCC = -0.02 , $p=0.66$). A small (SCC = -0.14) but statistically significant ($p<0.01$) association was found between CA and axial length.

Predictors of Significant Internal Astigmatism in Myopic Individuals at the 14-year Visit—Sixty-two participants in the COMET cohort had IA of 1.00D or more using the inverse power transformation of IAJ0 and IAJ45 at the 14-year follow-up visit. Potential demographic and ocular predictors of high IA were explored using logistic regression and are shown in Table 2. Gender, ethnicity, baseline age, central corneal thickness at 14 years, and axial length at 14 years were not associated with IA ≥ 1.00 D (all p 's >0.21). The only factor significantly associated with high IA in both the univariate and multivariate analyses was CA. When CA is low, there is a reduced risk for high IA.

Longitudinal Changes in Internal Astigmatism in the COMET Cohort over 14 years of Follow-up

Changes in refractive, corneal and internal J0 and J45 over time: The mean and standard errors of the refractive, corneal and internal astigmatism for J0 and J45 are shown in Figure 5 for each visit, beginning at the baseline examination through 14 years of follow-up. During the clinical trial phase from baseline to follow-up year 5, CAJ0 and RAJ0 are positive (WTR) and increase slightly but in parallel (slope = 0.028 D/yr, [SE= 0.0023 D/yr] for RAJ0; $p<0.001$ and slope = 0.029 D/yr, [SE= 0.0023 D/yr] for CAJ0; $p<0.001$). However, IAJ0 is negative (ATR) and is essentially constant over this same time period (slope = -0.0001 D/yr [SE= 0.0018 D/yr]; $p=0.95$, the slope is not different from zero). After year 5 of follow-up the pattern changes: CAJ0 is stable (slope = 0.002 D/yr [SE= 0.001 D/yr], $p=0.08$, not different from zero), but RA and IA become slightly more positive (RAJ0 slope = 0.008 D/yr [SE= 0.001 D/yr], $p<0.001$, and IAJ0 slope = 0.005 D/yr [SE= 0.001 D/yr], $p<0.001$). RAJ45, CAJ45 and IAJ45 are small and change very little over the 14 years of follow-up. RAJ45 increases at a rate of 0.0016 D/yr (SE= 0.0007 D/yr), $p=0.03$; CAJ45 increases at a rate of 0.0005 D/yr (SE= 0.0007 D/yr), $p=0.50$ and IAJ45 increases at a rate of 0.001 D/yr (SE= 0.0005 D/yr), $p=0.04$. Therefore, the remaining results will be limited to the J0 component.

The association of demographic variables with IAJ0: Due to the different IA slope observed from baseline to year 5 compared to that noted between year 5 to year 14 of follow-up, the associations between IAJ0 and gender, baseline age (categorically: 6-7 years, 8 years, 9 years, 10 years, 11 years), baseline lens assignment (SVLs or PALs) and ethnicity (Asians, African-Americans, Hispanics, Mixed/Others, and Caucasians) were explored to see how these characteristics affect IAJ0 over time by study period. No significant slope differences between any groups defined by the above mentioned baseline variables were detected from baseline to 5-year (interactions between time and the group variables all $p>0.25$) or from 5-year to 14-year (interactions between time and the group variables all $p>0.23$). In addition, as shown in Table 3, there were no intercept differences in IAJ0 by gender, baseline lens assignment or baseline age for either of the two time periods. However, there were significant differences by ethnicity ($p<0.0001$) during both periods of follow-up.

These ethnic differences are displayed in Figure 6 where IAJ0 is plotted over the 14 years of follow-up for the 5 different ethnic groups. As shown in Figure 6, IAJ0 is negative (ATR) for all ethnic groups. African-Americans have, on average, more ATR IAJ0 than any of the other ethnic groups throughout the 14-year observation period except in year 14 where the magnitude of IAJ0 is similar to that of Caucasians. Due to the low number of subjects in the Mixed/Other (baseline $n=23/457$ [5%], year 14 $n=17/351$ [4.8%]) and Asian groups (baseline $n=35/457$ [7.7%], year 14 $n=30/351$ [8.6%]) the results from these groups should be viewed with caution.

Post-hoc analysis of the IAJ0 intercept difference for the 2 observation periods showed that from baseline to year 5 of follow-up the IAJ0 of African-Americans was different than the IAJ0 in each of the other ethnic groups (Dunnett's adjustment; all p 's > 0.03). From year 5 to year 14 of follow-up, the IAJ0 of African-Americans differed from the IAJ0 in all other groups (all p 's < 0.02) except Asians ($p=0.17$). However, the slope of IAJ0 between 5 to 14 years remained significantly different from zero when African-Americans were excluded from the analysis, indicating that the changes in IAJ0 are not solely due to African-Americans.

DISCUSSION

Summary

The findings from the analyses of IA comparing young adult myopes to age-, gender-, and ethnicity matched non-myopes show: 1) the magnitude of IAJ0 varies by refractive error, with COMET 12-year myopes having less IAJ0 than non-myopes (Table 1); 2) regardless of the level of myopia, myopes had less complete compensation of CA by IA than non-myopes of the same age (Figures 1 and 3), and compensation was also less complete at the COMET 12-year compared to COMET BL (Figure 1); 3) within each refractive error group, compensation of CA by IA varied with the magnitude of CA, with better compensation when CA was low than when CA was high (Figure 2); 4) change in axial length were not associated with change in IA cylinder or RA cylinder (COMET BL to COMET 12-year) but was weakly associated with CA cylinder (Figure 4); 5) the only predictor of higher amounts of IA ($-1.00D$) was CA; when CA was low there was a lower chance of observing high IA (Table 2); and 6) examination of IAJ0 longitudinally over 14 years found some differences in IAJ0 by ethnicity (Figure 6, Table 3), but the changes were very small; and 7) no evidence for an active compensatory role for IA as CA changed over time in the myopes followed over 14 years (Figure 5).

BL and 12-year Investigations

The IAJ0 and IAJ45 values reported in Table 1 are similar to those found by Tong and colleagues¹⁷ in a group of 7 to 12 year old myopic subjects using a vector approach. Extrapolating from their correlations between refractive and corneal astigmatism, IAJ0 was $-0.28D$, and IAJ45 was $+0.01D$, very similar to $-0.27D \pm 0.21D$ for IAJ0 and $-0.06D \pm 0.17D$ for IAJ45 found in our myopic cohort at baseline who were of similar age (6 to < 12 years). Park and colleagues⁷ report IAJ0 of $-0.30D \pm 0.27D$ and IAJ45 of $+0.00D \pm 0.23D$ for 356 myopic eyes with a mean age of 27.6 ± 5 years, slightly older than our

myopic sample at year 12 of follow-up (mean age of 21.91 years $\pm$ 1.31 years) where IAJ0 was $-0.25\text{D} \pm 0.24\text{D}$ and IAJ45 was $-0.07\text{D} \pm 0.18$. When comparing the non-myopic sample to the COMET myopes at 12 years, IAJ0 was more negative in the non-myopes than in the myopic sample. Others^{13,20} have also reported greater amounts of IA in non-myopes compared to myopes using vector-based techniques.

The differences in IA by refractive error noted above are also consistent with the results from our compensation analysis that demonstrates significant differences in the amount by which IA (in diopters) reduces the contribution of CA to RA across refractive error groups. Comparing the distribution of the IA/CA ratios by magnitude of the axis difference between RA and CA across refractive error groups showed differences in compensation between non-myopes and the COMET 12-year sample ($p < 0.001$). Additional support for differences in IA by refractive error was found by comparing COMET 12-year myopes split by sphere quartiles to age- and ethnicity-matched non-myopes. Compensation did not differ across the myopic quartiles, but each quartile was significantly different than the non-myopes. The differences in IA between myopes and non-myopes could be due to differences in the distribution of RA or due to differences in spherical refractive error, axial length or corneal astigmatism as significant differences were demonstrated for all of these components in Table 1. A more definitive answer as to the etiology of the differences in IA between myopes and non-myopes would require a large randomly selected sample from a general population with a wide range of spherical refractive error, corneal astigmatism with no restriction on the magnitude of refractive astigmatism, and a greater overlap of axial length between the refractive error groups.

Looking at compensation within a refractive error group by level of CA, compensation was less effective when higher versus lower amounts of CA were present. The poorer compensation of the COMET 12-year sample when compared to COMET BL could be due to higher amounts of CA at 12 years. We also found a significant association between changes in CA between COMET BL and COMET 12-year and changes in axial length over the same time period. CA was greater when axial length was longer but the association was weak. It is unclear if the poorer compensation that occurs with higher amounts of CA is due to differences associated with the posterior cornea or changes brought about by increases in axial length or a combination of the two.

Conventional LASIK correction was reported to be only half as effective in a group of patients with high IA compared to those with low IA¹⁰, indicating the importance of trying to predict factors associated with larger amounts of IA that might impact the outcome of refractive surgery. Identifying predictors of high IA would also be useful to cataract surgeons, but the age of our sample limits generalization to this important patient group. The only factor that was predictive of IA -1.00D compared to IA $<1.00\text{D}$ in our sample of myopes at the 14-year follow-up visit was the magnitude of CA; when CA was low, high amounts of IA were less likely. This is not surprising given RA was generally low in our study sample; thus, higher IA would be associated with high CA. It is not clear if the same would be true for other samples with higher amounts of RA, but Shankar and Bobier¹¹ found no difference in IA between higher and lower RA in children 3 to 5 years of age. Others have also not been very successful in finding useful predictors of higher amounts of

calculated IA, though males were found to be 26% less likely than females to have IA 1.00D¹⁴. Park and colleagues⁷ reported that since the mean spherical equivalent was negatively correlated with IAJ0 and RA was positively correlated with IAJ0, RA and mean spherical equivalent might be predictors of IA. However, spherical equivalent was not explored in our study due to its relationship with RA. RA was not a significant predictor for high IA when explored alone.

Longitudinal Investigations

The results of the 14- year follow-up (Figure 5) show no support for an active compensatory role for IA responding to changes in CA to keep RA stable over time. During the first 5 years of follow-up, both the mean CAJ0 and RAJ0 changed in parallel, becoming more WTR with no compensating change in IA. After the first 5 years of the study, the mean CAJ0 remained stable with very small increases in the mean RAJ0 (more WTR) and IAJ0 (less ATR). It should be noted that at follow-up year 5, COMET participants were given the option to wear contact lenses. However, additional analysis of the slopes of IAJ0 between years 5 and 6 found no difference between the contact lens wearers and those remaining in spectacles and no significant interaction between time and lens switch ($p=0.78$; data not shown). Thus, the small changes in IAJ0 between follow-up year 5 and 6 were not dependent on the type of refractive correction. The longitudinal data do not support an active compensatory role for IA to reduce RA in response to changes in CA. This result is in contrast to that recently reported by Harvey et al¹² that concluded an active process may be in place that contributes to the stability of RA based on a negative correlation between changes in CAJ0 and IAJ0. However, IA was calculated from CA rather than measured directly, making these correlations less definitive in support of an active process.

IAJ0 was associated with ethnicity. IAJ0 in African-Americans differed from all other ethnic groups during the first five years of follow-up and differed from all but Asians in years 6 through 14. The IAJ0 of African-Americans was more ATR than the other ethnicities at baseline and became less ATR over the duration of the follow-up. It is not clear what is responsible for the larger amounts of ATR IAJ0 seen in African-Americans, but ethnic differences for other factors, including progression of myopia, have been previously reported in this cohort^{23, 29-31}. Given the large contribution of the cornea to RA^{1, 2} the thinner corneas³⁰ reported for African-Americans may be the most relevant to IAJ0 differences reported here. Since most other studies have not explored IA by ethnicity, comparisons with the literature are limited, but one study³² found no differences in IA (termed residual astigmatism) between Asian and Caucasian adults (18 to 30 years; $n=70$).

Strengths and Limitations

Strengths of these analyses include a large, ethnically-diverse sample of myopic participants tested by a small group of trained and certified examiners using standard instrumentation across study sites and over the 14 years of follow-up. Retention over the 14 years of follow-up was 78% (367/469) across the study. For comparisons to this myopic cohort, a sample of non-myopes was recruited from the same centers, tested by the same investigators using the same equipment, and were age-, gender- and ethnically-matched to the longitudinal sample of myopes at year 12 of follow-up.

The new method developed for these analyses to examine compensation of CA by IA based on cylinder power and axis has several advantages over the previous compensation factor used by Park and colleagues⁷ based on vector analysis. Our method, like that of Park et al⁷, uses vector analysis to calculate IA from CA and RA when the axes of RA and CA are not perpendicular. However, unlike Park, we used the inverse transform to express the IA calculated from J0 and J45 in diopters and axis and compare it to CA as measured by the keratometer. Displaying compensation in terms of the IA/CA ratio in diopters and the difference in axes between IA and CA in a 3 dimensional plot rather than IAJ0/CAJ0 and IAJ45/CAJ45 as done previously⁷ enables visualization of the compensation that includes both magnitude and axis simultaneously for all individuals rather than looking at the 2 meridians separately at a sample level.

The calculation of IA from CA and RA has been the most common method to determine IA and allows for comparisons of our results with others, but the assumptions involved in this calculation pose some limitations. The measurements of CA used in this study were obtained by an autokeratometer that used the keratometric index of 1.337 (approximating the index of the aqueous)³³ rather than the corneal refractive index of 1.376 used by Gullstrand³³. This keratometric index was adopted by the manufacturers to estimate the total cornea power by considering the negative power introduced by the posterior cornea^{34, 35} and was the standard for keratometers at the time of this study. Since the posterior cornea has been hypothesized to contribute to IA, including it in the measure of CA through these assumptions rather than measuring it directly may result in an underestimation of IA.

CONCLUSIONS

The sources of IA remain speculative. Possible candidates include the posterior cornea^{2,6, 8, 9}, lens^{2,6} (Javal 1890 as cited by Kratz and Walton⁵) and the centration of the eye's optical components⁷ (Young 1801 as cited by Bannon and Walsh⁸). However, no difference in residual astigmatism was reported after lens extraction and IOL placement¹⁵, suggesting the posterior cornea may be the primary contributor to internal astigmatism. Park et al⁷ has suggested that longer axial lengths might alter the internal optics through lens tilt or foveal eccentricity. While in our study IA differed between non-myopes and myopes, with greater ATR IAJ0 in non-myopes than myopes, this result is inconsistent with the notion that axial length might lead to increased IA as the axial lengths of the non-myopes were shorter than those of our myopes. We also found no association between changes in IA between baseline and 12 years and changes in axial length observed over the same time period in the COMET myopes. Our longitudinal data also does not support the suggestion of Park et al⁷ since mean IAJ0 of the group remained essentially constant as myopia and axial length increased. With the development of new instrumentation, direct measurements of the potential contributors to IA have been emerging^{22,36} that will continue to expand the understanding of the role of IA and its contribution to the refractive error. Longitudinal studies and comparisons of IA across refractive error groups using these newer technologies will be needed to confirm the results reported here. Since IA varies with refractive error and ethnicity and compensation of CA by IA varies by the magnitude of CA, IA is not a constant. The longitudinal data does not support an active compensatory role for IA reducing the contribution of CA to RA in progressing myopes.

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APPENDIX

If the corneal astigmatism data point meets condition 1 and one of the conditions 2-3 then it was removed.

1. If corneal J0 > 1.75D or corneal J0 < -0.875D or abs(corneal J45) > 0.875D.
2. For corneal cylinder power, if the observation deviates from the mean (across all visits) by at least 2 * 0.50D and 2SD (across-visit standard deviation away from the mean).
3. For corneal J0 and J45, if the observation deviates from the mean (across all visits) by at least 2 * 0.25D and 2SD (across-visit standard deviation away from the mean).

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Figure 1.

The percentage of subjects shown on the z-axis with various levels of compensation (Compensation = internal astigmatism [IA] divided by corneal astigmatism [CA]) plotted on the x-axis by the angle, in degrees, between the internal and corneal astigmatism on the y-axis for the COMET cohort at baseline (Figure 1A, n = 347), at the 12 year follow-up visit (Figure 1B, n = 347) and the non-myopic cohort (Figure 1C, n=196). (Note subjects with CA of zero could not be included in this analysis, as the ratio cannot be calculated). Black bar shows near perfect compensation (IA/CA ratio near 1 and axes separated by about

90deg); purple bar shows over compensation ($IA > CA$ [ratio > 1.25] and axes separated by about 90deg); orange bar shows under compensation ($IA < CA$ [ratio < 0.75] and axes separated by about 90deg); yellow bars show incomplete compensation by axis with ratios close to 1 with axes not separated by about 90degrees; and blue and red bars show poorer compensation with ratios farther from 1 and the angle between axes farther from 90 degrees.

Figure 2.

(A) As in Figure 1 for participants with corneal astigmatism of 0.75D and 1.00D for the COMET cohort at baseline ($n = 130$), at the 12-year follow-up visit ($n = 105$) and the non-myopic cohort ($n=80$). (B) As in Figure 1 for participants with corneal astigmatism of 1.25D and 1.50D for the COMET cohort at baseline ($n=63$), at the 12year follow-up visit ($n=96$) and the non-myopic cohort ($n=33$).

Figure 3.

Percentage of subjects by compensation level (levels color coded as in Figure 1) for non-myopes (far left) age-, gender- and ethnicity- matched to COMET 12-year myopes by quartile of spherical myopia (4 bars to the right)

Figure 4.

Change in AL (mm) vs. change in astigmatism component (D) from baseline to 12-year.

Left panel: Scatterplot showing change in RA from baseline to 12 years by change in axial length from baseline to 12 years for the 361 subjects with axial length measures;

SCC=Spearman Correlation Coefficient. Middle panel: Same as left panel for CA. Right panel: Same as left panel for IA.

Figure 5.

RA, CA, IA, J0 and J45 by visit. The mean and standard errors of the J0 (solid lines) and J45 (dashed lines) vector components from the longitudinal sample of myopes from the baseline examination through 14 years of follow-up. CAJ0 and CAJ45 in green, RAJ0 and RAJ45 in red, and IAJ0 and IAJ45 in black.

Figure 6.

Internal astigmatism J0 by visit and ethnicity. Internal astigmatism J0 (in diopters) from baseline (BL) through 14 years of follow-up for Hispanic (red with open diamonds), Asian (green with open circles), Caucasian (brown filled circle), Mixed/other (blue with “*”), and African-American (black with open triangles) participants.

Table 1

Demographic and Refractive variables in the myopic COMET group and the non-myopic group.

	COMET BL	COMET 12-yr	Non Myopes	p ¹	p ²
Variable	(n=363)	(n=363)	(n=204)		
Gender [n (%)]					0.874
<i>Males</i>	168(46.28%)	168(46.28%)	93(45.59%)		
<i>Females</i>	195(53.72%)	195(53.72%)	111(54.41%)		
Ethnicity [n (%)]					0.966
<i>Asians</i>	29(7.99%)	29(7.99%)	18(8.82%)		
<i>African Americans</i>	97(26.72%)	97(26.72%)	54(26.47%)		
<i>Hispanics</i>	57(15.70%)	57(15.70%)	28(13.73%)		
<i>Caucasians</i>	161(44.35%)	161(44.35%)	92(45.10%)		
<i>Mixed and others</i>	19(5.23%)	19(5.23%)	12(5.88%)		
Age				<0.001	0.971
<i>Mean (SD)</i>	9.78(1.30)	21.91(1.31)	21.91(1.47)		
<i>(Min, Max)</i>	(6.17, 11.98)	(18.37, 24.61)	(18.05, 24.63)		
ODSph*				<0.001	<0.001
<i>Mean (SD)</i>	-2.05(0.76)	-4.20(1.65)	0.81(0.43)		
<i>(Min, Max)</i>	(-4.31, -0.69)	(-9.87, -0.50)	(-0.00, 2.09)		
ODMSE*				<0.001	<0.001
<i>Mean (SD)</i>	-2.28(0.75)	-4.64(1.65)	0.62(0.41)		
<i>(Min, Max)</i>	(-4.36, -1.06)	(-10.31, -0.86)	(-0.25, 1.79)		
ODAL[#]				<0.001	<0.001
<i>Mean (SD)</i>	24.14(0.73)	25.36(0.96)	23.44(0.74)		
<i>(Min, Max)</i>	(21.75,26.18)	(22.03,27.87)	(21.09,25.77)		
Refractive astigmatism (D)					
<i>Mean J0 (SD)</i>	0.04(0.24)	0.24(0.41)	0.02(0.18)	<0.001	<0.001
<i>J0 (Min, Max)</i>	(-0.58, 0.68)	(-1.05, 1.60)	(-0.44, 0.53)		
<i>Mean J45 (SD)</i>	-0.01(0.14)	-0.01(0.24)	-0.04(0.12)	0.657	0.092
<i>J45 (Min, Max)</i>	(-0.54, 0.50)	(-0.79, 1.03)	(-0.37, 0.42)		
Corneal astigmatism (D)					
<i>Mean J0 (SD)</i>	0.31(0.27)	0.49(0.39)	0.33(0.25)	<0.001	<0.001
<i>J0 (Min, Max)</i>	(-0.51, 1.25)	(-0.62, 1.61)	(-0.49, 1.00)		
<i>Mean J45 (SD)</i>	0.05(0.18)	0.06(0.25)	0.03(0.17)	0.428	0.205
<i>J45 (Min, Max)</i>	(-0.76, 0.5)	(-0.77, 0.96)	(-0.46, 0.56)		
Internal astigmatism J0 (D)					
<i>Mean J0 (SD)</i>	-0.27(0.21)	-0.25(0.24)	-0.32(0.21)	0.03	<0.001

	COMET BL	COMET 12-yr	Non Myopes	p ¹	p ²
Variable	(n=363)	(n=363)	(n=204)		
<i>J0 (Min, Max)</i>	(-1.00, 0.70)	(-1.32, 0.40)	(-0.92, 0.46)		
<i>Mean J45 (SD)</i>	-0.06(0.17)	-0.07(0.18)	-0.07(0.18)	0.652	0.74
<i>J45 (Min, Max)</i>	(-0.55, 0.76)	(-0.85, 0.55)	(-0.68, 0.34)		

p¹: COMET BL vs. COMET 12-yr paired t- test

p²: COMET 12-yr vs. non-myopes unpaired t-test

SD = standard deviation; Min= minimum, Max=maximum; RA = refractive astigmatism at the corneal plane; OD = right eye; MSE = mean spherical equivalent; D = diopters

*
: vertex plane adjusted

: number of subjects 361 for COMET 12-year due to missing AL data for two subjects

Table 2
Potential Predictors of High Internal Astigmatism (astigmatism 1.00D) at 14 year follow-up visit.

14-yr	High IA (Cyl 1.00D)	Low IA (Cyl<1.00D)	Univariate Logistic Regression		Multivariate Logistic Regression	
Total	n=62	n=289	Odds Ratio	95% CI	p-value	95% CI
Gender					0.48	
<i>Males</i>	24	126	0.82	(0.47, 1.43)		0.84 (0.46, 1.53)
<i>Females</i>	38	163	1.00	Reference		Reference
Ethnicity					0.53	
<i>Asians</i>	2	28	0.32	(0.07, 1.40)		0.26 (0.06, 1.21)
<i>African Americans</i>	20	78	1.13	(0.60, 2.14)		0.96 (0.49, 1.89)
<i>Hispanics</i>	9	40	0.99	(0.43, 2.27)		0.95 (0.41, 2.23)
<i>Mixed or others</i>	2	15	0.59	(0.13, 2.72)		0.70 (0.15, 3.35)
<i>Caucasians</i>	29	128	1.00	Reference		Reference
Baseline Age					0.71	
<i>6-7 years old</i>	4	31	0.61	(0.18, 2.01)		0.61 (0.18, 2.11)
<i>8 years old</i>	10	49	0.96	(0.39, 2.37)		1.19 (0.46, 3.08)
<i>9 years old</i>	19	67	1.33	(0.61, 2.92)		1.48 (0.65, 3.36)
<i>10 years old</i>	16	81	0.93	(0.41, 2.07)		1.00 (0.44, 2.30)
<i>11 years old</i>	13	61	1.00	Reference		Reference
Central corneal thickness (µm)⁺			1.00	(0.99, 1.01)	1.00	1.00 (0.99, 1.01)
Refractive astigmatism (D)⁺			0.76	(0.50, 1.17)	0.21	Not included
Corneal astigmatism (D)^{+,*}			0.62	(0.42, 0.92)	0.02	0.60 (0.40, 0.89)
Refractive spherical (D)⁺			0.99	(0.85, 1.15)	0.88	Not included
Axial length (mm)⁺			0.80	(0.60, 1.06)	0.12	0.83 (0.61, 1.13)

IA = Internal Astigmatism; Cyl = cylinder; D = diopters

⁺ measured at the 14 year visit

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*mathematically increasing astigmatism when expressed in negative cylinder means astigmatism power is decreasing

Table 3

Association of IAJ0 and key demographic variables.

Variables	BL to Year 5 p values	Year 5 to Year 14 p values
Gender	0.33	0.29
Baseline Lens Assignment (SV or PALs) ⁺	0.15	0.21
Baseline Age (5 groups) [*]	0.15	0.17
Ethnicity	<0.0001	<0.0001
Asian vs. AA	0.03	0.17
Hispanic vs. AA	<0.0001	<0.0001
Caucasians vs. AA	<0.01	<0.01
Mixed/others vs. AA	0.02	0.01
Baseline MSE	<0.001	<0.01
Three-year progression rate	0.49	0.93

All numbers are p values from a linear mixed model that includes time and all the factors listed in the table without the non-significant interaction terms.

BL=baseline; SV = single vision spectacle lens; PALs= progressive addition lenses; AA=African Americans; MSE = mean spherical equivalent

⁺ At the 5 year visit participants were allowed to change lens assignment and/or wear contact lenses

^{*} 6-7 years, 8 years, 9 years, 10 years, 11 years