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Comparison of Whole Eye vs. First-Surface Astigmatism in Down Syndrome

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Abstract

Purpose—Individuals with Down syndrome (DS) have structural differences in the cornea and lens, as compared to the general population. This study investigates objectively measured refractive and corneal astigmatism, as well as calculated internal astigmatism in subjects with and without DS.

Methods—Refractive (Grand Seiko autorefraction) and anterior corneal astigmatism (difference between steep and flat keratometry obtained with Zeiss Atlas corneal topography) were measured in 128 subjects with DS (mean age = 24.8 ± 8.7 yrs) and 137 controls without DS (mean age = 24.9 ± 9.9 yrs), with 1 eye randomly selected for analysis per subject. Refractive astigmatism and corneal astigmatism were converted to vector notation (J_0 , J_{45}) to calculate internal astigmatism (Refractive – Corneal) and then converted back to minus cylinder form.

Results—Mean refractive astigmatism was significantly greater in subjects with DS than controls (-1.94 ± 1.30 DC vs -0.66 ± 0.60 DC, $t = -10.16$, $p < 0.001$), as was mean corneal astigmatism (1.70 ± 1.04 DC vs 1.02 ± 0.63 DC, $t = 6.38$, $p < 0.001$) and mean internal astigmatism (-1.07 ± 0.68 DC vs -0.77 ± 0.41 DC, $t = -4.21$, $p < 0.001$). A positive linear correlation between corneal and refractive astigmatism was observed for both study populations for both the J_0 and J_{45} vectors ($p < 0.001$ for all comparisons, R^2 range = 0.31 to 0.74). The distributions of astigmatism orientation differed significantly between the two study populations when compared across all three types of astigmatism (Chi-Square, $p < 0.001$).

Conclusions—This study demonstrates that corneal astigmatism is predictive of overall refractive astigmatism in individuals with DS, as it is in the general population. The greater magnitudes of astigmatism and wider variation of astigmatism orientation in individuals with DS for refractive, corneal, and calculated internal astigmatism is likely attributable to previously reported differences in the structure of the cornea and internal optical components of the eye from that of the general population.

Keywords

astigmatism; corneal topography; Down syndrome; internal astigmatism; refractive error

Individuals with Down syndrome are known to have a greater prevalence of ocular complications than the general population, such as strabismus,¹⁻¹⁰ nystagmus,^{1, 2, 5-9} reduced visual acuity,¹¹⁻¹⁴ and reduced accommodation.^{10, 14-20} In addition, these individuals appear to have a failure to emmetropize^{21, 22} and commonly have significant refractive errors,^{1, 5-8, 11, 20, 23} often hyperopic,^{5, 7, 8, 20, 23, 24} and large amounts of astigmatism.^{1, 2, 7, 8, 11, 20, 24, 25} More recently, biometric studies of the ocular components of the eyes of individuals with Down syndrome have demonstrated structural differences from the general population, such as thinner²⁶⁻²⁹ and steeper corneas,²⁷⁻³⁰ thinner crystalline lenses,²⁷ shorter axial length,²⁷ and abnormalities of corneal morphology suggestive of early or mild keratoconus.^{24, 30} It has been hypothesized that these structural corneal differences may be related to the previously reported higher prevalence of keratoconus clinically observed in this population.^{2, 5, 31-33}

Aside from a potential association with corneal disease, it is reasonable to presume that the structural differences observed in the optical components of the eyes of individuals with Down syndrome should be directly related to the clinical observations of increased refractive error, particularly the elevated levels of astigmatism. Previous studies in typically developed individuals have demonstrated a clear linear relationship between the magnitude of corneal toricity and refractive astigmatism,³⁴⁻³⁸ as well as some evidence for a relationship between corneal curvature and the magnitude of spherical refractive error, with steeper corneas being associated with greater myopia (or less hyperopia).^{39, 40} Little et al. published the first study investigating the relationship between corneal curvature and refractive error in individuals with Down syndrome as compared to age-matched controls.²⁵ Little et al. found no significant relationship between corneal curvature and spherical or astigmatic refractive error in the 29 children with Down syndrome included in their study.²⁵ This lack of relationship was surprising and leads to the need for further investigation in a larger sample of individuals with Down syndrome to better understand the impact that the observed structural differences in individuals with Down syndrome may or may not have on their overall refractive status.

The purpose of this study was to investigate the relationship between corneal power (as measured by corneal topography) with refractive error (as measured by autorefraction) in a large sample of individuals with Down syndrome from the general public and compare the relationships to an age and sex-matched control population without Down syndrome. Of specific interest is the relationship between corneal toricity and refractive astigmatism, both in magnitude and orientation. These findings may further elucidate whether clinicians can utilize measures of corneal astigmatism as predictive of refractive astigmatism, or whether this relationship is diminished, or even absent in patients with Down syndrome. Lastly, we sought to expand upon the previous study by including calculations of internal astigmatism to more fully evaluate the potential contributions of different optical components to the overall refractive status and how this may differ between individuals with and without Down syndrome.

METHODS

Subjects

This study compared autorefractometry and corneal topography measurements from subjects with Down syndrome and control subjects without Down syndrome. In order to avoid a patient-based sample, subjects with Down syndrome were recruited from the Down syndrome Association of Houston, TX facility and their sponsored activities, as well as from the Special Olympics Lion's Club International Opening Eyes (SOLCIE) vision screenings events located around the state of Texas. All individuals with Down syndrome at these events/locations were invited to participate, although 10 were unable to complete study measurements due to an inability to fixate accurately (e.g. due to inattention to the task, nystagmus, strabismus, etc.), or due to an inability of the instruments to capture measurements (e.g. substantial lenticular or corneal opacities). Two subjects were also excluded due to a history of ocular surgery (e.g. refractive surgery or lens extraction).

In order to avoid a patient based control sample, control subjects were recruited from the University of Houston faculty, staff, students, their family and friends with the intention to match the age and gender distribution of the group with Down syndrome. Subjects were excluded if they had a history of refractive surgery. Faculty with optometric degrees, optometry students, and clinic patients were not recruited in attempts to include a sample more representative of the general population.

Protection of Human Subjects

This research was approved by the University of Houston Committee for the Protection of Human Subjects and adhered to the tenets of the Declaration of Helsinki. Parental permission was obtained from all subjects with Down syndrome recruited from the Down syndrome Association of Houston events. A consent waiver was approved by the University of Houston Committee for the Protection of Human Subjects for subjects with Down syndrome recruited from SOLCIE vision screenings since the measurements were included as a part of the free vision screening, and all information collected for study analysis was collected without individually identifying information. Willingness to sit for study measurements was accepted as subject assent for participants with Down syndrome. Informed consent was collected from all control subjects 18 years and older and parental permission and subject assent collected for control subjects less than 18 years of age.

Measurements Collected

Corneal topography measurements were obtained using the Zeiss Atlas 9000 corneal topographer (Carl Zeiss Meditec, Inc. Jena, Germany). A minimum of four images were attempted per eye, although due to difficulty maintaining fixation, some subjects had less. Images were later assessed individually for quality (as described below) and a random number generator was used to select one image from the category of highest quality available for a given subject for one eye. This strategy was used to avoid a potential testing order bias that could be brought about if we instead selected the first image from each subject. Simulated keratometry measurements (flat and steep K separated by 90 degrees over a 3mm diameter and assuming a keratometric index of refraction = 1.3375) were

exported to represent corneal power and corneal astigmatism. The orientation of corneal astigmatism was termed the meridian associated with the flattest K. This value was used to categorize the orientation of corneal astigmatism, as well as to calculate astigmatic components of the power vector describing corneal astigmatism (described below).

Distance autorefraction measurements were obtained using the Grand Seiko WAM 5500® open-field autorefractor set to measure at the corneal plane (RyuSyo Industrial Co., Ltd. Hiroshima, Japan) as subjects viewed either a movie or letter chart placed at 20 feet. Five repeated measurements were attempted per eye, although some subjects had less, due to difficulty maintaining fixation. A random number generator was used to select one measurement for each subject for the same eye randomly selected for the corneal topographer analysis. This strategy was used (versus using a power vector average of the autorefraction readings) due to the fact that: 1) Five readings were not attainable from every subject with Down syndrome and 2) this methodology is equivalent to that used for topography in which averages were not used. Refractive astigmatism was obtained from the cylinder power of the autorefraction measurement, as well as spherical equivalent refraction (spherical power + 1/2 cylinder power). The axis of refractive astigmatism was utilized for the classification of astigmatism orientation, as well as the calculation of power vectors to describe refractive astigmatism (described below).

Topographic Quality Assessment

Due to the difficulty of testing subjects with Down syndrome, a cornea and contact lens specialist with over 40 years of clinical experience assessed the quality of each topography image from the subjects with Down syndrome to identify data that, due to its marginal quality, should be excluded from further study. This specialist was masked to both the purpose of the study and the subject populations included in the study. The specialist was instructed to use stringent criteria when rating images and to rate images based upon capture quality only (sharpness of the mires, occlusion of the cornea by the lid or eyelashes, etc.) and not based upon any potentially observed corneal abnormalities (corneal dystrophy, irregular astigmatism, etc.). In other words, an image that appeared suspect for keratoconus could still be classified as a good quality image if the rings were in focus and the subject fixating appropriately. The specialist was allowed to evaluate all outputs for a given image capture (axial, tangential, elevation maps and rings images), as well as simultaneously compare multiple captures within each subject to identify outliers. The specialist rated each individual image as good (no concerns about quality), moderate (some concerns about quality which may impact interpretation, such as minor focusing concerns, minor tear film abnormalities, etc.), and poor (bad quality which should not be used in analysis).

Representative examples of the image quality categorizations can be seen in Figure 1. As stated above, a random number generator was used to select one image for each subject from the highest quality images available. For example, subjects who had good images would have only those images considered in random selection (leaving out the moderate images), whereas subjects who had no good images would have an image selected from the moderate group. If a subject only had one useable image, that one was selected.

There was less concern about the quality of images for control subjects given the group's uniform ability to sit and fixate steadily for the duration of the topography measures. However, to ensure that the investigators (who were not masked to the study purpose or study populations) could adequately judge the quality of the control subject images, the same specialist and an unmasked study investigator independently rated a sample of images from the control subject population (118 images total from 12 subjects). Images were identically rated by these two examiners 90% of the time and any disputes occurred at neighboring rating levels rather than extremes (i.e. there were no instances for which the specialist rated poor and the examiner rated good, or vice versa). It was thus decided that the unmasked study investigator could accurately assess the quality of the remaining control subject images.

Power Vector Analysis

Vector notation was used to allow comparison of refractive astigmatism and corneal astigmatism while retaining orientation information regarding astigmatism, as well as to calculate mean corneal power and spherical equivalent refractive error.⁴¹ The formulas previously described by Thibos, et al.⁴¹ were applied to calculate M (spherical equivalent refraction and mean corneal power), and the J_0 (with and against the rule) and J_{45} (oblique) astigmatism components for both refractive and corneal measures. Positive J_0 values indicate with the rule astigmatism (minus cylinder axis 180) whereas minus J_0 values indicate against the rule astigmatism. For the J_{45} component, positive values indicate a minus cylinder axis of 045 whereas minus values indicate a minus cylinder axis of 135. Internal (residual) astigmatism was then calculated for both the J_0 and J_{45} vectors by subtracting corneal measures from refractive measures. The calculated internal J_0 and J_{45} vectors were later converted back to minus cylinder form using the formulas described by Thibos, et al.⁴¹ to allow categorization of calculated internal astigmatism orientation. Given that the Zeiss Atlas 9000 measures the front surface corneal power only, the calculated internal astigmatism represents contributions from any internal structure, including posterior corneal surface, anterior/posterior lens surfaces and lenticular gradient index.

Data Analysis

Refractive power (spherical equivalent), mean corneal power, and the magnitude of refractive, corneal, and calculated internal astigmatism were compared between subject groups (Down syndrome versus controls) with t-test analysis of the group means and F-test analysis of the group variance. The relationship between spherical equivalent refraction and mean corneal power was then evaluated by linear regression for both subjects with and without Down syndrome. Next, the distributions of refractive and corneal astigmatism for each group were graphically explored by plotting J_0 versus J_{45} vectors for refractive and corneal measures separately. F-tests were performed to compare the variance in the distributions refractive and corneal astigmatism vectors between subjects with and without Down syndrome. The relationship between corneal and refractive astigmatism was then tested by linear regression of the J_0 corneal and refractive vectors, as well as linear regression of the J_{45} corneal and refractive vectors. This analysis was performed for both subjects with and without Down syndrome and the slopes of the regression models compared between groups with ANCOVA. Lastly, chi-square analysis was used to compare

the distributions of refractive, corneal, and calculated internal astigmatism orientation between subjects with Down syndrome and controls. Astigmatism orientation was classified as *with the rule*: axis 001–030 & 150–180, *against the rule*: axis 060–120, or *oblique*: axis 031–059 & 121–149.⁴²

RESULTS

After excluding subjects for poor corneal topography image quality (10 subjects with Down syndrome), or lack of autorefractometer measurements (12 subjects with Down syndrome, 1 control subject), analysis was performed on measurements from 128 individuals with Down syndrome (57 female, 71 male, mean $\pm$ sd age = 24.8 ± 8.6 yrs, age range = 8 to 55 yrs) and 137 control subjects without Down syndrome (69 female, 68 male, mean $\pm$ sd age = 24.9 ± 9.9 yrs, age range = 7 to 59 yrs).

Pupil centration data were extracted from the topography images and compared between subjects with and without Down syndrome as an indicator of fixation accuracy. The topographer successfully located the pupil for 100% of control subjects and 73% of subjects with Down syndrome. There were no significant differences in horizontal pupil centration (with respect to the topography rings) for subjects with and without Down syndrome (in whom the pupil was found) for right (t-test, $p = 0.09$) or left eyes (t-test, $p = 0.66$). The mean horizontal centration position of the pupil for all subjects combined was -0.21 ± 0.15 mm for right eyes and $+0.25 \pm 0.15$ mm for left eyes with respect to the topography rings. The images of the 35 subjects with Down syndrome (27%) in whom the pupil was not found were visually inspected and no obvious fixation errors were observed in these images; however, a common finding among many of them was a smaller aperture or lower-hanging eyelashes on the upper lid margin which may have interfered with the instrument's detection of the upper pupil margin.

The percentage of subjects with topography images rated as *good* and *moderate* were 66% and 34%, respectively, in Down syndrome subjects and 97% and 3% in control subjects. All analyses were compared between sampling including all subjects versus only those with *good* images. There were no meaningful differences in the results when making these comparisons, and thus the data presented in this manuscript includes all subjects combined (both *good* and *moderate* quality). Throughout the results, findings termed *refractive* indicate measurements obtained with autorefractometer, whereas findings termed *corneal* indicate measurements obtained with topography.

Comparison of Refractive and Corneal Power Distributions

Figure 2 shows a comparison of spherical equivalent refraction (2A), mean corneal power (2B), and refractive, corneal, and calculated internal astigmatism magnitude (2C) for subjects with and without Down syndrome. The group mean ($\pm$ sd) spherical equivalent refractive error was significantly less myopic in subjects with Down syndrome (-0.43 ± 4.03 DS) as compared to control subjects (-1.31 ± 2.42 DS) ($t = 2.13$, $df = 205$, $p = 0.03$) (Figure 2A, Table 1). Mean ($\pm$ sd) corneal power was significantly higher in subjects with Down syndrome than controls (45.82 ± 1.80 D vs 43.37 ± 1.58 D, $t = 11.77$, $df = 253$, $p < 0.001$) (Figure 2B). Mean ($\pm$ sd) refractive cylinder magnitude was significantly greater in subjects

with Down syndrome (-1.94 ± 1.30 DC) than controls (-0.66 ± 0.60 DC) ($t = -10.16$, $df = 177$, $p < 0.001$) (Table 1), as was mean front surface corneal toricity (1.70 ± 1.04 DC versus 1.02 ± 0.63 DC, $t = 6.38$, $df = 206$, $p < 0.001$), and mean calculated internal astigmatism (-1.07 ± 0.47 DC versus -0.77 ± 0.17 DC, $t = -4.21$, $df = 205$, $p < 0.001$) (Figure 2C). Refractive astigmatism was then grouped as minimal (0 to -0.50 DC) versus significant (< -0.50 DC) for both groups, demonstrating that the majority of subjects with Down syndrome had significant amounts of refractive astigmatism (88% of subjects with Down syndrome versus 43% of controls) (Table 1). For all measures compared in Figure 2, the variance was greater for subjects with Down syndrome than controls. These differences in variance reached statistical significance for spherical equivalent, refractive, corneal, and internal astigmatism (F-test, $p < 0.001$) and approached significance for corneal power (F-test, $p = 0.068$).

Refractive Error in Relation to Corneal Power

Linear regression analysis was performed to assess the relationship between the magnitude of spherical equivalent refractive error and the mean corneal power for each subject group. There was no significant correlation for subjects with Down syndrome ($p = 0.91$, $R^2 = 0$) despite the large range of refractive and corneal powers observed, and there was only a minimal correlation of increasing myopic refractive error with increasing corneal power for control subjects and this did not account for a meaningful proportion of the variance in refractive error ($y = 8.74 - 0.23x$, $R^2 = 0.022$, $p = 0.02$) (Figure 3).

Overall Observations of Refractive, Corneal, and Calculated Internal Astigmatism

Power vectors (J_0 & J_{45}) were plotted for both refractive astigmatism (Figure 4A) and corneal astigmatism (Figure 4B) for both subject groups. Subjects with Down syndrome had a greater distribution of large magnitudes of both refractive and corneal astigmatism as evidenced by the large vector magnitudes (spread of data away from zero) which occurred at a large variety of orientations (as evidenced by the spread of the data along all axes). By comparison, control subjects had lower vector magnitudes of refractive and corneal astigmatism (data more tightly packed around zero) with corneal astigmatism largely concentrated around the positive J_0 axis, indicating a large percentage of *with the rule* (negative axis 180) astigmatism. This visual observation was confirmed statistically with greater variance found in both the refractive and corneal J_0 and J_{45} vectors for subjects with Down syndrome (F-test, $p < 0.001$). Despite the increased variance, there were no statistically significant differences in mean J_0 and J_{45} vectors for refractive or corneal astigmatism (t-test, $p = 0.14$), indicating a similar centration of the data as seen in Figures 4A&B. Similar to refractive and corneal findings, internal astigmatism had a wider distribution of both magnitude and orientation in subjects with Down syndrome than control subjects whose data clustered around the negative J_0 axis (*against the rule*, axis 090) (Figure 4C). The variance in J_0 and J_{45} internal astigmatism vectors was significantly greater in subjects with Down syndrome (F-test, $p < 0.001$). Control subjects had significantly more negative mean J_0 values (*against the rule*) for internal astigmatism (t-test, $p < 0.001$) with no significant difference in mean J_{45} vector magnitude (*oblique* orientation) (t-test, $p = 0.30$).

Correlation between Refractive and Corneal Astigmatism

Linear regression analysis was performed to investigate the relationship between refractive and corneal astigmatism. As corneal astigmatism increased, refractive astigmatism increased for both subject samples for both the J_0 and J_{45} vectors ($p < 0.001$ for all comparisons, R^2 range = 0.31 to 0.74) (Figure 5). The strongest correlations occurred for subjects with Down syndrome (as evidenced by the R^2 values) and the slope of the fits differed significantly between subjects with Down syndrome and controls for both J_0 and J_{45} vectors (one-way ANCOVA, $p = 0.01$).

Distribution of Astigmatism Orientation

Chi-square analysis was performed for subjects with more than 0.50D of refractive astigmatism to compare the distribution of astigmatism orientation between subjects with ($n = 113$) and without ($n = 59$) Down syndrome. As described in the methods, calculated internal J_0 & J_{45} vectors were converted to minus cylinder form using the formulas described by Thibos, et al.⁴¹ to determine the axis of orientation for internal astigmatism. The distribution of astigmatism orientation was significantly different between subjects with and without Down syndrome for corneal and internal astigmatism (Chi-Square, $p = 0.007$), but did not differ significantly for refractive astigmatism (Chi-Square, $p = 0.46$) as shown in Figure 6. Other notable comparisons include the smaller percentage of *with the rule* corneal astigmatism in individuals with Down syndrome (63.7% versus 86.4%), and the smaller percentage of *against the rule* calculated internal astigmatism in individuals with Down syndrome (39.8% versus 69.5%).

DISCUSSION

This study found a strong linear relationship between the magnitude of corneal and refractive astigmatism for the J_0 and J_{45} vectors in both subjects with Down syndrome and age and sex-matched controls. The relationship was strongest in the group with Down syndrome, perhaps as a result of the increased sampling of large magnitude astigmatism in this subject group. Our findings are in agreement with previous studies from populations of typically developed individuals^{34–37, 43} supporting the expectation that corneal toricity is predictive of overall refractive astigmatism. However, our findings differ from those of Little et al. who found no significant relationship between corneal and refractive astigmatism in their subjects with Down syndrome.²⁵ There are several potential explanations which may account for the different findings between our study and the Little et al. study. For one, Little et al.'s study only included children (mean age = 12.8 ± 1.9 yrs) versus our broader and older aged study population (mean age = 24.8 ± 8.6 yrs).²⁵ Little et al. also had fewer subjects with significant astigmatism (12 subjects with Down syndrome (41%) had astigmatism greater than 0.50DC)²⁵ versus our study in which the majority of subjects with Down syndrome had significant refractive astigmatism (113 subjects (88%) had astigmatism greater than 0.50DC) (Table 1). The differences in the proportion of subjects with astigmatism between the two studies may be related to the older mean age of our sample (particularly if astigmatism is developing as part of a disease process), or may have been related to the differences in measurement techniques (Little et al. used Mohindra retinoscopy²⁵ whereas our study used Grand Seiko autorefraction). Methodology also differed for measures of corneal toricity:

Little et al. used handheld keratometry,²⁵ whereas our study used a Zeiss corneal topographer and utilized a masked examiner to assess quality of the captured images to select the measurement of highest quality. One other potential source for differences in astigmatism between the two studies could be the ethnic distribution of the subjects included in the study, given that ethnicity has previously been reported to have an association with refractive astigmatism magnitude.^{44–46} Although ethnicity was not formally documented for the present study, the general population in southeast Texas is diverse and both groups recruited for this study (subjects with Down syndrome and controls) are believed to have included subjects of many different ethnicities. While the ethnic distribution of subjects with and without Down syndrome is not believed to have differed from each other within our study since they were recruited from the same geographic region, it is possible that the distribution of ethnicities differed from that in the study by Little et al.

Mean corneal power was significantly steeper in our subjects with Down syndrome than controls, which is consistent with previous studies comparing individuals with and without Down syndrome.^{25, 27–30} The mean corneal power observed for the two subject groups in this study (Down syndrome: 45.82D, Controls: 43.37D) agrees well with that reported by Little et al. (Down syndrome: 45.62D, Controls: 43.10D)²⁵ despite the difference in mean age of each study's subjects and the different measurement techniques.

As noted in the introduction, one might expect that steeper corneal power would lead to greater myopic (or less hyperopic) refractive error,^{39, 40} but this was not the case for our subjects. Similar to Little et al., our study found no significant relationship between mean corneal power and spherical equivalent refractive error in subjects with Down syndrome, and a minimal relationship between mean corneal power and spherical equivalent refractive error in controls.²⁵ While this lack of a relationship may be somewhat surprising, it should also be noted that other aspects of ocular biometry differ in individuals with Down syndrome such as thinner and weaker crystalline lens and shorter axial length, both of which demonstrate a stronger relationship with spherical refractive error in the eyes of individuals with Down syndrome than corneal power.²⁷

Similar to other studies of individuals with Down syndrome, we observed greater magnitudes of hyperopic refractive error and astigmatism in our subjects with Down syndrome than controls.^{7, 8, 20, 23, 24}

Previous studies have also reported a greater prevalence of oblique refractive astigmatism in individuals with Down syndrome,^{22, 25} potentially related to eyelid morphology.²⁷ For specific comparison, Little et al. reported approximately 50% of subjects with significant refractive astigmatism (greater than 0.50DC) having oblique orientation and did not report the number of control subjects with oblique orientation. Our study found no significant difference in the percentage of individuals with obliquely orientated refractive astigmatism compared to control subjects, with percentages of 21.2% and 13.6%, respectively. The difference in prevalence between our study and Little et al. is likely due to the different criteria used for astigmatism orientation classification (Little et al. classified oblique if axes were greater than ± 15 degrees from horizontal or vertical, whereas we used a criterion of greater than ± 30 degrees from horizontal or vertical). If we apply the criteria of Little et al.

to our sample, the percentage of subjects with Down syndrome who have obliquely oriented refractive astigmatism reaches 54%, but the percentage of control subjects with obliquely oriented refractive astigmatism also increases to 42%.

In this study we used independent measures of refractive and corneal astigmatism to calculate internal astigmatism. Although this analysis may provide potential insight into the interaction of the optical components of the eyes in individuals with Down syndrome, the interpretation of the data should be made with caution given that internal astigmatism was calculated and not measured independently. Based upon the calculated measures, internal astigmatism, in general, centered at small magnitudes of against the rule astigmatism in both individuals with and without Down syndrome (Figure 4C). However, individuals with Down syndrome had a much larger variation of magnitudes and orientation of internal astigmatism than controls (Figures 4C & 6). Classically, internal astigmatism has been reported to average 0.50DC of against the rule astigmatism in the general population (as originally described by Javal⁴⁷ and now commonly termed Javal's Rule) and is believed to be compensatory for the commonly observed with the rule corneal astigmatism.^{48–50} Our control subjects appear to follow this expectation with the majority demonstrating against the rule internal astigmatism which compensates for with the rule corneal astigmatism, leading to refractive astigmatism centered at zero (Figure 4). However, the same robust pattern is not observed in subjects with Down syndrome who demonstrated a wide spread of magnitude and orientation of astigmatism occurring for both corneal and refractive measures. This raises the question as to whether the commonly believed compensatory mechanism of internal astigmatism differs in individuals with Down syndrome, or is altogether absent.

One limitation to this study is the use of a single, randomly selected, autorefraction measurement for quantification of refractive error and a single, randomly selected topography image for simulated keratometry measurement. This methodology was used to provide similar measurement certainty across subjects, given that not all subjects had multiple measures available from autorefraction or topography. However, the use a single refraction measurement is not dissimilar to studies which use a single retinoscopic measurement to quantify refractive error, such as the previous study by Little et al.²⁵ Despite the use of a single measurement for both refractive error and corneal toricity, our study still found strong correlations between corneal and refractive astigmatism for both study populations, with the strongest correlations being observed in the subjects with Down syndrome. It is possible that inaccurate subject fixation or poor image quality could have produced measurement errors, particularly with respect to the large magnitude of astigmatism measured by topography. However, if this factor had a large influence on the data collected from subjects with Down syndrome, it is unlikely they would have had such strong correlations between autorefraction and topography measures (here, stronger than the control group). The fact that subjects with Down syndrome and controls had similar pupil centration measures during topography, as well as the fact that the overall findings did not differ when eliminating subjects with moderate quality images further supports the argument that fixation accuracy and image quality did not play a significant role in measurement certainty in this study.

Another limitation to this study is that the autorefraction measurements were performed without the use of cycloplegia, and thus may not reflect the full magnitude of hyperopia for some subjects and may be influenced by fluctuations in subject accommodation. However, given the previous strong evidence for poor accommodative ability in individuals with Down syndrome,^{14–19} and the use of an open field autorefractor, this is likely to have had minimal impact on the measurements obtained in this study. To further investigate this limitation, the variance of spherical equivalent measurements was compared between subjects with Down syndrome (n = 96) and controls (n = 136) for individuals with 3 repeated measurements of autorefraction for the eye included in the present study. The group mean of the individual variance (standard deviation of 3 repeated spherical equivalent measures) was significantly greater in subjects with Down syndrome (0.37D) than controls (0.09D) (t-test, $p < 0.001$); however, the magnitude of the mean variance was relatively small for both groups suggesting that for the majority of subjects, large fluctuations in accommodation during autorefraction measurements did not occur.

A third study limitation is the use of calculated internal astigmatism for data analysis rather than direct measurement of internal astigmatism. In particular, it should be noted that errors may be introduced in the calculation of internal astigmatism due to the fact that the topographer and autorefractor use different axes to obtain measurements. Corneal topography data is centered on the ‘vertex normal’ which measured approximately 0.25 ± 0.15 mm, on average, from the pupil center in this study, versus the autorefractor which is centered on the pupil. The instrumentation used in this study was selected based upon expectations of a high success rate to capture measurements in our population of interest. The Zeiss Atlas 9000 provides a longer working range and higher capture rate and the Grand Seiko autorefractor allows the use of an external distance stimulus to maintain subject attention. Future studies that utilize instrumentation capable of independently measuring internal astigmatism will allow further investigation into the manner in which the individual contributions of the internal ocular structures impact the refractive state of eyes in individuals with Down syndrome.

Lastly, subjects in this study participated in only two clinical measurements rather than a comprehensive eye examination, and thus additional information about corneal health (specifically findings that could assist in the diagnosis of suspected keratoconus) is unavailable. One of the unique goals of this study was to include a large sample of individuals with Down syndrome from the general population, rather than include those seeking visual interventions, and thus the methodology was limited to instruments that could easily be transported to events at which individuals with Down syndrome were present. Given this limitation, we are unable to comment as to whether any individuals with corneal disease were included in the study population; however, it is likely that some of the individuals with Down syndrome had corneal abnormalities given the fact that the sample was representative of the Down syndrome population and there are multiple previous reports of an increased prevalence of keratoconus in this population.^{2, 5, 31–33}

CONCLUSIONS

This study demonstrates that corneal astigmatism is predictive of overall refractive astigmatism in individuals with Down syndrome, as it is in the general population. The greater magnitudes of astigmatism and wider variation of astigmatism orientation in individuals with Down syndrome for refractive, corneal, and calculated internal astigmatism is likely attributable to previously reported differences in the structure of the cornea and internal optical components of the eye from that of the general population.

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Figure 1.

Representative examples of the image quality assessment categories: Good (**A**), Moderate (**B**), Poor (**C**). Figure 1A (good) contains sharp mires and a full pupil. Figure 1B (moderate) contains slightly blurred mires and the image of the eyelashes can be seen occluding several of the mires superiorly. Figure 1C (poor) shows blurred mires and partial occlusion of the pupil by the upper eyelid. A color version of this figure is available online at www.optvissci.com.

Figure 2.

Boxplots showing the distribution of spherical equivalent refractive error as measured by autorefraction (A), mean corneal power as measured by topography (B), and cylindrical refractive power (expressed as absolute values), corneal toricity (as measured by autorefraction and topography, respectively), and calculated internal astigmatism (expressed as absolute values) (C). Solid lines represent median values, dashed lines represent mean values, box boundaries represent 25th and 75th percentiles, and whiskers represent 10th and 90th percentiles. Dots represent outliers beyond the 10th and 90th percentiles. Comparisons of the group means for each of these five components differed significantly between subjects with and without Down syndrome (t-test, $p < 0.03$).

Figure 3.

Linear regression analysis of mean corneal power (as measured by topography) versus spherical equivalent refractive power (as measured by autorefraction).

Figure 4.

Power vector plots for refractive (A), corneal (B), and calculated internal (C) astigmatism. For all comparisons, subjects with Down syndrome had greater magnitudes of astigmatism (spread of data away from zero) with more varied orientation (as evidenced by the spread of the data along all axes).

Figure 5.

Corneal and refractive power vectors were significantly linearly related for both correlations of J₀ (A) and J₄₅ (B) vectors for both subjects with and without Down syndrome.

Figure 6. Distributions of astigmatism orientation for refractive, corneal, and calculated internal astigmatism. Distributions differed significantly between subjects with and without Down syndrome for comparisons of corneal and calculated internal astigmatism (Chi-Square, $p < 0.007$), but not refractive astigmatism ($p = 0.46$).

Table 1

Summary of autorefraction measures for subjects with and without Down syndrome.

	Spherical Equivalent (mean ± sd)	Refractive Astigmatism (mean ± sd)	Subjects with 0.50 DC of Refractive Astigmatism	Subjects with > 0.50 DC of Refractive Astigmatism
Subjects with Down syndrome	-0.43 ± 4.03 D Range: -14.25 to +8.13	-1.94 ± 1.30 DC Range: -5.50 to -0.12	n = 15 (12%)	n = 113 (88%)
Control Subjects	-1.31 ± 2.42 D Range: -9.75 to +3.63	-0.66 ± 0.60 DC Range: -3.87 to 0	n = 78 (57%)	n = 59 (43%)