Longitudinal Evidence of Crystalline Lens Thinning in Children

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Purpose. Most earlier studies indicated that the eye's crystalline lens grows continually throughout life, but cross-sectional results of crystalline lens thinning during childhood have been reported. The authors investigated crystalline lens thickness in childhood using cross-sectional and longitudinal data.

Methods. The Orinda Longitudinal Study of Myopia is a community-based study of normal eye growth and myopia development in school-age children. During a 1- to 3-year period, A-scan ultrasonographic lens thickness measurements of 869 children 6 through 14 years of age were analyzed.

Results. On average, between the ages of 6 and 10 years, the crystalline lens thins in its axial dimension by almost 0.2 mm. This thinning can be depicted by a cubic model. In this sample, the children with myopia had thinner crystalline lenses than the children with emmetropia of the same age.

Conclusions. This article provides the first longitudinal evidence that the crystalline lens thins during the period of coordinated ocular growth between the ages of 6 and 10 years. Further, it shows that lens thickness is associated with refractive error. Thinner crystalline lenses in children with myopia may result from one of two underlying mechanisms: Either the crystalline lens exhausts its ability to compensate for axial elongation after undergoing accelerated lens thinning before the onset of myopia, or the crystalline lens in the myopic eye may be thinner throughout childhood, during which it thins at a rate consistent with other refractive errors. If mechanical forces link eye growth to crystalline lens compensation, more complex, visually guided feedback loops may not be needed to explain the normal eye growth that results in emmetropization. Invest Ophthalmol. Vis Sci. 1995;36:1581-1587.

The length of the human eye increases rapidly until a child is 3 years of age; after that, it undergoes a 10-year period of slow growth, increasing approximately 1 mm in overall length during that time.1-3 This 1 mm of growth is coordinated with a decrease in the optical power of the eye through the process known as emmetropization, whereby the eye's axial length is optically matched to its focal length so that images of distant objects are in focus on the retina. This results in emmetropia in a disproportionately large segment of the population.4-6

The human crystalline lens, which accounts for almost 20% of the eye's refracting power,7 increases in weight and volume throughout life through the production of new protein fibers.8-12 Although this implies that the lens increases in axial thickness as well, cross-sectional results13 have provided evidence of crystalline lens thinning of 0.50 mm between birth and age 13 years, with 60% of the effect occurring before age 3 years. Additionally, Larsen13 found no difference in lens thickness between gender and no correlation of lens thickness with refractive error.

We present the first longitudinal evidence of crystalline lens axial thinning during childhood and provide support for a passive mechanism of coordinated growth that may help explain the emmetropia found in the majority of the population. We also document that persons with myopia have thinner lenses than those with emmetropia and hyperopia. This observation is in agreement with a model of myopic eye growth.
growth in which the crystalline lens is unable to continue to compensate for axial elongation as abnormal myopic eye growth continues past a certain critical point.

METHODS

We measured lens thickness and refractive error in the right eyes of 869 children enrolled in the Orinda Longitudinal Study of Myopia.14 Children entered the study as a cohort of first, third, and sixth graders (average ages at entry, 6.5, 8.5, and 11.5 years, respectively). Parents gave informed consent after the nature and possible consequences of the study were explained, the tenets of the Declaration of Helsinki were followed, and approval of the study protocol and informed consent procedures were obtained from the University of California at Berkeley's Committee for the Protection of Human Subjects. Four such cohorts—enrolled in 1989, 1990, 1991, and 1992 and followed annually for 1 to 3 years—are reported here.

Topical 1% tropicamide after 0.5% proparacaine was instilled to induce cycloplegia. Ultrasonography and autorefraction were conducted 25 minutes after instillation of the first drop of tropicamide. Lens thickness in the right eye was measured by A-scan ocular ultrasonography (model 820; Humphrey Instruments, San Leandro, CA) under topical anesthesia (0.5% proparacaine) while the left eye maintained distance fixation. Five ultrasound readings taken in the device's semiautomatic mode were averaged. Cycloplegic refraction was performed with an autorefractor (R-I model; Canon Europa, Amstelveen, Netherlands). Ten consecutive readings were obtained while the child viewed a reduced eye chart at optical infinity through a +4.00 D Badal system. These readings were analyzed and averaged to produce a single refractive error value for the vertical meridian for each child.15

RESULTS

Figure 1 presents a scatter plot of 2242 crystalline lens thickness measurements at various ages. Superimposed on this point cloud is a cubic polynomial growth curve that exhibits a marked decrease in lens thickness between 6 and 10 years of age. We fit the cubic growth curve to these data by maximum likelihood estimation using a mixed model analysis of covariance,16 which accounts for the correlation between repeated measurements on the same individual through a compound symmetry covariance structure. The model assumes that, for each individual, the population growth curve displayed in Figure 1 is shifted by a random, child-specific amount (the variance of which accounts for the between-child variability) and is perturbed over time by measurement error and lability in lens thickness (leading to within-child variability).

To choose the shape of the growth curve, we fit a nested series of polynomials ranging from 0 (representing no trend in lens thickness with age) to 4 (representing a quartic trend). We compared their goodness of fit by likelihood ratio tests and found that the cubic model fit better than the quadratic \((P<0.001)\), whereas the quartic did not produce a significant improvement in fit \((P = 0.41)\).

We repeated our analysis for the 530 subjects with at least three measurements and obtained a cubic growth curve nearly indistinguishable from that presented in Figure 1, confirming that the observed trend was not the result of a cohort effect introduced by the inclusion of subjects with fewer than three visits.

To allow us to examine the individual growth curves in relation to the model, Figure 2 presents the observed lens thicknesses from three groups of 20 children randomly selected from the first cohort's first-, third-, and sixth-grade recruitment groups respectively. (Children leave the study after eighth grade; thus, those who enter as sixth graders are followed for 2 years.) Figure 2A shows the decrease in lens thickness experienced by children between 6 and 9 years of age. The child-specific growth curves displayed in Figure 2 appear to follow a common trend subject to a random shift plus noise, confirming that the cubic model underlying the population growth curve in Figure 1 provides a plausible description of the data.
These figures also illustrate that the between-subject variance, estimated as 0.021 under the model, greatly exceeds the within-subject variance, estimated as 0.003.

Figure 3A displays the maximum likelihood estimates of the expected gender-specific cubic growth curves for lens thickness assuming a common covariance structure. These estimates suggest that girls, unlike boys, undergo a small increase in lens thickness beginning at 12 years of age. Figure 3B, however, displays the expected difference in lens thickness between genders at various ages along with a 95% simultaneous confidence band. The confidence bands include 0.0 for all ages, indicating that the trend is not statistically significant. Yet, because the apparent lens thickening among girls occurs in a relatively sparse portion of our data, this trend may warrant reexamination as we accrue additional longitudinal data for these ages or in other studies of adolescents.

Figure 4 explores the relationship between crystalline lens thickness and cycloplegic refractive error in the eye’s vertical meridian. Persons with myopia have at least −0.75 D of refractive error in the vertical meridian, those with emmetropia have between −0.75 D and +1.00 D in the vertical meridian, and those with hyperopia have at least +1.00 D of refractive error in the vertical meridian. In general, for all persons older than 7 years of age, those with myopia tend to have thinner crystalline lenses than those with emmetropia and hyperopia.

We tested the significance of these trends using a mixed model analysis of covariance with fixed effects terms to distinguish persons with myopia and hyperopia from those with emmetropia. We found a statistically significant difference in lens thickness between persons with myopia and emmetropia (P = 0.001) but not between those with hyperopia and emmetropia (P = 0.63). For example, the model estimates the average lens thickness for 10-year-old children with myopia to be 0.029 mm less than for children of the same age with emmetropia (standard error = 0.009).

**DISCUSSION**

We have confirmed previous cross-sectional evidence of crystalline lens thinning during childhood with the first reported longitudinal evidence. Our results suggest that the lens thins from ages 6 to 10 years, then maintains its thickness through age 14 years.

It is unlikely that the observed lens thinning is an...
FIGURE 3. (A) The cubic growth curves for boys and girls assuming a common compound symmetry covariance structure. (B) The solid line represents the expected female−male difference in growth curves under this model. The dotted and dashed pair of lines represents the 95% simultaneous confidence bands for this difference. The dotted line is plotted at a difference of 0.0 for reference.

artifact of age differences either in ultrasound velocity in the crystalline lens or in residual accommodation under cycloplegia. Every 50 m/second error in the assumed velocity of ultrasound in the crystalline lens produces a 0.1 mm error in lens thickness estimates. The decrease in expected lens thickness under our model from 3.61 mm at age 6 years to 3.42 mm at age 10 years—nearly 0.20 mm—therefore requires an increase in ultrasound velocity of 100 m/second. This degree of change over 2 years of childhood is highly unlikely given that even adult, cataractous lenses do not differ in ultrasound wave velocity by that amount when compared to normal adult lenses.

It has been suggested that adjustments to lens thickness measurements by ultrasonography must be made to produce agreement with results from Scheimpflug photography of the anterior segment. Such adjustments are suggested based on the underlying premise that the Scheimpflug technique is superior to ultrasonography and requires fewer assumptions. Data from Koretz et al are too limited to confirm any premise of superior repeatability or validity of Scheimpflug photography compared to ultrasonography; moreover, their acoustic velocity correction factor is −2.8 m/second per year, which is physiologically unlikely and not supported by in vitro measures in normal or cataractous lenses. In addition, other data from Scheimpflug photography yield extraordinarily flat anterior and posterior crystalline lens curvatures, inconsistent with those from phakometry.

Similarly, every diopter of excess accommodation produces only a 0.06-mm increase in lens thickness. The observed 0.20-mm decrease in lens thickness requires 3.33 D of excess residual accommodation at age 6 years compared to age 10 years, which also is highly unlikely given the tropicamide cycloplegia dosage used in this study.

The association between refractive error and crystalline lens thickness is in the correlation of thinner lenses with myopic, presumably larger, eyes. Similar results were reported in a study of adults that compared adult-onset myopia with emmetropia. These results are consistent with the theory that emmetropization occurs through compensation by the anterior segment for the 1 mm of axial elongation during the elementary school years. If not compensated for, this amount of eye growth results in an average development of −2.50 D of myopia across the population. The crystalline lens is the more likely component to play a role in emmetropization because the cornea does not display dioptric changes of this magnitude during childhood.

If one were to envision a mechanism of emmetropization that includes thinning of the crystalline lens, it would be pictured as overall growth in axial and equatorial directions of the eye. In this model, lens thinning during the childhood period of coordinated ocular growth could be produced by equatorial ocular growth that results in crystalline lens stretching in the equatorial direction. Concurrent flattening of lens surface radii of curvature and reduction in lens...
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FIGURE 4. Age-specific sets of boxplots for lens thickness categorized by current refractive error status. M = myopia (at least −0.75 D); E = emmetropia (between −0.75 D and +1.00 D); H = hyperopia (at least +1.00 D). For each group of subjects, the shaded bar represents the interquartile range (connecting the 25th and 75th percentiles), whereas the white box within the bar represents the median. The dotted lines extend 1.5 times the length of the interquartile range or, if closer, to the most extreme observation; points beyond this range are represented by horizontal dashes.

power known to occur during this time could also result from this stretching.3,14 Even though lens growth occurs during this period, equatorial stretch may result in marked lens thinning between 6 and 10 years of age and may prevent axial lens thickening beyond 10 years of age.

The matching of axial and focal lengths to produce emmetropia across species29,30 and evidence of increased frequency of myopia and higher refractive error variability when normal visual input is disrupted31,32 have prompted others to assume that eye growth and the process of emmetropization are controlled by visually guided feedback loops.28,33 Detailed models of feedback loops have been proposed based on the apparent tuning of refractive error to applied spectacle lenses in young chickens.33 We propose a mechanical model in which the connection between globe axis, equator, and crystalline lens forms a simple, mechanical feedback loop that may obviate the need for more complex models involving neuronal pathways or accommodation to explain the process of emmetropization.

This model points to the crystalline lens as the primary agent of anterior segment optical power reduction that compensates for axial elongation. In persons with emmetropia, this reduction of crystalline lens power and increase of the eye’s focal length, in concert with the eye’s increasing axial length, is perfectly coordinated to produce no net error. In persons with myopia, who have excess axial elongation, the crystalline lens presumably lacks sufficient ability to make compensating power changes. The thinner crystalline lenses seen in persons with myopia may have reached some physical limit, possibly because of restrictions in the lens fibers themselves, excessively flat lens geometry, weak zonular tension, or anatomic lim-
its on equatorial expansion from the extracranial muscles or the orbit itself. As the eye destined for myopia continues to grow and axial length starts to exceed focal length, the crystalline lens is unable to thin further or to decrease its power further. Alternatively, before the onset of myopia, the premyopic eye may have a thinner crystalline lens that undergoes lens thinning at a rate similar to that of emmetropic and hyperopic eyes. Although our longitudinal data on incident myopia are insufficient to distinguish between these two models, our initial cross-sectional data did not reveal differential lens thickness between eyes with a positive family history of myopia, even though these eyes had less hyperopia and deeper anterior and vitreous chambers. 

Understanding the role of the crystalline lens in ocular development during childhood is central to understanding how emmetropization occurs. Determining why the crystalline lens responds to ocular growth in some individuals—and what limits its response in others—should be a key element in understanding the process of emmetropization and the development of myopia and in predicting when a child is at risk for myopia.

Key Words

crystalline lens, emmetropization, lens, lens thinning, myopia

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