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ORIGINAL ARTICLE

Ciliary Muscle Thickness in Anisometropia

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ABSTRACT

Purpose. The purpose of this study was to investigate the relationships between ciliary muscle thickness (CMT), refractive error, and axial length both across subjects and between the more and less myopic eyes of adults with anisometropia.

Methods. Both eyes of 29 adult subjects with at least 1.00 D of anisometropia were measured. Ciliary muscle thickness was measured at the maximum thickness (CMTMAX) and at 1.0 (CMT1), 2.0 (CMT2), and 3.0 mm (CMT3) posterior to the scleral spur, and also at the apical region (Apical CMTMAX = CMTMAX − CMT2, and Apical CMT1 = CMT1 − CMT2). Multilevel regression models were used to determine the relationship between the various CMT measures and cycloplegic refractive error or axial length, and to assess whether there are CMT differences between the more and less myopic eyes of an anisometropic adult.

Results. CMTMAX, CMT1, CMT2, and CMT3 were negatively associated with mean refractive error (all $p \leq 0.03$), and the strongest association was in the posterior region (CMT2 and CMT3). Apical CMTMAX and Apical CMT1, however, were positively associated with mean refractive error (both $p < 0.0001$) across subjects. Within a subject, i.e., comparing the two anisometropic eyes, there was no statistically significant difference in CMT in any region.

Conclusions. Similar to previous studies, across anisometropic subjects, a thicker posterior region of the ciliary muscle (CMT2 and CMT3) was associated with increased myopic refractive error. Conversely, shorter, more hyperopic eyes tended to have thicker anterior, apical fiber portions of their ciliary muscle (Apical CMTMAX and Apical CMT1). There was no difference between the two eyes for any CMT measurement, indicating that in anisometropia, an eye can grow longer and more myopic than its fellow eye without resulting in an increase in CMT.

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Key Words: myopia, ciliary muscle, refractive error, eye growth, anisometropia, hyperopia

Although there is not a large body of literature on the topic, several studies have evaluated the relationship between ciliary muscle thickness and refractive error or axial length. In 1961, van-Alphen used in vitro globe expansion experiments to predict that the ciliary muscle would thin with an expansion of the globe.[1] Conversely, Oliveira and co-workers (2005) used ultrasound biomicroscopy to show that ciliary muscle thickness was greater in adults with myopic/longer eyes.[2] This result has since been replicated in children in our laboratory.[3] In addition, a study of adult subjects with unilateral high axial myopia found a thicker ciliary body in the more myopic eye of most subjects.[4] The nature and significance of this relationship, however, is unknown. It is possible, for instance, that longer eyes simply have larger ciliary muscles, much in the same way that a tall man has much larger biceps than a toddler. Oliveira and coworkers (2005) alluded to this when they suggested that the major association was between ciliary muscle thickness and axial length, not refractive error. If a thicker posterior ciliary muscle is only a feature of a larger eye, this would suggest that the relationship is of little clinical significance. If, however, there are some circumstances where the posterior ciliary muscle does not become larger with increasing myopia, then the presence or absences of thickness differences may point to different mechanisms of eye growth.

In the present study, we tested for differences in ciliary muscle thickness and refractive error or axial length between eyes within subjects with moderate, axial anisometropia. In general, refractive error varies little between the two eyes of a person. When the refractive error of one eye does differ from that of the other, the person is said to have anisometropia. Estimates for the prevalence of anisometropia with ≥1.00 D difference between eyes range from just under 20% in a German/Austrian population of refractive surgery candidates[5] to just under 7% in a population of Iranian nationals.[6] The wide range may depend in part on the fact that the definition of anisometropia, i.e., comparing sphere versus spherical equivalent, varies from study to study. In the German/

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Austrian sample, the majority of anisometropic subjects had only a mild amount of anisometropia (1.00 to 2.00 D) and the prevalence of anisometropia ≥3.00 D in the sample was only 1.4%.[5] Reports of the prevalence of anisometropia ≥1.00 D among children in the United States are generally in the range of 2.0%.[7,8] The literature generally agrees, however, that a difference of at least 1.00 D between the eyes is required to be classified as anisometropia, which guided our recruitment criteria for this study. Utilizing an anisometropic study population allowed us to filter out the possibility that the overall size of a person could influence his/her axial length and thus his/her ciliary muscle thickness. Genetics has long been implicated as the predominant risk factor for myopic development,[9] so comparing the two eyes within with anisometropia allowed us to compare eyes with different refractive errors without the confounding factors that would otherwise impact comparisons across subjects, such as genetic makeup.

In addition to studying the general thickness of the ciliary muscle, which can be thought of as a measurement of the abundance of muscle fibers at a particular measurement location, we also considered the muscle fiber composition. The composition of the ciliary muscle is not homogenous. The smooth muscle bundles throughout the ciliary muscle run in three different orientations: an outer longitudinal portion, an intermediate radial portion, and an inner circular portion. These portions are not distinct but rather form a functional syncytium that rearranges to effect the changes in ciliary muscle shape and position seen during accommodation.[10] It is impossible to determine which fiber types we are evaluating in vivo, but we attempted to do so by considering two separate regions of the muscle: the apical fiber region of the muscle, which should be predominantly circular with some radial fibers, and the posterior fiber region, which should be predominantly longitudinal fibers. We have also considered the various regions of the ciliary muscle in another study in children from our laboratory.[11]

In summary, we studied the relationship between ciliary muscle thickness, refractive error, and axial length across anisometropic subjects. In addition, we compared the two eyes within an anisometropic subject to determine if differences exist in ciliary muscle thickness between the two eyes. Comparisons made between the two eyes of anisometropic subjects reduce the potential influence of genetic and environmental factors, which differ between individuals, and simulate temporal eye growth.

METHODS

Subjects

Subjects were recruited via study advertisements including emails to faculty, staff, and students at The Ohio State University (OSU) College of Optometry, letters sent to patients of OSU Optometry Services who had a code of anisometropia in the computerized patient records, and also through flyers emailed to offices of local eye care practitioners and placed in the Optometry Services and the OSU Student Health Center.

Thirty subjects, 23 of whom were female (77%), with at least 1.00 D difference between the two eyes in the spherical component of their habitual refractive error correction were recruited to participate in the study. The spherical component was chosen, rather than spherical equivalent, in an effort to make it easier to recruit subjects with axial anisometropia, rather that anisometropia that was due to more corneal cylinder in one eye, as most potential subjects would not know their axial length measurements. For all subjects who were enrolled, anisometropia was at least partly axial in nature, i.e., the more myopic eye was always longer, was naturally occurring, and was not due to previous surgeries or injuries of any kind. The mean ± SD age was 28.2 ± 5.6 years (range: 21.1 to 40.8 years). Of the 30 subjects, six subjects were Asian, one subject was African American, 23 subjects were Caucasian, and one Caucasian subject also reported that he/she was Hispanic.

Subjects were included within the ages of 18 and 40 years so that they were old enough to have completed the juvenile period of emmetropization and/or refractive error development, but young enough to ensure that the ciliary muscle dimensions had not changed due to advancing age.[12] After cycloplegia, one subject was found to have only 0.40 D of anisometropia and was excluded from subsequent analyses, although the relationships between ciliary muscle thickness, refractive error, and axial length were the same with or without his/her inclusion. Of these remaining 29 subjects, one subject was emmetropic in one eye and hyperopic in the other eye, five subjects were hyperopic in both eyes, and 23 subjects were myopic in both eyes. Exclusion criteria were amblyopia, mental disability that would prevent the subject from completing the testing protocol, previous ocular surgery of any kind, the use of any ocular medications that would affect the ciliary muscle, or pregnancy by self-report. For the purposes of this study, amblyopia was defined as best-corrected visual acuity of worse than 20/40 in either eye as measured using a high-contrast logMAR chart at 4 m under normal room illumination with habitual correction. Although the sample did include four subjects with visual acuity of 20/32 in one eye, the analyses were essentially identical with and without their inclusion, so we have included all 29 subjects in the reported analyses. Written informed consent was obtained from each subject. The study was approved by the Institutional Review Board of The Ohio State University and adhered to the tenets of the Declaration of Helsinki.

Cycloplegia and Measurement Procedures

All measurements were made on both eyes. Cycloplegia was achieved by instilling one drop of 0.5% proparacaine followed by two drops of 1% tropicamide spaced 5 minutes apart. Cycloplegic measurements were made 25 minutes after the second drop of tropicamide. This cycloplegic agent was chosen because it has been previously shown to control accommodation effectively during the measurement of refractive error and other ocular components, but it does not completely eliminate accommodation,[13,14] preserving the natural tonus of the ciliary muscle.

Refractive Error Measurements

Cycloplegic, spherical equivalent refractive error in each eye was obtained from the mean of ten readings with the Grand Seiko WV-500 (Grand Seiko Co., Hiroshima, Japan) autorefractor. One eye was occluded while the other eye was measured. A Badal optometer system was used to place a row of letters that served as a fixation target at a distance that allowed a clear view of the letters for each subject.

Axial Length Measurements

Axial length (AL) measurements were made using the Zeiss IOL Master. Five consecutive measurements were taken on each eye and the mean of these five measurements was used as the axial length measurement for each eye. Measurements were limited to those with a signal to noise ratio >2.0 to ensure only high confidence measurements were recorded.

Ciliary Muscle Thickness Measurements

Images of the nasal ciliary muscle of each eye were obtained with the Zeiss Visante Anterior Segment OCT under cycloplegia as previously described.[15] Briefly, four images were obtained on the nasal ciliary muscle of each eye in the Enhanced High Resolution Corneal Mode. Subjects viewed a target that was placed on the outside of the machine in the subject's lateral gaze.[15] Subjects were encouraged to turn their heads slightly towards the target. Radial ciliary muscle thickness measurements were made in the anterior region of the muscle, at the point of maximum ciliary muscle thickness (CMTMAX) and at 1.0 mm (CMT1) posterior to the scleral spur, and in the posterior region of the muscle, at 2.0 mm (CMT2), and 3.0 mm (CMT3) posterior to the scleral spur using a semiautomatic extraction algorithm as described previously by Kao et al (2011).[15] Fig. 1 is a representative image showing these measurements. To parse out the apical portion of the ciliary muscle, i.e., the portion that represented mostly circular and some radial fibers, we subtracted the thickness of CMT2 from the thickness of CMT1 and CMTMAX.

$$\text{Apical fibers at CMTMAX} = \text{CMTMAX} - \text{CMT2}$$

$$\text{Apical fibers at CMT1} = \text{CMT1} - \text{CMT2}$$

The algorithm has been shown to provide both repeatable and valid measurements of the ciliary muscle.[15]

Statistical Analyses

Across-Subject Relationships Between CMT and Refractive Error or Axial Length

While one of the goals for this study was to compare the shorter/more hyperopic eye to the longer/more myopic eye within a person, some of our analyses also sought to make comparisons across all subjects. Multilevel linear regression models were used to model CMT as functions of mean spherical equivalent refractive error or mean axial length. In these models, the means of the right and left eye measurements were used. Age and gender were included in the models as covariates. The across-subject model had the form:

$$Outcome_{ij} = A + B^{*}SPHEQ_{\text{ij}}\,(or\ AL_{\text{ij}}) + C^{*}\text{Female} + \text{D} * Age_i + u_i + \varepsilon_{ij}$$

In the model, i indexes the subject and j is his/her measure taken from eye j. The u term is a random effect that corrects the intercept (A) for between-subject variation in CMT variation. It is needed to account for repeated within-subject measures of the outcome (one from each eye). For all models, age was centered at 28.2 years, mean spherical equivalent refractive error was centered at −2.56 D, and mean axial length was centered at 24.54 mm. Each CMT location (CMTMAX, CMT1, CMT2, CMT3, and Apical CMTMAX and Apical CMT1) was an outcome in its own model.

Within-Subject Relationship Between CMT and More Myopic Eye

Paired t tests of differences between the more and less myopic eyes were performed for all CMT values (CMTMAX, CMT1, CMT2, CMT3, and Apical CMTMAX and Apical CMT1). Pearson's correlation coefficients were also used to determine if

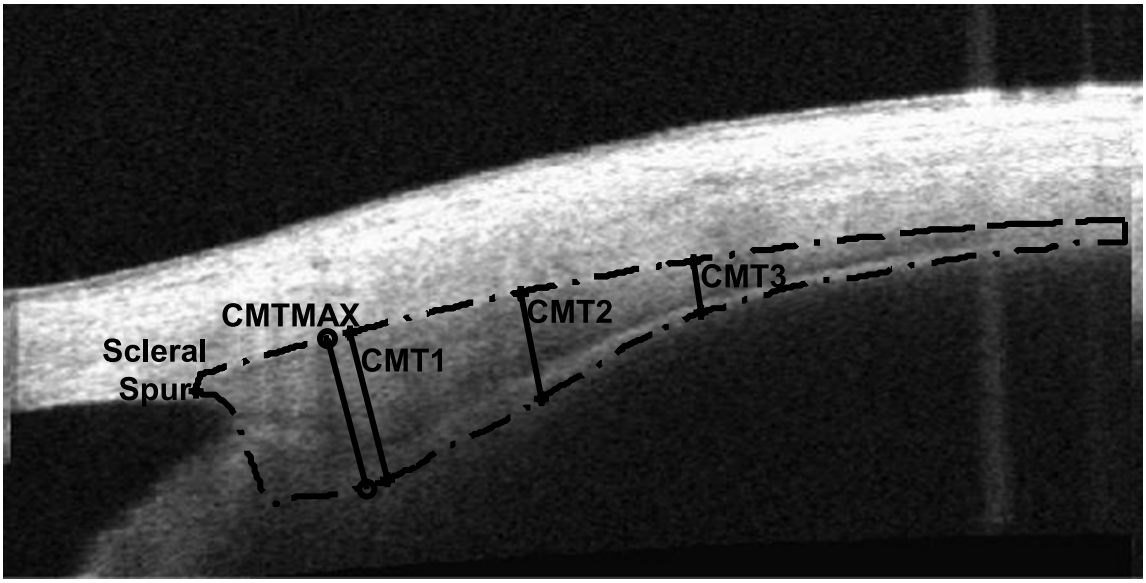

FIGURE 1.

Representative Visante image of the nasal ciliary body while the subject views an external fixation target. The thickness measurements 1 mm (CMT1), 2 mm (CMT2), and 3 mm (CMT3) posterior to the scleral spur are shown. The maximum thickness of the ciliary body (CMTMAX) is also shown.

TABLE 1.

Summary statistics describing the characteristics and ocular components of the study subjects

	Mean	Standard deviation	Minimum	Maximum
Age, yr	28.2	5.6	21.1	40.8
Spherical equivalent refractive error, D*	−2.56	3.29	−8.40	5.84
Axial length, mm*	24.54	1.34	21.36	26.51
Anisometropia, D†	1.85	1.24	0.75	6.57
CMTMAX, μm*	855.30	76.56	640.00	1003.75
CMT1, μm*	826.51	77.29	586.25	963.75
CMT2, μm*	598.56	100.66	306.25	801.25
CMT3, μm*	348.62	84.53	156.25	475.00

*Both eyes of all subjects were included in the summary statistics.

†The difference between a subject's two eyes for the spherical component of the cycloplegic autorefraction.

CMT indicates ciliary muscle thickness at 1 mm (CMT1), 2 mm (CMT2), and 3 mm (CMT3) posterior to the scleral spur or at point of maximum thickness (MAX).

there was a relationship between the magnitude of the within-subject difference in refractive error or axial length and each of the CMT measurement locations. Finally, the multilevel regression model (across-subject model) described in the previous section was also used to assess whether there were within-subject differences between the more and less myopic eyes. As with the previous model, the outcome was the CMT measure, and the predictors SPHEQ and AL were the average of a subject's two values. The within-subjects model added an additional predictor, i.e., an indicator of the more myopic eye. The indicator was coded 0 for the CMT value associated with a subject's less myopic eye and 1 for the CMT value associated with a subject's more myopic eye.

RESULTS

General characteristics of the study sample are displayed in Table 1. The mean ± SD spherical equivalent refractive error was −2.56 ± 3.29 D (range: −8.40 to +5.84 D). The overall refractive error for the anisometropic subjects recruited for this study ranged from highly hyperopic to highly myopic. Although the inclusion criteria stated that all subjects must have habitual anisometropia of at least 1.00 D, several had slightly less than this amount after cycloplegia (Table 1). In all subjects, the more myopic eye was also the longer eye.

Across-Subject Relationship Between CMT and Refractive Error and Axial Length

We recognized at the outset of this study that the cause of one eye becoming more myopic than the other within an anisometropic person may not be the same as that which causes a person to become myopic as a whole. Thus, we began by looking at relationships across subjects, rather than within a subject, to determine if the previously reported relationships between CMT and refractive error and axial length[2–4] were present across anisometropes. There was a statistically significant, negative association between the mean cycloplegic refractive error and the mean measurements of CMT from the anterior (CMTMAX and CMT1) and posterior (CMT2 and CMT3) regions of the ciliary muscle (all p values ≤0.03, Table 2, columns 2–5).The strong negative association between all measures of anterior and posterior CMT values and mean refractive error meant that subjects with a more negative, or more myopic, mean refractive error tended to have thicker ciliary muscles than subjects with a more positive, or more hyperopic, mean refractive error (Fig. 2). The greatest negative association was between CMT2 and mean refractive error (slope = −22.42, $p < 0.0001$). Multilevel regression models were also fitted for the relationship between CMTMAX, CMT1, CMT2, and CMT3 and axial length, and the results were nearly identical to what was found with refractive error except that, as one would expect, the direction of the association was positive (data not shown). After this evaluation of the data on a subject level, we were encouraged that our sample of anisometropes showed the same relationships between ciliary muscle thickness and both refractive error and axial length that the previous studies showed across individuals.[2–4]

TABLE 2.

An evaluation across subjects with anisometropia of the relationship between refractive error and ciliary muscle thickness using multilevel regression models

	Anterior region		Posterior region		Apical region	
Predictor	CMTMAX	CMT1	CMT2	CMT3	Apical CMTMAX	Apical CMT1
Intercept	858.81	828.91	588.38	331.06	270.43	240.54
Refractive error, D*	−9.51 (p = 0.03)	−11.22 (p = 0.01)	−22.42 (p < 0.0001)	−17.58 (p < 0.0001)	12.91 (p < 0.0001)	11.2 (p < 0.0001)
Age, yr†	1.67 (p = 0.5)	1.53 (p = 0.5)	−1.03 (p = 0.7)	−0.13 (p = 0.95)	2.7 (p = 0.09)	2.56 (p = 0.07)
Gender‡	0.39 (p = 0.99)	2.78 (p = 0.93)	25.7 (p = 0.5)	32.01 (p = 0.3)	−25.31 (p = 0.2)	−22.92 (p = 0.2)

*Centered at −2.56 D.

†Centered at 28.2 years.

‡Reference is male.

CMT indicates ciliary muscle thickness at 1 mm (CMT1), 2 mm (CMT2), and 3 mm (CMT3) posterior to the scleral spur or at point of maximum thickness (MAX); Apical CMT, thickness of the apical ciliary muscle fibers at the point of maximum thickness (Apical CMTMAX = CMTMAX − CMT2) and at 1 mm posterior to the scleral spur (Apical CMT1 = CMT1 − CMT2).

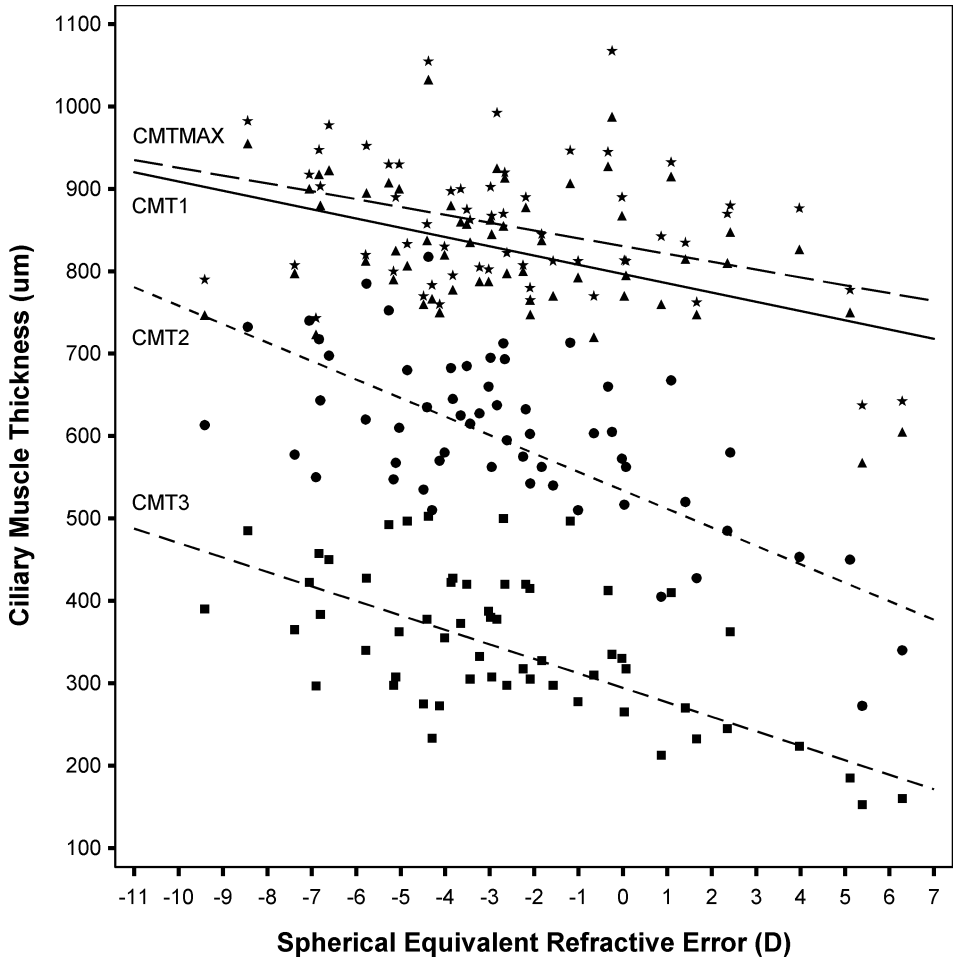

FIGURE 2.

The plotted points are observed measures of ciliary muscle thickness plotted against the corresponding spherical equivalent refractive error. The mean measurement for each subject is shown. The curves are modeled projections for a typical subject based on the models presented in Table 2.

Across-Subject Relationship Between the Apical Fibers at CMTMAX and CMT1 and Refractive Error and Axial Length

Table 2 (columns 6 and 7) shows the multilevel linear regression model results for the apical fibers at CMT1 and CMTMAX. When compared to the results for CMT above, refractive error was associated with the thickness of the apical fibers at CMTMAX and CMT1 in the opposite direction. The apical fibers at CMTMAX and CMT1 were associated with mean refractive error in a positive manner; i.e., subjects with a more hyperopic mean refractive error had thicker apical fibers at CMTMAX and CMT1, while the subjects with a more myopic mean refractive error tended to have thinner apical fibers CMTMAX and CMT1 (Fig. 3). A similar reversal of the trend was found for axial length (data not shown).

Within-Subject Relationship Between CMT and More Myopic Eye

Table 3 shows the results of paired *t* tests to measure any difference in CMT, refractive error, and axial length between the two eyes of an anisometropic subject. Not surprisingly, there was a significant difference in refractive error and axial length between the two eyes, i.e., these were patients with anisometropia. There were no statistically significant differences between eyes in ciliary muscle thickness at any location tested.

Table 4 shows the results of Pearson's correlations for the relationship between the within-subject difference in refractive error and the within-subject difference in each of the CMT measurement locations. None of the correlations were statistically significant in this sample of patients with anisometropia, indicating that the magnitude of the difference in refractive error between the two eyes was not significantly related to the magnitude of the difference in any CMT measurement location. Identical Pearson's correlations for the relationship between the within-subject difference in axial length and the within-subject difference in each of the CMT measurement locations were also calculated. None of the axial length correlations were statistically significant either. The magnitude of the axial length correlations was similar to what is reported in Table 4 for refractive error and the sign was opposite in direction (data not shown).

In multilevel regression analyses that compared the two eyes within anisometropic subjects, for all locations, there were no detectable differences in the ciliary muscle thickness of the more myopic eye (Table 5, columns 2–5). The same relationship also held true when axial length and an indicator for the longer eye

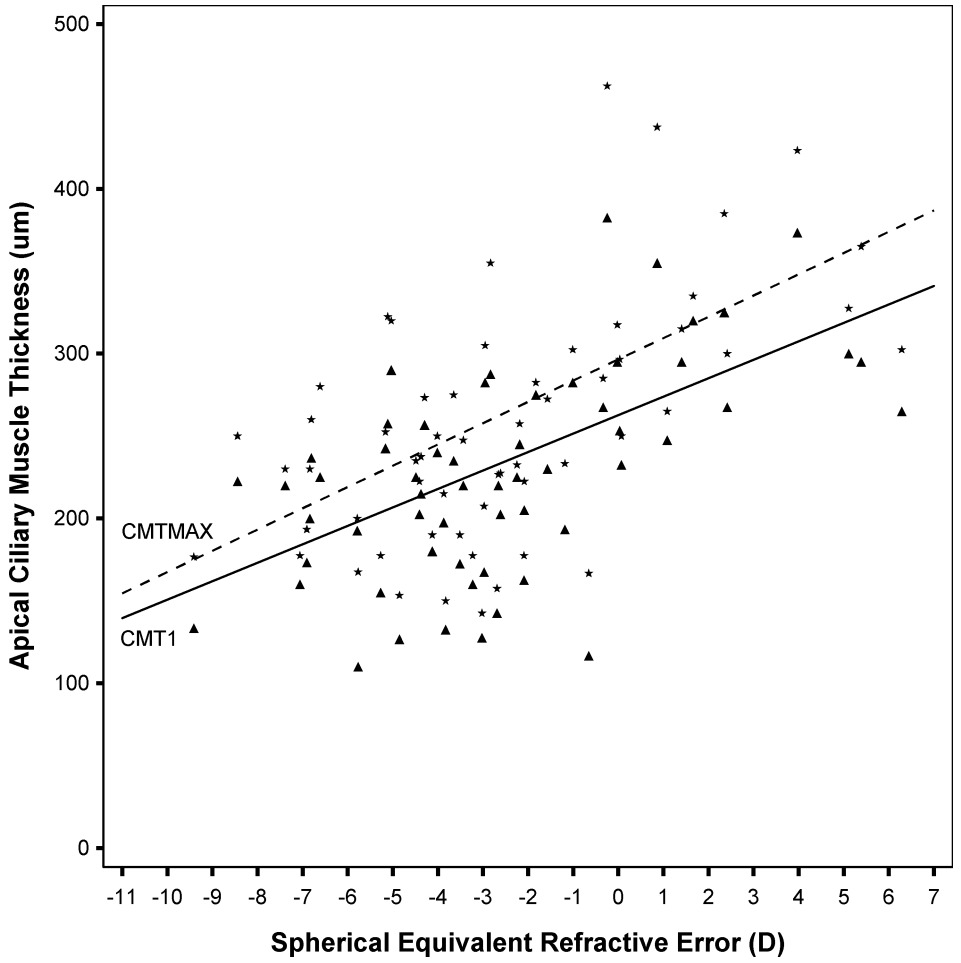

FIGURE 3.

Apical fibers at CMTMAX and the apical fibers at CMT1 are plotted against the mean spherical equivalent refractive error for each subject. The mean measurement for each subject is shown. The curves are modeled projections for a typical subject based on the models presented in Table 2.

were both included in the statistical model; the multilevel regression analyses showed a significant positive correlation between ciliary muscle thickness and axial length, but within a subject, the ciliary muscle thickness of the longer eye was not different from the shorter eye (data not shown). The results did not even trend toward a thicker ciliary muscle in the longer, more myopic eye of the person. In fact, the trend was in the opposite direction, i.e., if there had been a statistically significant relationship, the longer, more myopic eye within a person would have had a thinner ciliary muscle than its fellow eye (Table 5).

TABLE 3.

Paired *t* tests of the hypothesis that the mean difference between the two anisometropic eyes is zero

Variable	Mean*	Standard deviation	95% Confidence interval	p
Spherical equivalent refractive error, D	1.72	1.14	(1.29, 2.16)	<0.0001
Axial length, mm	−0.74	0.52	(−0.94, −0.54)	<0.0001
Apical CMTMAX, μm	5.58	76.55	(−23.57, 34.66)	0.7
Apical CMT1, μm	5.20	66.19	(−19.98, 30.38)	0.7
CMTMAX, μm	13.08	71.93	(−14.29, 40.44)	0.3
CMT1, μm	12.73	58.64	(−9.58, 35.04)	0.3
CMT2, μm	7.53	51.40	(−12.02, 27.08)	0.4
CMT3, μm	5.35	50.00	(−13.67, 24.36)	0.6

CMT indicates ciliary muscle thickness at 1 mm (CMT1), 2 mm (CMT2), and 3 mm (CMT3) posterior to the scleral spur or at point of maximum thickness (MAX).

*The more myopic eye was subtracted from the less myopic eye. A positive CMT value will indicate that the more myopic eye was thinner, if statistically significant.

TABLE 4.

Correlations between the within-subject difference in the various measurements of ciliary muscle thickness and the within-subject difference in refractive error*

Correlation with refractive error		r	p
Anterior region	CMTMAX	0.15	0.4
	CMT1	0.23	0.2
Posterior region	CMT2	−0.09	0.6
	CMT3	−0.02	0.9
Apical region	Apical CMTMAX	0.20	0.3
	Apical CMT1	0.28	0.1

*The more myopic eye was subtracted from the less myopic eye.

CMT indicates ciliary muscle thickness at 1 mm (CMT1), 2 mm (CMT2), and 3 mm (CMT3) posterior to the scleral spur or at point of maximum thickness (MAX).

Within-Subject Relationship Between the Apical Fibers at CMTMAX and CMT1 and the More Myopic Eye

The above analyses showed that the apical fibers at CMTMAX and CMT1 are positively correlated with mean refractive error of a subject and negatively correlated with mean axial length of a subject. Next, we examined the relationship between the apical fibers at CMTMAX and CMT1 and the more myopic eye. Table 5 shows the results of these multilevel linear regression models. The apical fibers at CMTMAX and CMT1 were not thinner or thicker in the more myopic eye (Table 5, columns 6 and 7) or the longer eye (data not shown) of an anisometropic person.

DISCUSSION

This sample of anisometropic subjects behaved in accordance with the literature[2–4] in that subjects with longer, more myopic eyes (when taken as an average of the two eyes) tended to have thicker ciliary muscles. This was what we expected to find and confirmed that anisometropic subjects do not follow a different trend from the rest of the population.

When we analyzed the apical fibers separately from the rest of the ciliary muscle, however, we found a surprising reversal of the trend noted above. When the apical fibers at CMTMAX and CMT1 were isolated from the rest of the muscle, we found that subjects with longer or more myopic eyes tended to have thinner ciliary muscles in the apical region. The significance of this is profound; it shows that although ciliary muscle thickness tends to increase with increasingly myopic refractive error or increasingly longer axial length, the trend reverses when the posterior, longitudinal fibers are factored out. This may suggest that longer, more myopic eyes have thicker longitudinal fiber portions of their ciliary muscles, while shorter, more hyperopic eyes have thicker circular/radial fiber portions of their ciliary muscles. Interestingly, we have found this same result in two other samples: a longitudinal study in children[11] and a sample of young adults (manuscript in preparation). Together, all three of these studies provide evidence that the apical fibers of the ciliary muscle may be impacted by workload and thicken with the increased accommodative demands experienced with uncorrected hyperopia.

Aside from confirming the relationship between ciliary muscle thickness and refractive error, we also sought to determine if there were any circumstances under which an increase in axial length *did not* result in an increase in ciliary muscle thickness, i.e., bigger eyes may just have bigger ciliary muscles without a causal or clinically meaningful relationship existing between the two parameters. The present study found no evidence that, in an anisometropic subject, the ciliary muscle thickness of the longer, more myopic eye is significantly different from that of the shorter, more hyperopic eye. Nor was the magnitude of the interocular difference in refractive error correlated with the interocular difference in any ciliary muscle thickness location. Although we have not ever compared the two eyes of patients with similar refractive errors, we suspect that the magnitude of the difference in ciliary

TABLE 5.

A comparison between the two eyes of subjects with anisometropia: a multilevel regression model for the relationship between ciliary muscle thickness and spherical equivalent refractive error

	Anterior region		Posterior region		Apical region	
Predictor	CMTMAX	CMT1	CMT2	CMT3	Apical CMTMAX	Apical CMT1
Intercept	808.28	767.95	457.62	228.25	350.66	310.33
Refractive error, D*	−9.51 (p = 0.03)	−11.22 (p = 0.01)	−22.42 (p < 0.0001)	−17.58 (p < 0.0001)	12.91 (p ≤ 0.0001)	11.20 (p ≤ 0.0001)
More myopic eye*	−13.07 (p = 0.3)	−12.73 (p = 0.3)	−7.53 (p =0.4)	−5.34 (p = 0.6)	−5.55 (p = 0.7)	−5.20 (p = 0.7)
Age, yr†	1.67 (p = 0.5)	1.53 (p = 0.5)	−1.03 (p = 0.7)	−0.13 (p = 0.95)	2.70 (p = 0.09)	2.56 (p = 0.07)
Gender‡	0.39 (p = 0.99)	2.78 (p = 0.9)	25.7 (p = 0.5)	32.01 (p = 0.3)	−25.31 (p = 0.2)	−22.92 (p = 0.2)

*Refractive error centered at −2.56. A negative value indicates that the ciliary muscle is thinner in a more myopic eye, if statistically significant.

†Centered at 28.2 years.

‡Reference is male.

CMT indicates ciliary muscle thickness at 1 mm (CMT1), 2 mm (CMT2), and 3 mm (CMT3) posterior to the scleral spur or at point of maximum thickness (MAX); Apical CMT, thickness of the apical ciliary muscle fibers at the point of maximum thickness (Apical CMTMAX = CMTMAX − CMT2) and at 1 mm posterior to the scleral spur (Apical CMT1 = CMT1 − CMT2).

muscle thickness between the two eyes in anisometropia is very similar to what we would find if we compared the two eyes of an isometropic patient.

At least in the case of mild or low levels of anisometropic eye growth, it appears to be possible that an eye can grow bigger without a concomitant increase in ciliary muscle thickness. When we considered the apical ciliary muscle fibers only, we also found no difference between the two eyes. Overall, these data suggest that even though the ciliary muscle is larger in myopia on average, it is possible for axial elongation to occur without a significant increase in ciliary muscle dimensions. We have noted some variability in the thickness of the ciliary muscle across levels of refractive error in our previous studies,[3,11] and we have wondered if this suggested that eye growth does not always result in a thicker ciliary muscle and/or that multiple factors may determine its dimensions. The present study suggests that further investigation into how the ciliary muscle changes during eye growth in a longitudinal study of children is warranted.

The trends for differences between the two eyes in anisometropia were unexpected. The data show that an eye can grow and become more myopic than its fellow eye without resulting in an increase in ciliary muscle thickness. This seemingly does not fit with the aforementioned cross-sectional studies,[2–4] but data from a longitudinal study of ciliary muscle thickness in children performed in our laboratory confirm that the ciliary muscle does not necessarily thicken more with faster versus slower eye growth (Bailey et al., 2010, Annual Meeting of the Association for Research in Vision and Ophthalmology, Abstract 2838). Also, this result is consistent with the findings of van Alphen's (1961) globe expansion studies, where he found in in vitro studies that the ciliary muscle stretched and thinned when the globe was expanded.

The results of the present study are in direct contrast with that of Muftuoglu and co-workers (2009), who found an increase in CMT in the more myopic and longer eye of most, but not all, patients with unilateral high myopia.[4] It is important to note, however, that the subjects in that study had a level of anisometropia that is different from the present study and not normally encountered in the general population. The prevalence of that degree of anisometropia (≥5.00 D) is unknown, but one study estimates that the prevalence of anisometropia ≥3.00 D in a German/Austrian population was only 1.4%.[5] It is possible that the mechanisms regulating eye growth in such a high degree of anisometropia are different from the mechanisms driving eye growth in lower amounts of anisometropia, such as the sample in this study. Perhaps the difference between the study by Muftuoglu and co-workers (2009) and the present study also suggests that the ciliary muscle is sometimes, but not always, a feature of myopia. In fact, this is consistent with the findings of Muftuoglu and co-workers (2009), who reported that there was "no or little difference in some subjects."

It is important to consider the limitations of the present study. The use of anisometropic subjects, while one of the strengths of the study, is also a limitation in that we cannot rule out the possibility that whatever caused one eye to grow longer than the other within a single subject is not, in fact, the same mechanism of myopic eye growth seen in the population at large. We also made some overriding assumptions regarding the composition of ciliary muscle fiber types at differing locations in the muscle. To truly verify these assumptions, histological comparison would be ideal.

Another limitation with the present study is its cross-sectional nature. Anisometropic subjects were used to simulate the effect of actual temporal eye growth by reasoning that there was clearly a difference in eye growth at some point between the two eyes that was not related to differences in the genetic and/or environmental background. While studying anisometropic subjects provides useful clues about myopic eye growth, it does not substitute for longitudinal studies that measure ciliary muscle thickness before, during, and after the period of myopic refractive error development. Cross-sectional studies such as the present study can only provide correlations. Thus, longitudinal studies in children are still needed to further investigate the role that ciliary muscle development may play in myopic eye growth.

Our study provided some interesting insights into the possible mechanisms underlying myopic eye growth, i.e., that an eye can grow longer and increase in myopic refractive error with or without an associated increase in ciliary muscle thickness. Others have speculated that when the ciliary muscle does change in myopic eye growth that it could be somehow related to the choroid. Muftuoglu and co-workers (2009) suggested a relationship between the choroid and tension from the zonules and crystalline lens,[4] and Vincent and co-workers (2003) suggested a relationship between the ciliary muscle and the choroid that was based on defocus.[16] Unlike the present study of ciliary muscle thickness, Vincent and co-workers (2003) did find a difference in subfoveal choroidal thickness between the eyes of adults with anisometropia in a study of comparable sample size.[16] In addition to hypotheses related to the choroid, it has also been suggested that the ciliary muscle somehow acts as a physically restrictive force to exacerbate eye growth in the axial direction.[17] Nonetheless, it seems unlikely, given the data presented in this study, that myopic axial elongation is always related to a restrictive force or to changes that occur in the choroid. At a minimum, these data suggest that there may be multiple ways that an eye can elongate in myopia and that myopia can occur with or without changes in ciliary muscle thickness.

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The Ohio State University has filed a non-provisional patent application on the behalf of the authors (MDB and C-YK): U.S. Utility Patent Application No. 13/757,243, filed February 1, 2013, entitled "Detection and measurement of tissue images."

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