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Evaluating relaxed ciliary muscle tone in presbyopic eyes

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Abstract
Purpose Studies of age-related changes in ciliary muscle (CM) morphology and contractility have variously reported that CM weakens or strengthens with age. In response, the aim of this study was to evaluate relaxed CM tone in vivo in pre-presbyopic and presbyopic patients using a predictor value (P_{CM}).
Methods Two groups of eyes—40 eyes of 40 healthy volunteers with a mean age of 28.1 ± 5.8 years and 40 eyes of 40 healthy volunteers with a mean age of 56.6 ± 7.3 years—formed the sample for this prospective, observational cross-sectional study. Used to evaluate relaxed CM tone, P_{CM} was calculated as the difference between the change in mean anterior chamber depth (ACD) and lens thickness (LT) before and after cycloplegia, as measured with swept-source optical biometry.
Results The P_{CM} for relaxed CM tone was 0.04 ± 0.04 mm in pre-presbyopic participants, 0.06 ± 0.03 mm in presbyopic ones, and significantly greater in presbyopic patients ($p = .018$).
Conclusion The statistical significance of P_{CM} between pre-presbyopic and presbyopic eyes might not signify clinical significance, since the difference was close to the repeatability limits for swept-source optical biometry. When relaxed, CM tone does not diminish with presbyopia according to changes in anterior chamber parameters due to cycloplegia.

Keywords Ciliary muscle · Cycloplegia · Presbyopia

Introduction

To accommodate increased optical power, young crystalline lenses can change shape, thereby allowing them to adapt their power to visualize objects at different distances. According to the traditionally accepted Helmholtz's theory of accommodation, the contraction of the ciliary muscle (CM) reduces zonular tension around the lens equator, thereby relaxing the lens. As zonular tension dissipates, the young crystalline lens thickens, and its radius of curvature steepens. When the CM is relaxed, it pulls the lens radially, thereby flattening it [1, 2].

Decreased accommodation becomes a problem for most people in later life, especially when they can no longer see clearly enough to perform tasks requiring nearsightedness. Known as presbyopia, the condition remains an ophthalmic mystery, although several reviews have summarized theories attempting to explain its mechanisms [3–6]. As those reviews show, two classic theories explaining the mechanics of presbyopia have surfaced as the product of longstanding debate [3, 6, 7], and differ with regard to CM involvement and predicted relationships between CM contraction and changes in lens shape. On the one hand, according to Gullstrand's theory, or lenticular theory, developed from concepts first described by Helmholtz in the mid-19th century, presbyopia is caused by the lens's decreased ability to change shape. The theory holds that throughout life, a constant amount of CM contraction is necessary for each diopter of accommodative change. Accordingly, as the amplitude of accommodation reduces due to lenticular changes, an increased proportion of potential CM contraction becomes latent in the fully accommodated eye, insofar as further contraction will not produce any change in accommodation.

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On the other hand, Duane–Fincham's theory, or extralenticular theory, assumes that as the eye ages, the force required to produce a given change in accommodation increases and that the CM will be maximally contracted when the near point is reached. Whereas Duane [8, 9] argued that the CM weakens with age, in agreement with Fisher's [10] later findings, Fincham [11] did not. Studies like Fisher's [12–14] and Glasser and Campbell's [2, 15] suggested that as the eye ages, greater force needs to be exerted on the lens and capsule in order to achieve the same change in accommodation, which led to the Duane–Fincham model as a result.

To understand the dynamic of accommodative behavior, dynamic biomechanical properties of the components of the accommodation mechanism have been identified [16]. Using that biomechanical model, Beers and van der Heijde [17] proposed that changes in the dynamic response are characteristics of a function of age, thereby indicating that changes in the lens's elastic properties are the chief cause of presbyopia.

As recent studies have demonstrated, the most accepted hypothesis for presbyopia is the progressive loss of lens elasticity [15, 18], although changes in the CM [19, 20], choroid [21], and vitreous body [22] probably contribute as well. Researchers have elucidated presbyopia in terms of lenticular changes that reduce lens elasticity [2, 13, 15, 23], whereas others have concluded that, in weakening with age, the CM becomes unable to perform the required release of zonular tension for accommodation [13, 21, 24]. By contrast, Fisher has proposed that the CM strengthens with age in order to produce accommodative changes [10].

In any case, due to the CM's anatomical location, its exact accommodative movement remains difficult to determine. In fact, functional theories of the CM's role in accommodation often draw upon research involving rhesus monkeys [21, 24], in-vitro studies [19], or imaging methods [10, 25–27]. Although imaging techniques do not provide a dynamic in-vivo image, they do provide an opportunity to analyze individual muscle fiber groups for age-related differences and accommodative changes.

Generally, the CM and zonular fibers suspend the lens in its normal position. In contrast to accommodation, cycloplegia, or CM paralysis, results in the backward movement of the crystalline lens and decreased lens thickness (LT). The chief determining factor in decreased LT is lens elasticity, not loss of CM tone. Due to changes in crystalline lens dynamics, anterior chamber depth (ACD) increases [28, 29], meaning that the difference between the change in mean ACD and LT with cycloplegia reflects the contributory effect of CM tone upon ACD. In physiology, relaxed muscle tone refers to continuous, passive, incomplete contraction or the muscle's resistance to passive strength during rest [30].

In response to all of the above, the aim of this study was to evaluate relaxed CM tone in vivo in pre-presbyopic and presbyopic patients using a predictor value (P_{CM}).

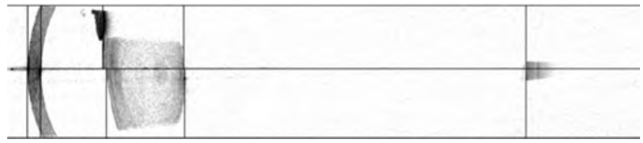

Fig. 1 The entire cross-sectional images generated by the IOLMaster 700 of a participant aged 30 years before (*upper half*) and after cycloplegia (*lower half*) are superimposed. The lower part demonstrates that decrease in lens thickness is more evident than the backward movement of the crystalline lens due to cycloplegia

Methods

Two groups of eyes—40 eyes of 40 healthy volunteers (23 men, 17 women) with a mean age of 28.1 ± 5.8 years (range, 21–38 years) and 40 eyes of 40 healthy volunteers (20 males, 20 females) with a mean age of 56.6 ± 7.3 years (range, 47–62 years)—formed the sample for this prospective, cross-sectional study. The exclusion criteria were spherical equivalent refractive error greater than ±1.0 D, previous ocular surgery, corneal opacities, severe dry eye, history of contact lens wear, retinal disease (e.g., cystoid macular edema or elevated scars), glaucoma, narrow iridocorneal angle, cataract, inability to open eyelids widely, ocular inflammatory disease, and poor ocular fixation. The study was approved by the ethics committee of Muğla University and conducted according to the Declaration of Helsinki. The aim of the study was explained to each patient, and his or her written informed consent was obtained.

To eliminate the effect of diurnal variation, all measurements were taken in room light during the period 9:00–11:00 am. All noncycloplegic and cycloplegic measurements were performed within 1 h on the same day by the same experienced operator and according to the manufacturer's recommendations. Three measurements were acquired using swept-source optical biometry (IOLMaster 700; Carl Zeiss Meditec AG, Jena, Germany) before and after cycloplegia. Quality control criteria were fulfilled in accordance with the manufacturer's recommendations. With the IOLMaster 700, the entire scan image was viewed, and the eye geometry and axis of measurements were visually assessed. Foveal scans confirmed the correct fixation. The entire cross-sectional images generated by the IOLMaster 700 of each participant before and after cycloplegia were

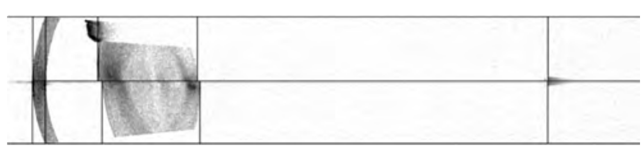

Fig. 2 The entire cross-sectional images generated by the IOLMaster 700 of a participant aged 54 years before (*upper half*) and after cycloplegia (*lower half*) are superimposed. The lower part demonstrates that the backward movement of the crystalline lens is more evident than the decrease in lens thickness due to cycloplegia

Table 1 The mean ACD and LT measurements obtained using swept source optical biometry with and without cycloplegia in pre-presbyopic subjects

Parameter	Noncycloplegia mean ± SD	Cycloplegia mean ± SD	Mean difference ± SD	*P* value*
ACD	3.42 ± 0.37	3.55 ± 0.34	0.13 ± 0.08	<0.001
LT	3.72 ± 0.25	3.63 ± 0.23	0.09 ± 0.04	<0.001

* Dependent samples *t*-test, *p* value for comparison of parameters in noncycloplegia and cycloplegia states

ACD, anterior chamber depth; LT, lens thickness

superimposed in consideration of the locations of corneas and foveas. The proper images were subsequently recorded for analysis (Figs. 1 and 2).

To create an optically smooth tear film over the cornea, participants were asked to blink immediately before measurements were taken. Cycloplegia was induced by administering three drops of an eye solution containing 1% cyclopentolate every 5 min. After cycloplegia, pupillary light reflex was assessed, and about 45 min later, measurements were taken. LT and ACD measurements were recorded before and after pupil dilation.

The P_{CM} used to evaluate relaxed CM tone was formulated as the difference between the change in mean ACD and LT before and after cycloplegia, as follows:

$$P_{CM} = \Delta ACD - \Delta LT$$

P_{CM} = Predictor value of relaxed CM tone

ΔACD = Change in mean ACD after cycloplegia

ΔLT = Change in mean LT after cycloplegia

Statistical analysis

The Statistical Package for the Social Sciences version 18.0 was used for statistical analysis. Normality was analyzed with Kolmogorov–Smirnov's test, and Levene's test was used for equality of variances. After acquiring normal distribution and equality of variances, changes before and after dilation were evaluated with a dependent samples *t*-test, and parameters between groups of pre-presbyopic and presbyopic participants were compared with Hotelling's two-sample *T*-squared test. For standard deviation of repeatability, three measurements of the ACD and LT parameters with and without cycloplegia taken by the same operator for both groups were analyzed. The standard deviation of repeatability was estimated by the square root of estimated variance due to measurement error, based on the random effects analysis of variance model. The coefficient of variability was calculated by the quotient of the standard deviation of repeatability and the mean of all measurements used. A *p* value of <.05 was considered to be statistically significant.

Results

Tables 1, 2, and 3 show ACD and LT measurements with and without cycloplegia in pre-presbyopic and presbyopic participants.

Table 2 The mean ACD and LT measurements obtained using swept source optical biometry with and without cycloplegia in presbyopic subjects

Parameter	Noncycloplegia mean ± SD	Cycloplegia mean ± SD	Mean difference ± SD	*P* value*
ACD	3.09 ± 0.28	3.17 ± 0.29	0.08 ± 0.03	<0.001
LT	4.55 ± 0.44	4.53 ± 0.43	0.02 ± 0.01	<0.001

*Dependent samples *t*-test, *p* value for comparison of parameters in noncycloplegia and cycloplegia states

ACD, anterior chamber depth; LT, lens thickness

Table 3 The comparison of the change in mean ACD, LT, and predictor values between pre-presbyopic and presbyopic subjects

Parameter	Pre-presbyopia	Presbyopia	Mean difference ± SD	*P* value*
Change in ACD	0.13 ± 0.08	0.08 ± 0.03	0.05 ± 0.02	0.004
Change in LT	0.09 ± 0.04	0.02 ± 0.01	0.07 ± 0.01	<0.001
Predictor value	0.04 ± 0.04	0.06 ± 0.03	0.02 ± 0.01	0.018

* Hottelling's two sample *T*-squared test, *p* value for comparison of parameters in pre-presbyopia and presbyopia. ACD, anterior chamber depth; LT, lens thickness

Firstly, the change in mean ACD with cycloplegia was 0.13 ± 0.08 mm in pre-presbyopic participants and 0.08 ± 0.03 mm in presbyopic ones, with a statistically significant difference in each group ($p < .001$). The change in mean ACD with cycloplegia between pre-presbyopic and presbyopic patients was 0.05 ± 0.02 mm, which was also statistically significant ($p = .004$).

Secondly, the change in mean LT with cycloplegia was 0.09 ± 0.04 mm in pre-presbyopic participants and 0.02 ± 0.01 mm in presbyopic ones, with a statistically significant difference in each group ($p < .001$, for each). The change in mean LT with cycloplegia between pre-presbyopic and presbyopic patients was 0.07 ± 0.01 mm, which was also statistically significant ($p < .001$).

Lastly, the P_{CM} was 0.04 ± 0.04 mm in pre-presbyopic participants, 0.06 ± 0.03 mm in presbyopic ones, and significantly greater in presbyopic participants ($p = .018$)..

Table 4 summarizes the standard deviation of repeatability, the limits of the measurements, and the coefficient of variability for ACD and LT in both groups. The standard deviations and the limits of repeatability were small and acceptable for both parameters with and without cycloplegia.

Discussion

Several authors have described changes in CM contractility with age, yet often with conflicting results [19, 31]. Duane [8, 9] proposed that accommodative loss occurs due to the CM's progressive weakening. In a postmortem human study, Nishida and Mizutani [32] reported that the age-related increase of connective tissue and decrease of nuclei in the CM, together with decreased circular fiber, suggest the possibility of CM atrophy with age-related deterioration of accommodation. In a study involving rhesus monkeys that sought to identify the pathophysiologic characteristics of presbyopia, which occurs in both humans and rhesus monkeys on a comparable relative time scale, researchers demonstrated that the contractile responses of CM to pilocarpine diminish with age [24]. In agreement with earlier studies using impedance cyclography [25], Pardue and Sivak [19] found that the CM retains its ability to contract throughout an individual's lifespan. Using anterior segment optical coherence tomography, Sheppard and Davies [33] suggested that no significant decrease in the contractile ability of the muscle occurs, even in eyes with established presbyopia. In a magnetic resonance imaging study, Strenk [27] found that CM contractile activity persisted in all participants, including presbyopic ones. Fisher [10, 34] suggested that the maximum force of contraction of the entire CM increases with age, as well as that lenticular sclerosis and increased size and weight with age might simply require extra force from the muscle to produce accommodative changes. According to Fisher, the CM's force of contraction is proportional to the square of the resultant accommodative change and not linearly related. In sum, most published data indicate that the CM maintains its contractile ability long after the onset of presbyopia, although

Table 4 Repeatability of parameters

Groups	Parameters		Mean	Repeatability SD	Limit	CoV (%)
Presbyopia	ACD (mm)	Noncycloplegia	3.079	0.0082	0.0229	0.266
		Cycloplegia	3.161	0.0093	0.0260	0.294
	LT (mm)	Noncycloplegia	4.552	0.0211	0.0590	0.463
		Cycloplegia	4.533	0.0226	0.0632	0.498
Pre-presbyopia	ACD (mm)	Noncycloplegia	3.421	0.0096	0.0268	0.280
		Cycloplegia	3.564	0.0117	0.0327	0.328
	LT (mm)	Noncycloplegia	3.729	0.0232	0.064	0.622
		Cycloplegia	3.631	0.0229	0.064	0.630

SD; standard deviation, CoV; coefficient of variability, ACD; anterior chamber depth, LT; lens thickness whether the nature of the response varies with age is not as clear [35, 36]. In light of a P_{CM} obtained from IOLMaster 700 measurements reflecting relaxed CM tone, CM tone was significantly greater—by 20 μm—in presbyopic eyes. However, the difference between presbyopic and pre-presbyopic eyes was close to the limits of standard deviations of repeatability for the device, which the manufacturer reports to be 10 μm and 19 μm for the ACD and LT respectively. Therefore, the statistically significant difference might not signify clinical significance. In any case, our results demonstrate that the relaxed CM tone of presbyopic patients is not inferior to that of pre-presbyopic ones.

High repeatability for all biometric parameters with IOLMaster 700 has been reported [37, 38]. For cataractous eyes, the standard deviations of repeatability of ACD and LT measurements were reported as 9.8 μm and 19.5 μm by Kunert et al. [37] and 9 μm and 29 μm by Srivannabonn et al. [38]. The present study found standard deviations of repeatability of ACD and LT measurements in presbyopic participants to be 8.2 μm and 21.1 μm without cycloplegia and 9.3 μm and 22.6 μm with cycloplegia; in pre-presbyopic participants, those values were 9.6 μm and 23.2 μm without cycloplegia and 11.7 μm and 22.9 μm with cycloplegia. Values of standard deviation of repeatability were fairly close to previously reported values [37, 38].

Not only muscle tone, but also changes in geometrical factors with age, including the width, length, and anatomic location of CM, the size and curvature of lens, and the positions of CM and zonules relative to the lens, can affect the P_{CM} of the current study. Quantitative and morphometric studies of aging eyes have reported geometrical changes, and that the CM of older participants contains greater amounts of connective tissue, is shorter and wider, and has a forward-moving internal apical edge [19, 32]. With age, an antero–inward displacement of muscle mass [33] and decrease in the diameter of the relaxed CM ring [27] cause the anterior movement of zonular insertions over the enlarged presbyopic lens. As a result, zonular insertions become more tangential to the lenticular surface, which can partly disable zonules from imparting tension upon the capsule [15, 18, 39, 40]. Although the width of the circumlental space in the relaxed eye diminishes with age, its effect on the zonule's tension can be compensated for by the axial movement of attachment points of zonular fibers to the lens capsule [5, 41, 42]. In the present study, even if the difference of P_{CM} was close to the limits of repeatability, it was clearly greater in presbyopic patients than in pre-presbyopic ones. In the light of the aforementioned studies, aging eyes demonstrate changes in the geometrical design of the accommodative system. However the role of zonules on the lens dynamics reduces or could be compensated with some anatomical variations of zonule insertions. Therefore, the findings may not be explained by age-related geometrical changes.

Various studies have reported changes in anterior segment parameters following pupil dilation with different devices—Pentacam [43], AL-Scan [44], Lenstar LS900 [45, 46], ultrasound biomicroscopy [47], A-scan ultrasonography [47], and IOLMaster 500 [46]—and significant increases in mean ACD have been detected with cycloplegia in all of these studies. Similarly to the above studies, we found a significant increase in mean ACD in cycloplegic individuals with a swept-source optical biometric device. However, participants with an ocular spherical refractive error above ±1 D or with other exclusion criteria (e.g., narrow iridocorneal angle, glaucoma, and cataract) were excluded from our sample, and the fact that the effects of cycloplegia in such eyes were not investigated represents a limitation of our study.

In summary, this study demonstrates that CM tone does not appear to diminish in aging presbyopic eyes. In future studies, researchers should use imaging techniques to correlate anatomical and functional changes of CM with age.

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Compliance with ethical standards

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Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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