Age-Related Changes in the Anterior Segment Biometry During Accommodation

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Purpose. We investigated the dynamic response of human accommodative elements as a function of age during accommodation using synchronized spectral domain optical coherence tomography devices (SD-OCT).

Methods. We enrolled 33 left eyes from 33 healthy subjects (age range, 20–39 years, 17 males and 16 females). Two SD-OCT devices were synchronized to simultaneously image the anterior segment through pupil and the ciliary muscle during 6.00 diopter (D) accommodation for approximately 3.7 seconds in two repeated measurements. The anterior segment parameters included the lens thickness (LT), radius of curvature of the lens anterior surface (LAC), maximum thickness of ciliary muscle (CMTMAX), and anterior length of the ciliary muscle (CMAL). A first-order exponential equation was used to fit the dynamic changes during accommodation. The age-related changes in the dynamic response and their relationship were calculated and compared.

Results. The amplitude ($r = -0.40$ and 0.53 for LT and LAC, respectively) and peak velocity ($r = -0.65$ and 0.71 for LT and LAC, respectively) of the changes in LT and LAC significantly decreased with age ($P < 0.05$), whereas the parameters of the ciliary muscle remained unchanged ($P > 0.05$), except for the peak velocity of the CMAL ($r = 0.44$, $P = 0.01$). The difference in the time constant between the lens reshaping (LT and LAC) and CMTMAX increased with age ($r = 0.46$ and 0.57 for LT and LAC, respectively, $P < 0.01$). The changes in LT and LAC per millimeter of CMTMAX change decreased with age ($r = -0.52$ and -0.34, respectively, $P < 0.05$). The ciliary muscle forward movement correlated with the lens deformation ($r = -0.35$ and 0.40 for amplitude, while $r = 0.36$ and 0.58 for time constant, respectively, $P < 0.05$).

Conclusions. Age-related changes in the lens reshaping and ciliary muscle forward movement were found. Lens reshaping was much slower than the contraction of the ciliary muscle, especially in aging eyes, and this process required the ciliary muscle to contract more to reach a given response.

Keywords: accommodation, optical coherence tomography, anterior segment, crystalline lens, ciliary muscle

Contemporary and classic theories for the accommodative mechanism are based on the concept that the contraction of the ciliary muscle is the initial event that leads to the reshaping of the crystalline lens, an idea initially developed by von Helmholtz.[1] The key elements of accommodation, such as the elasticity of the crystalline lens and the activity of the ciliary muscle, decline with age, which degenerates the capacity of accommodation.[2–7] Restoring the accommodative ability has been a substantial challenge. The implantation of accommodating intraocular lenses (AIOL) has been shown to restore less than 2 diopters (D) of objective accommodation,[8,9] partly due to the difficulty in predicting the dynamic response of the accommodative apparatus during accommodation. The dynamic relationship between ciliary muscle contraction and its ability to reshape the crystalline lens during the real-time processes of the human eye has not been fully studied in vivo, which may further limit the improvements in the restoration of accommodation.

Hess[10] and Gullstrand[11] developed a lenticular theory, which stated that presbyopia was caused by a decrease in the lens reshaping capacity. The ciliary muscle normally contracts in the region where the lens still is capable of a response, but it cannot produce an accommodative response above this level due to the lens hardness, even though muscle still is capable of contracting. In contrast, the extralenticular theory of Duane[12,13] showed that a slight weakening of the ciliary muscle decreased the accommodative amplitude. Fincham[14,15] proposed a reconciliation of these two extremes, suggesting that the lens is responsible primarily for the loss of accommodation and that the contraction of the ciliary muscle required for lens reshaping increases with age. Although these early theories all predict the

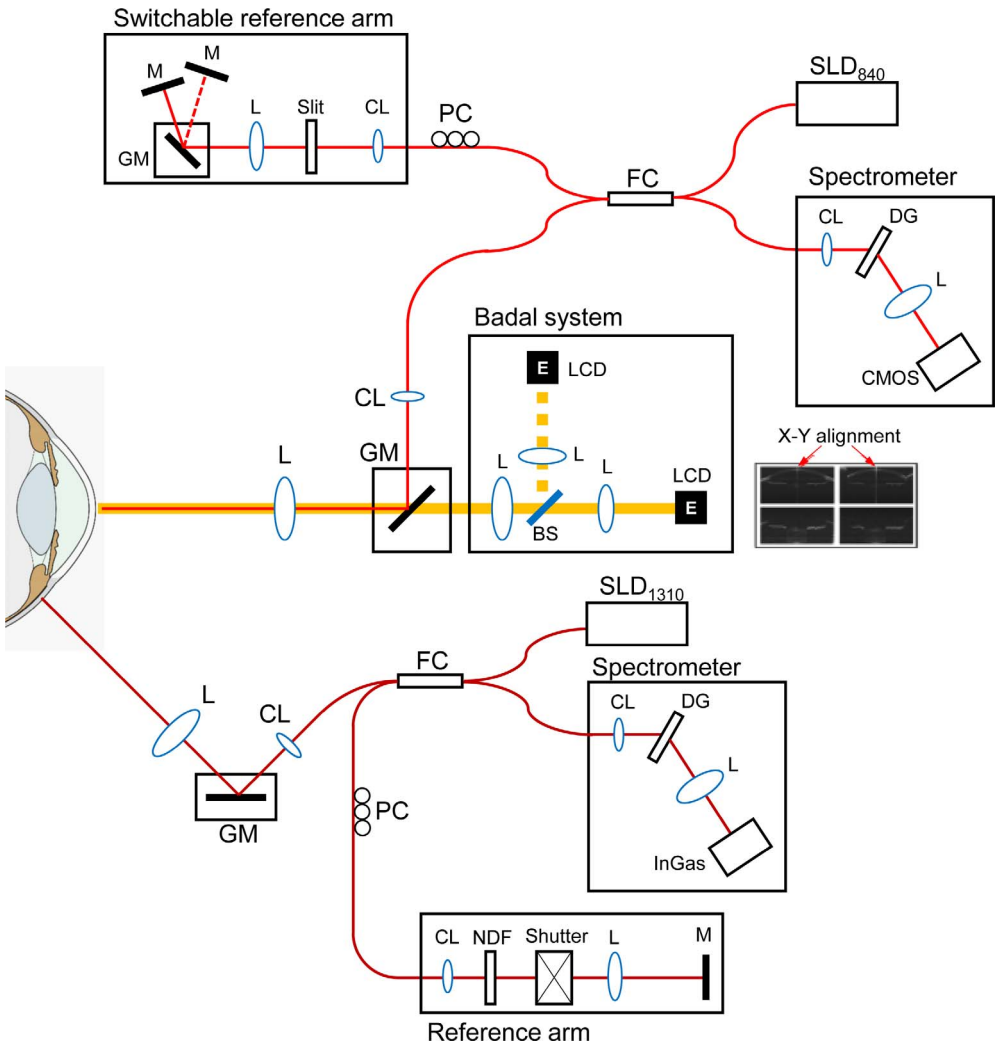

FIGURE 1. Schematic diagram depicting the combined OCT systems. SLD_{1310}, superluminescent diode with a central wavelength of 1310 nm; SLD_{840}, superluminescent diode with a central wavelength of 840 nm; FC, fiber coupler; PC, polarization controller; CL, collimating lenses; L, objective lenses; M, refractive mirror; GM, galvanometer mirror; DG, diffraction grating; BS, beam splitter; LCD, liquid-crystal display; NDF, neutral density filter; CMOS, complementary metal-oxide-semiconductor transistor camera; InGas, indium gallium arsenide.

age-related changes in muscle-lens relationship, none of them is fully supported.

The in vivo assessment of the dynamic response of the crystalline lens to ciliary muscle contraction is critical to understand the mechanism of accommodation and the age-related decline of accommodation. The difficulty in simultaneously imaging the entire anterior segment, including the crystalline lens and ciliary muscle, has limited in vivo studies of accommodation. In nonhuman primate models with iridectomies, the movement of ciliary processes and the lens equator during accommodation has been visualized using goniovideography under the stimulation of the Edinger-Westphal nucleus.[16,17] This method may not be applicable to human subjects. Others have used magnetic resonance imaging (MRI), which allows the entire eye (including the ciliary muscle and entire lens) to be imaged, to visualize accommodation.[18,19] The low scanning speed limits the application of dynamic measurements in accommodation research. To date, to our knowledge no study has simultaneously assessed the biometric changes in the ciliary muscle and crystalline lens as the function of age in real time in a cohort of human subjects.

Optical coherence tomography (OCT) allows the noninvasive and rapid imaging of the ocular anterior segment in the static and dynamic states.[20–28] Previously, we developed a system that combined two spectral-domain OCT (SD-OCT) devices.[27] One has extended the scan depth to approximately 12 mm in air for the imaging of the entire anterior segment through the pupil, while the other was equipped with a light source that was centered at a wavelength of 1310 nm to image the ciliary muscle in real time. The objective of this study was to investigate the age-related changes in the dynamic responses of human accommodative elements, and the relationship between lens reshaping and muscle contraction during accommodation using the synchronized SD-OCT system.

METHODS

Subjects

We included in this study 33 left eyes of 33 subjects (17 males and 16 females, mean ± SD age, 30.0 ± 5.45 years; range, 20–39 years). The spherical equivalent (SE) of the refractive error ranged from 0.00 to −7.75 D (mean ± SD, −2.50 ± 2.25 D). The ophthalmic examinations of all subjects were normal with a best-corrected visual acuity of 20/20 or more, and none of the

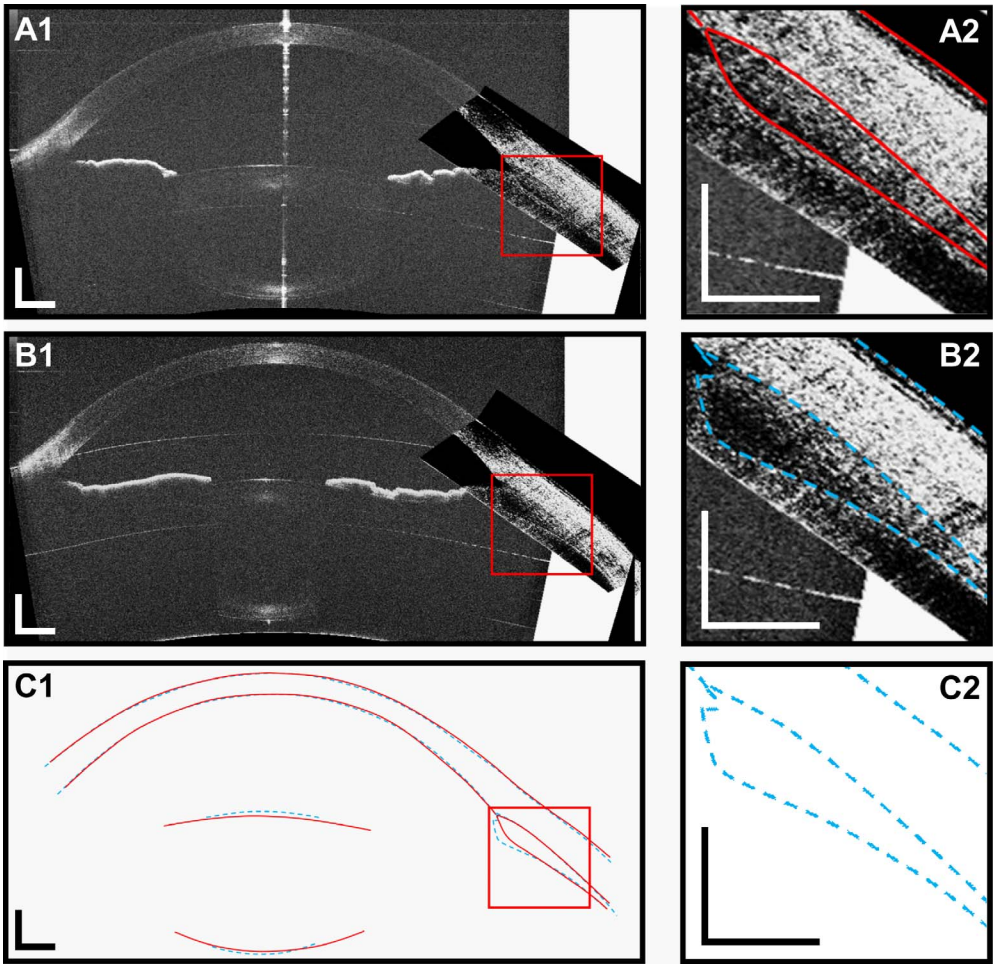

FIGURE 2. The combined images from the AS-OCT and CM-OCT under the relaxed (**A1**) and accommodative (**B1**) states. The boundaries of the anterior segment was outlined to show the ciliary muscle contraction and lens reshaping (**C1**). (**A2**, **B2**, **C2**) Enlarged images of the ciliary muscle from (**A1**, **B1**, **C1**), respectively. *Scale bars*: 1 mm.

subjects reported a history of ocular disease, surgery, trauma, or contact lens wearing for at least 1 week before testing. This study was approved by the research review board of the University of Miami. Informed consent was obtained from each subject, and all subjects were treated in accordance with the tenets of the Declaration of Helsinki.

Instruments

The combined system used to image the entire anterior segment has been described in our previous study (Fig. 1).[27] Briefly, an anterior segment SD-OCT (AS-OCT) with a wavelength of 840 nm and a scan depth of 12.5 mm extended via the design of switchable reference arm was used to image the entire anterior segment through the pupil in real time. Another SD-OCT (ciliary muscle OCT, CM-OCT) used a light source with a central wavelength of 1310 nm to scan the ciliary muscle through the sclera in real-time. The sample arms of the two OCT devices were combined and mounted on a modified slit-lamp microscope. The scanning of the combined system was synchronized to ensure simultaneous scanning.

The accommodative stimulus was provided by two Badal systems, which were combined with a 50:50 beam splitter.[29] Two liquid-crystal display (LCD) screens were installed in the two Badal systems. A white Snellen letter "E" with the size of approximately 0.4 in logMAR visual acuity chart on a black background with the contrast of 100% was displayed in each LCD, which served as the fixation target and accommodative stimulation. One system provided a low stimulus (far viewing), whereas the other system provided a high stimulus (near viewing). A white letter "E" on a black background, which served as the fixation target and accommodative stimulus, was alternatively displayed on the two LCD screens, which were controlled by a computer. The entire accommodative stimulus module was placed on the slit-lamp and combined with the probe of the AS-OCT with a hot mirror.

Experimental Procedures

The left eye of each subject was imaged in real time. The Badal system corrected the refractive error for far viewing, and a 6.00 D accommodative stimulus was added to the near viewing. The target was displayed in far viewing at first, and the display alternated to near viewing 1 second after the onset of acquisition. The subjects were asked to sit in front of the probe and look forward to the target with the tested eye. During the experiment, the right eye of each subject was covered by an eyepatch. The subject was asked to focus on the fixation target.

The scanning protocol was described in our previous study.[27] Briefly, the beam from the AS-OCT was centered on the corneal apex and was perpendicular to the iris plane at the horizontal and vertical meridians based on the cross-hair live view to ensure scanning at the same sagittal plane of the eye.

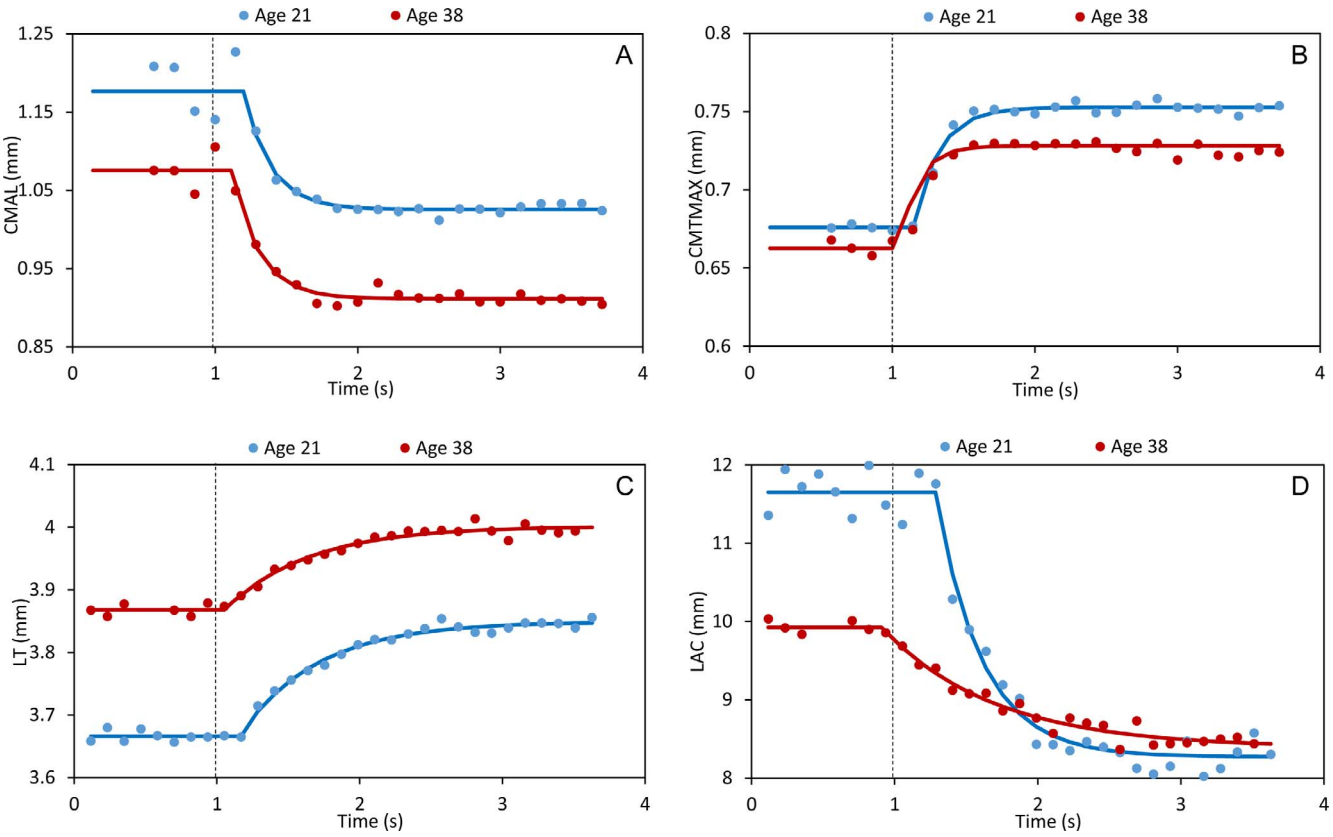

FIGURE 3. The dynamic changes in CAML (**A**), CMTMAX (**B**), LT (**C**), and LAC (**D**) as a function of time in subjects aged 21 and 38 years. *Red dots* and *lines* represent the dynamic parameters of the 21-year-old subject. *Blue dots* and *lines* represent the dynamic parameters of the 38-year-old subject.

In addition, the beam from the CM-OCT was prealigned with the beam from the AS-OCT, which was at the same altitude before the experiment. The experiment was then repeated following the same protocol.

Data Analysis

As mentioned in a previous study, the images from the OCT system were analyzed using custom-developed software.[27] The images of the anterior segment through the pupil from AS-OCT were automatically processed, including segmentation, registration, and optical correction. In this study, the dimensional parameters of the crystalline lens, including the thickness (LT) and radius of curvature of the anterior surface (LAC), were obtained for further analysis. The images of the ciliary muscle were segmented for the boundaries in a semiautomated fashion. The maximum thickness of the ciliary muscle (CMTMAX) was then evaluated, and the ciliary muscle anterior length (CMAL) was defined as the distance from the scleral spur to the position of maximum thickness.

The dynamic changes in LT, LAC, CMTMAX, and CMAL were fitted using the following first-order exponential equation for each individual subject without any averaging[30,31]:

$$y = y_0 + a \times \left(1 - e^{-(t-t_0)/\tau}\right) \quad (1)$$

where y represents the values in millimeters, y_0 represents the value at the baseline, a represents the amplitude, t represents the time in seconds, t_0 represents the latency in seconds, and τ represents the time constant. The latency is the time that has elapsed from the stimulus onset to the start of the accommodation, and the time constant is the time for the response to attain 63% of the amplitude.[32] The peak velocity was calculated by dividing the amplitude by the time constant.

The accuracy of the fit was evaluated based on the squared correlation coefficient (R^2) between the measurement and the fit. A fit with $R^2 > 0.80$ was considered to be accurate and used for further analyses. A total of eight curves were fitted for each subject. The dynamic parameters from the two repeated measurements, including the latency, time constant, amplitude, and peak velocity, were averaged for the statistical analysis.

RESULTS

Figure 2 presents the anterior segment of a 26-year-old subject, including the cornea, iris, crystalline lens, and ciliary muscle, imaged using the combined system before and after accommodation. The diagram (Figs. 2C1, 2C2) shows that the lens becomes thicker and the anterior surface steepens, and the anterior portion of the ciliary muscle is thicker during the accommodative stage.

Figure 3 shows the anterior segment dynamic measurements and the exponential fits from two subjects aged 22 and 38 years. The contraction of the ciliary muscle was comparable between the two subjects (Figs. 3A, 3B). However, the amplitude and velocity of lens reshaping were lower in the older than in the younger subject (Figs. 3C, 3D).

Table 1 summarizes the age-related changes in the dynamic parameters of the lens and ciliary muscle. In brief, the contraction of the ciliary muscle did not change with age, but the CMAL as well as the reshaping of the lens (magnitude and velocity) decreased. The latency period between stimulus

Table 1. Age-Related Changes in the Dynamic Parameters of the Ciliary Muscle and Lens

	Latency		Time Constant		Amplitude		Peak Velocity	
Parameters	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***
CMTMAX	−0.12	0.28	−0.23	0.13	0.15	0.23	0.28	0.08
CMAL	−0.26	0.10	0.73*	<0.01*	0.17	0.19	0.44*	0.01*
LT	0.25	0.10	0.51*	<0.01*	−0.40*	0.02*	−0.65*	<0.01*
LAC	0.24	0.11	0.52*	<0.01*	0.53*	<0.01*	0.71*	<0.01*

* Significance below the 0.05 level.

presentation and initiation of accommodation changed little with age.

The amplitude of ciliary muscle contraction remained constant with age, while that of lens reshaping decreased (Figs. 4A, 4B). The analysis of the relationship between the ciliary muscle and lens indicated an age-related reduction in the deformation of the crystalline lens (LAC and LT) per millimeter of the change in CMTMAX (Figs. 4C, 4D). Therefore, the same contraction of ciliary muscle results in less lens reshaping for older compared to younger subjects.

The time constants of CMAL, LT, and LAC positively correlated with age (Figs. 5A, 5C) and negatively correlated with the peak velocity (Figs. 5B, 5D). A positive difference in the time constant between the lens and ciliary muscle was evident for each subject, which indicated a reaction time between the ciliary muscle and lens; this time increased with age (Fig. 6).

Figure 7 presents the relationship between the forward movement of the ciliary muscle and the lens reshaping. The amplitudes of the CMAL and LT negatively correlated, while those of the CMAL and LAC positively correlated (Figs. 7A, 7B). Moreover, the time constant of CMAL positively correlated with those of LT and LAC (Figs. 7C, 7D).

Discussion

To the best of our knowledge, this clinical study was the first to quantify the age-related change in the magnitude and time-course of the human anterior segment during accommodation. To gain a better understanding of the mechanism of the accommodation and presbyopia, the ciliary muscle and crystalline lens must be observed simultaneously. Others have used MRI[18,19,33] and ultrasound biomicroscopy (UBM)[34,35] to perform static measurements. Unlike these methodologies, SD-OCT can image the anterior segment in real time.[25,27,36] Dynamic measurements offer several advantages over static measurements, such as the assessment of latency, velocity, acceleration, and microfluctuations. Furthermore, the alignment at the horizontal and vertical meridians ensured that the beam from the AS-OCT remained perpendicular to the corneal center. During the image acquisition, the test eye kept fixating on the fixation target and the other eye was patched. The convergence may happen in the patched eye, but the test eye did not change its position due to the fact that we did not notice large eye movement by viewing the real-time OCT images. Moreover, the CM-OCT was prealigned with the AS-OCT, which facilitated the scanning at the same sagittal plane of the ciliary muscle. The combination of the two SD-OCT

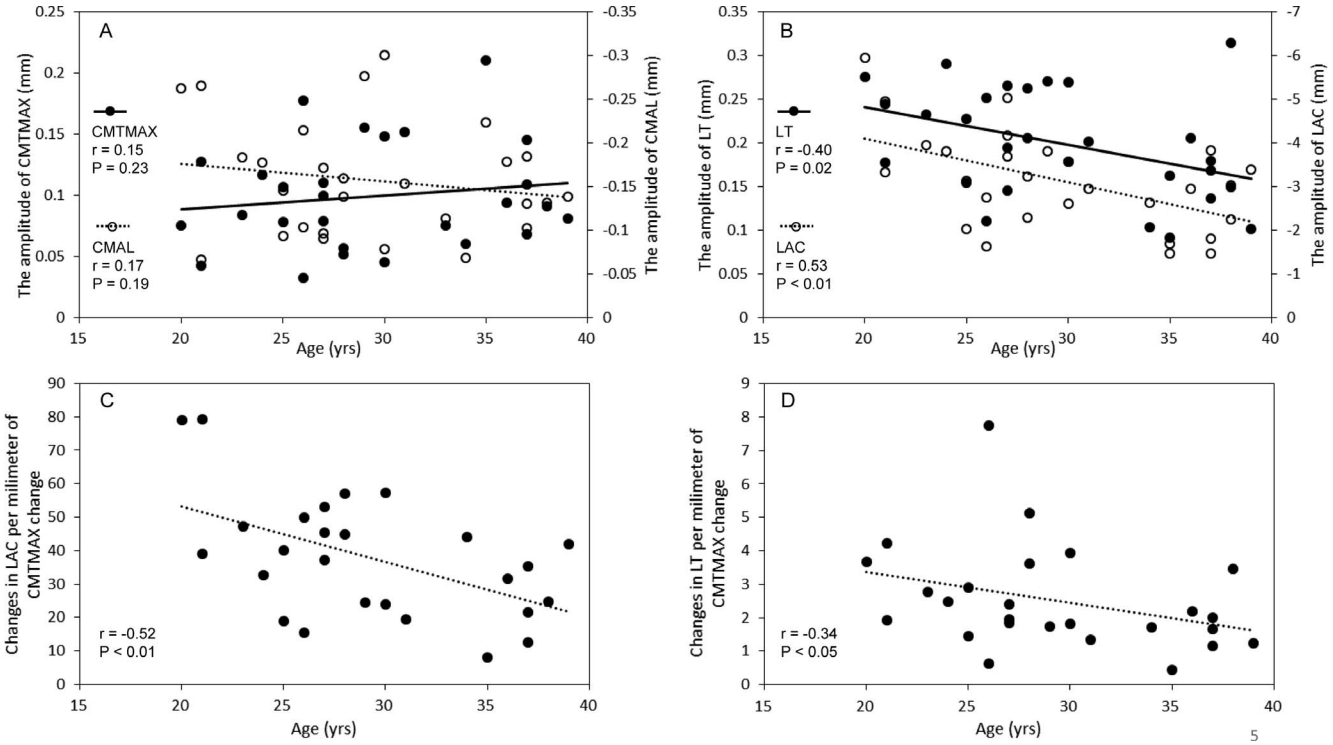

Figure 4. (**A**) The age-related changes in the amplitudes of CMTMAX and CMAL. (**B**) The age-related changes in the amplitudes of LT and LAC. (**C**, **D**) The changes in the LAC (**C**) and LT (**D**) per millimeter of CMTMAX change as a function of age.

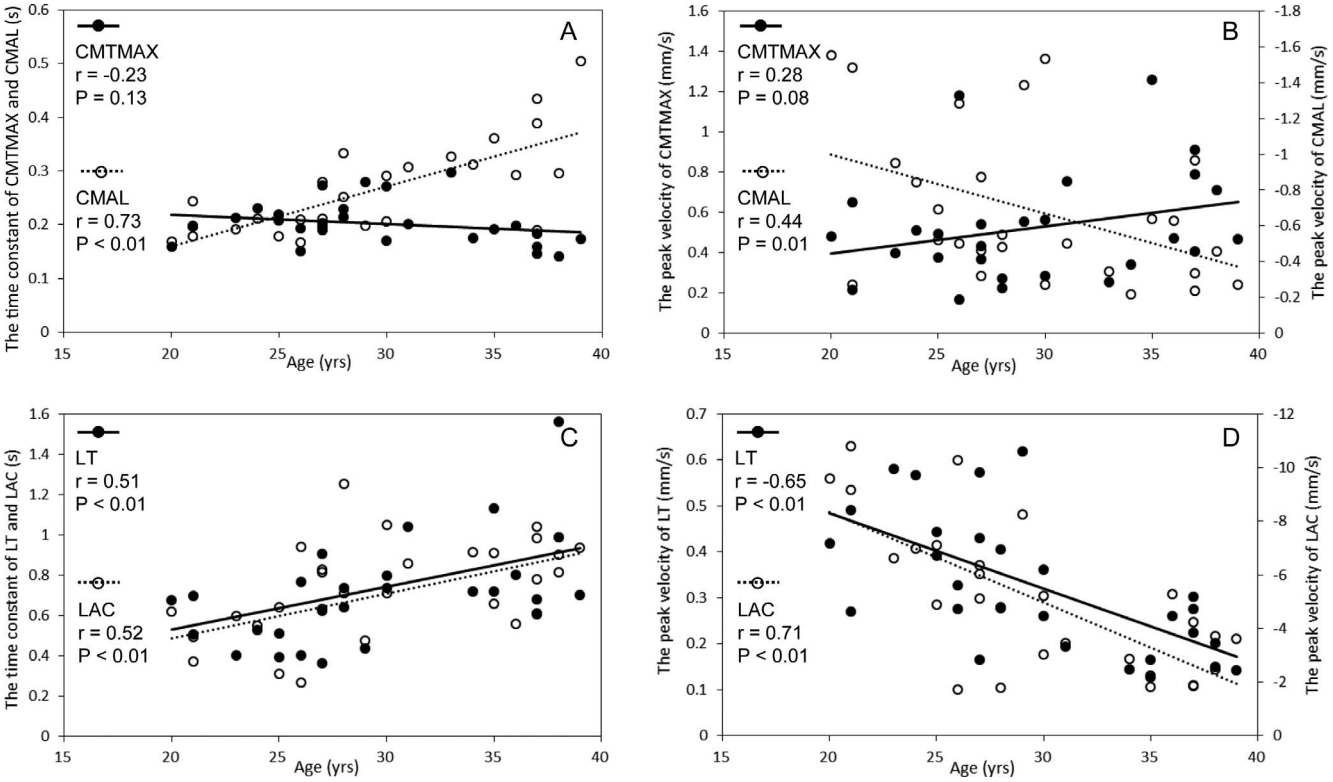

FIGURE 5. (A, B) The age-related changes in the time constant (A) and peak velocity (B) of CMTMAX and CMAL. (C, D) The age-related changes in the time constant (C) and peak velocity (D) of LT and LAC.

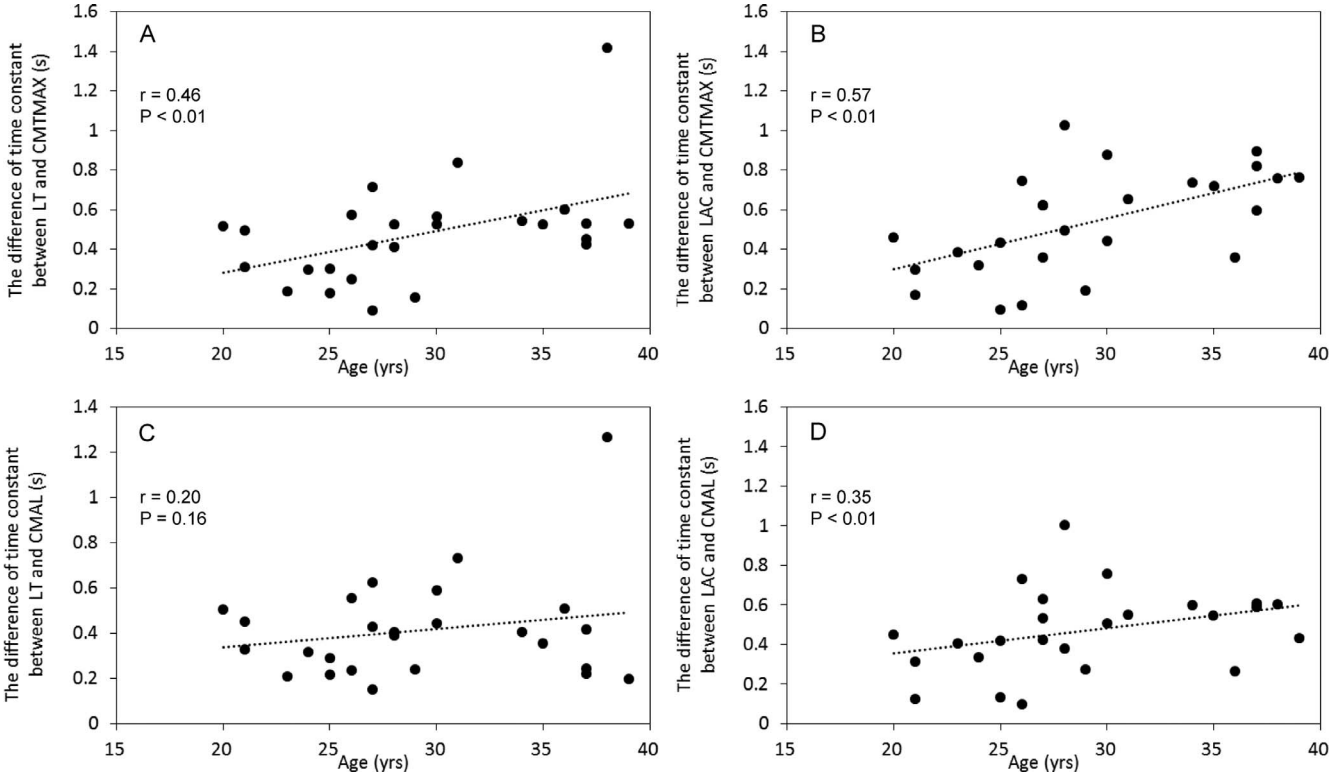

FIGURE 6. (A, B) The difference in the time constant between the lens ([A], LT; [B], LAC) and CMTMAX as a function of age. (C, D) The difference in the time constant between the lens ([C], LT; [D], LAC) and CMAL as a function of age.

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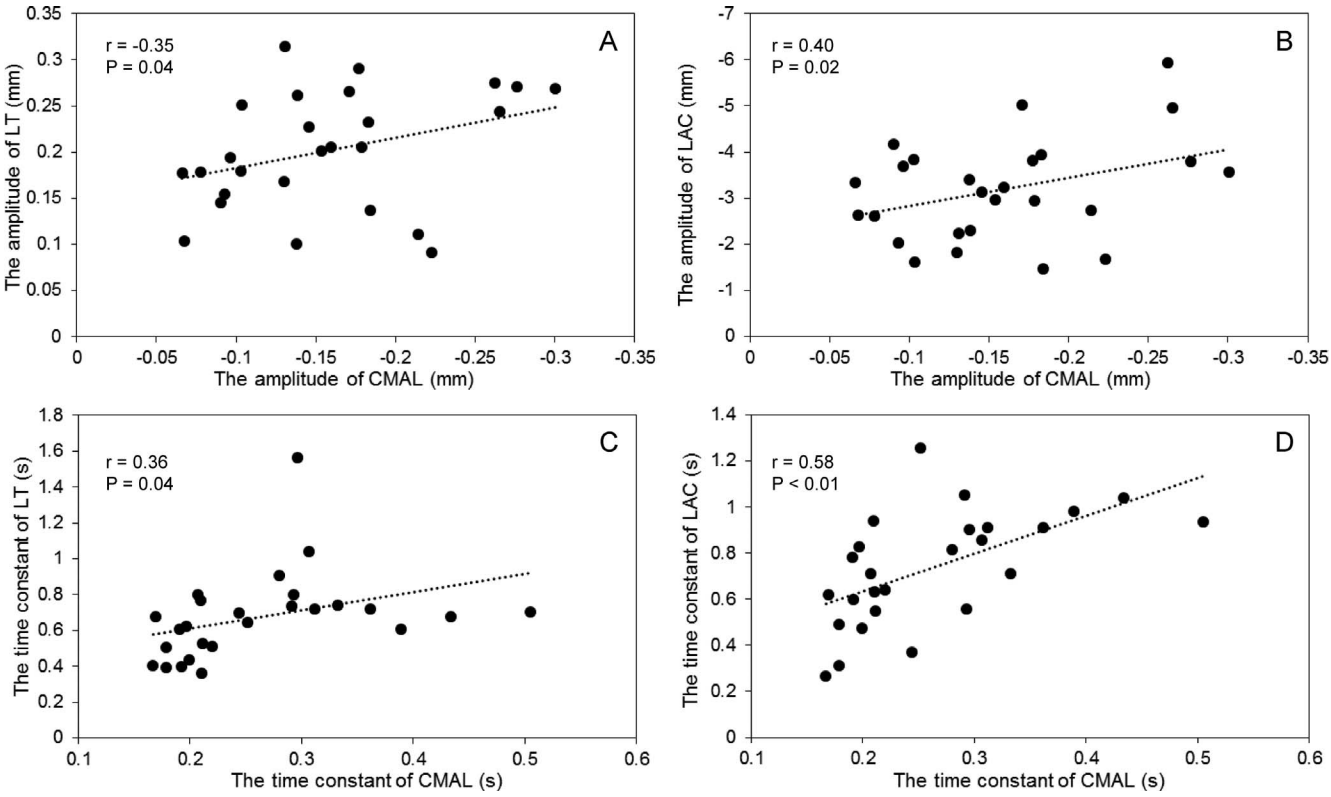

FIGURE 7. (**A**, **B**) The correlation between the amplitude of the lens ([**A**], LT; [**B**], LAC) and CMAL. (**C**, **D**) The correlation between the time constant of the lens ([**C**], LT; [**D**], LAC) and CMAL.

methods in our previous[27] and present studies facilitates the simultaneous and real-time imaging of the ciliary muscle and crystalline lens, which allows the assessment of dynamic changes in the accommodative structures and their decline with age.

One of the most important advances applied in the present study was the comparison of the dynamics of the ciliary muscle and crystalline lens as a function of age in vivo. The exponential functions provided the time constant, which was defined as the time to reach approximately 63% of the amplitude,[32] which facilitated the direct comparison of differences in the dimensional parameters of different magnitude (i.e., the magnitude of the lens curvature radius was approximately 20 to 30 times larger than the ciliary muscle thickness); a greater time constant indicated a lower shifting speed. The results demonstrated that the deformations of the ciliary muscle and crystalline lens were not parallel; the ciliary muscle contracted faster than the lens reshaped in all subjects, indicating that the lens required a reaction time to follow the ciliary muscle contraction. The rapid contraction of the ciliary muscle may be due to its multiunit smooth muscle,[37] which contracts as rapidly as skeletal muscle, while the crystalline lens passively begins deformation. Our finding agreed with a study of rhesus monkeys,[17,38] which used goniovideography to demonstrate that the reduction of the ciliary ring occurs distinctly faster than the movement of the lens equator.

A significant age-related reduction in the thickening and steepening of the lens anterior surface was observed, which was mentioned in previous studies (Table 2).[18,19,25,31,33–35] Moreover, we found that the response time between the ciliary muscle contraction and lens deformation increased with age, and even the forward movement was restricted in the aging muscle. Fincham[14] further developed the theory of von Helmholtz,[1] which states that only the elastic properties of the capsule are responsible for changes in the lens shape and that the lens returns to the unaccommodated form if its

TABLE 2. Image Technology, Age Range and Accommodative Stimulus in Previous Studies

Authors	Image Technology	Age Range (Sample Size)	Accommodative Stimulus
Kasthurirangan et al.[18]	MRI	19–29 y (15) 60–70 y (15)	4.8–6.9 D
Strenk et al.[19]	MRI	22–83 y (25)	8.0 D
Strenk et al.[33]	MRI	22–91 y (40)	8.0 D
Ruggeri et al.[25]	SD-OCT	24 y (1) 35 y (1)	7.0 D
Beers and van der Heijde[31]	A-scan ultrasound	15–55 y (20)	1.0 D
Richdale et al.[34]	A-scan ultrasound, MRI, OCT and phakometry	30–50 y (26)	2.0, 4.0, and 6.0 D
Croft et al.[35]	Ultrasound biomicroscopy	19–65 y (12)	Maximum accommodation induced by pilocarpine

capsule is removed. In a dynamic accommodation study using ultrasound, Beers and Van Der Heijde[31] built an accommodation model that evaluated the viscoelasticity of the lens, which was shown to increase with age. These observations suggest that the accommodative velocity depends on the deforming speed of the crystalline lens rather than on the contracting speed of the ciliary muscle; the accommodative response slowed in older subjects,[32,39] which may be primarily due to the inability of the lens deformation with age.

The dynamic imaging of the ciliary muscle showed that the thickening of the ciliary muscle remained unchanged in magnitude and velocity, which implies that the contractility of the muscle did not decline with age. Fisher[40] showed that the force of the ciliary muscle contraction in humans declined only after age 50. Poyer et al.[41] also found that age did not significantly affect the contractile responses of isolated rhesus monkey ciliary muscle to muscarinic agonists. In contrast, the forward movement of ciliary muscle apex significantly slowed with age, while the amplitude slightly changed between ages 20 and 40, although this change was not significant. Similarly, Croft et al.[16,17,38] and others also found using UBM that the forward ciliary body movement decreased in monkeys. The subjects enrolled in the current study were young and middle-age humans, while previous studies examined monkeys of all ages. This difference may be responsible for the fact that only a trend was observed in our study. Unlike the strength of the ciliary muscle contraction, the deterioration of the elastic components of the ciliary body and choroid throughout adulthood is well known based on previous studies. For instance, morphologic studies showed an age-related limitation in the forward movement of the ciliary muscle in rhesus monkeys, which was mostly restored when the posterior attachments were cut.[42] Moreover, Wyatt[4] analyzed the approximate values of the choroidal spring constant, which differed by more than 3-fold between ages 15 and 55. Therefore, the increasing ciliary muscle restriction in the forward movement may be due to an increasingly stiff posterior attachment[42,43] rather than the weakening of the ciliary muscle, and the loss of velocity occurred much earlier than that of the amplitude.

Given a stimulus of 6 D, the thickening of ciliary muscle did not change with age, indicating that the accommodative response caused by the stimulation may be similar among the subjects. However, the reshaping of the lens may require a much stronger contraction of the ciliary muscle because the lens deformation per millimeter of ciliary muscle thickening decreased with age. This phenomenon supported the theory of presbyopia proposed by Fincham,[14,15] which states that the loss of accommodation with age is primarily lenticular and that the demand of the ciliary muscle contraction for lens reshaping also increases. Croft et al.[38] also found a weakly positive relationship between the ciliary process movement and lens equator movement in middle-age and older monkeys. Furthermore, the restriction in the forward movement of the ciliary muscle may somewhat influence the lens thickening and steepening because the lens deformation and forward muscle movement clearly correlated in terms of the amplitude and time constant, as mentioned in previous studies. Therefore, the degeneration of the posterior attachment of the ciliary body has at least a secondary role in the loss of accommodation by constricting the ciliary muscle forward movement, as observed in previous animal studies.[16,38]

The present study also is subject to limitations. First, the accommodative experiments were performed using real-time biometry, and the accommodative response was not measured as part of the optical outcome. We did not determine the optical responses to a 6 D demand. In the future, the ocular optics, such as the refractive power or wavefront aberrations, should be measured to address this limitation. Second, this study involved the far-to-near accommodation but not the near-to-far accommodation. The study of the near-to-far accommodation, for which the elastic force from the peripheral zonules and choroid pulls the relaxed ciliary muscle and the crystalline lens, may expose the elastic tension of the accommodative component elements. Third, only young and middle-age adults were enrolled in the present study, and further studies that examine a larger age range will help elucidate the mechanisms of accommodation and presbyopia. Fourth, the cross hair (X-Y scanning alignment) scanning protocol was used to locate the corneal apex. Although the same location can be relocated to perform the anterior segment biometry, it cannot ensure to scan the maximum lens thickness. At last, we determined the radius of curvature of the anterior lens surface by the entire segmentation line, so the narrower view of the anterior lens surface during accommodation may give a less accurate measurement of the radius of curvature due to the fact that the edge is relatively steeper than the center. While we could not rule out the possible error, we still found steeper radius of curvature during accommodation, which indicated the error could be neglected.

In summary, we investigated the time-course and magnitude of the ciliary muscle and crystalline lens deformations as a function of age during accommodation using a combined SD-OCT system. The loss of lens deformation was marked with age, which may be the leading cause of the loss in accommodation. In aging eyes, the same reshaping of lens may require a stronger contraction of the ciliary muscle compared to young eyes. An age-related change in the ciliary muscle forward movement was observed, which might be due to the stiffness of the choroid, posterior ciliary muscle tendons, or posterior vitreous zonule; this change partly influenced lens reshaping. The design of the accommodating intraocular lens was suggested to rely on the centripetal movement of the ciliary muscle to achieve the accommodative effort.

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