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Effects of aging on corneal biomechanical properties and their impact on 24-hour measurement of intraocular pressure

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Abstract

Purpose—To study effects of aging on corneal biomechanical properties and their impact on 24-hour measurement of intraocular pressure (IOP).

Design—Experimental study.

Methods—Fifteen older volunteers with healthy eyes (ages, 50–80 years) were housed for one day in a sleep laboratory with 16-hour diurnal/wake period and 8-hour nocturnal/sleep period. Every two hours, sitting corneal hysteresis, corneal resistance factor, and IOP were measured. Central corneal thickness (CCT) was measured using an ultrasound pachymeter. Data were compared with previous observations in fifteen healthy younger volunteers (ages, 20–25 years).

Results—Variations in 24-hour corneal hysteresis and corneal resistance factor were not significant in the older subjects, but there were time-dependent variations in CCT and IOP. The nocturnal CCT was thicker than the diurnal CCT, but the IOP difference between the diurnal and nocturnal periods was not significant. Cosine-fits of CCT and IOP showed synchronized 24-hour rhythms. The phase timing of CCT rhythm appeared significantly earlier than the phase timing of IOP rhythm. Comparing to younger subjects, older subjects had a lower mean 24-hour corneal hysteresis and corneal resistance factor, but not CCT. Phase timings of 24-hour rhythms of CCT and IOP were significantly delayed by aging.

Conclusions—Aging may lower corneal hysteresis and corneal resistance factor, but neither parameter shows a significant 24-hour variation. Aging may not change CCT significantly, but can shift its 24-hour rhythm. The 24-hour IOP pattern in this group of older subjects is not an artifact due to a variation in corneal hysteresis, corneal resistance factor, or CCT.

Keywords

aging; central corneal thickness; circadian rhythm; corneal hysteresis; corneal resistance factor; intraocular pressure

INTRODUCTION

Corneal biomechanical properties can influence clinical determinations of intraocular pressure (IOP).¹ In cross-sectional population studies, a thicker central corneal thickness (CCT) was

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associated with a high IOP regardless of age.^{2,3} Corneal swelling of 40–63 μm induced by contact lens wear with eye closure was also associated with a high IOP in both younger and older adults.^{4–6} However, we observed that 24-hour IOP variation in a group of healthy younger adults (age range, 20–25 years) was not associated with 24-hour changes in corneal biomechanical properties including a swelling of the cornea by 20 μm at night.⁷ Whether or not the latter observation was applicable to the 24-hour IOP pattern in the aging population was not known.^{8–10} Since an IOP elevation and aging are both major risk factors for glaucoma, accurate determination of 24-hour IOP variation in older subjects with minimal artifacts from the variations in corneal biomechanical properties is essential for assisting the diagnosis and treatment of glaucoma.

There are age-related alterations in corneal micro-structure and physiology, including the stress-strain behavior.^{11,12} Aging may affect office-hour CCT and two newly characterized corneal biomechanical parameters; corneal hysteresis and corneal resistance factor.^{2,13,14} These three corneal biomechanical parameters and IOP were measured in the present study around the clock in a group of volunteers over 50 years old. Results were compared to our previous observations on the corneal biomechanical properties in healthy younger subjects⁷ to determine the aging effects during and outside office hours. Whether the 24-hour IOP variation in this group of older subjects was associated with a 24-hour change in the three corneal biomechanical parameters was evaluated.

METHODS

Fifteen non-smoking older volunteers with healthy eyes (61.9 ± 9.7 years, mean $\pm$ SD; range, 50 to 80 years) were recruited. They were selected for having a regular sleep period close to 8 hours. Subjects were 4 males and 11 females, including 12 Caucasians and 3 Asians. Each subject had a complete ophthalmologic examination demonstrating absence of any eye disease. The mean IOP, CCT, refractive state, and axial length during office hours were 14.7 ± 2.5 mm Hg, 548.6 ± 34.0 μm , -0.20 ± 2.20 diopter, and 23.31 ± 1.10 mm, respectively.

Protocol for data collection was similar to that previously used in younger subjects.⁷ In brief, participants were instructed to maintain a daily 8-hour custom sleep period for 7 days. Each subject wore a wrist monitor (Actiwatch, Mini Mitter, Sunriver, OR) for light exposure and physical activity and kept a wake/sleep log. They were instructed to abstain from alcohol for 3 days and caffeine for 1 day. Subjects arrived at the laboratory at approximately 2 PM and stayed in individual rooms for 24 hours. The 8-hour period of darkness in the room was adjusted to correspond to each individual's sleep period. For presentations, the corresponding clock times were aligned as if each subject had a sleep period from 11 PM to 7 AM.

Measurements of corneal hysteresis, corneal resistance factor, IOP, and CCT were taken from the left eye in the sitting position every 2 hours by trained technicians. Using a Reichert Ocular Response Analyzer (Depew, NY), corneal hysteresis, corneal resistance factor, and IOP (referred as IOPg by the manufacturer) were determined.^{15,16} Central corneal thickness was measured using an ultrasound pachymeter (DGH Technology, Model 550, Exton, PA) with one or two drops of 0.5% proparacaine as local anesthetic. Value of CCT was the average of three consecutive readings. Blood pressure and heart rate were measured using an automated wrist monitor (Omron, Model HEM-608, Vernon Hills, IL) at corresponding time points.

Before turning off lights at 11 PM, measurements were taken at 3:30 PM, 5:30 PM, 7:30 PM, and 9:30 PM. Nocturnal measurements were taken at 11:30 PM, 1:30 AM, 3:30 AM, and 5:30 AM. Dim room lights were used during the nocturnal measurements.^{17,18} Room lights were turned back on at 7 AM and subjects were awakened, if necessary. Measurements continued at 7:30 AM, 9:30 AM, 11:30 AM, and 1:30 PM.

Means of each study parameter (corneal hysteresis, corneal resistance factor, IOP, CCT, mean blood pressure, and heart rate) from these older subjects were calculated for each time point, the diurnal period (7 AM to 11 PM), the nocturnal period (11 PM to 7 AM), and the 24-hour period. Statistical comparisons between the diurnal and the nocturnal means were made using the paired t-test. The criterion for statistical significance was $P < 0.05$. Mathematical estimation of the 24-hour rhythm was performed for corneal hysteresis, corneal resistance factor, IOP, and CCT using the best-fitting cosine curve for data obtained at the 12 time points from each individual.^{7,19} Phase timing of the fitted peak (acrophase) and height of the rhythm (amplitude) were determined. The null hypothesis of a random distribution of 15 phase timings around the clock was evaluated using the Rayleigh test.²⁰ The phase timings for the 24-hour IOP rhythm and the 24-hour CCT rhythm were compared using the Wilcoxon signed-rank test for paired data.

The correlations between CCT and IOP during the diurnal period and the nocturnal period were examined using linear regression. Linear regression was also used to examine the correlations of CCT versus corneal hysteresis and CCT versus corneal resistance factor. One analysis was performed using the 15 pairs of mean CCT versus mean corneal hysteresis or mean CCT versus mean corneal resistance factor collected during the diurnal period, the nocturnal period, and the 24-hour period. For this analysis, one pair of means from each individual was used. The other analysis of linear regression was performed using the 12 pairs of time-dependent CCT versus corneal hysteresis or time-dependent CCT versus corneal resistance factor. For this analysis, 12 pairs of data from the same individual were used.

To examine the aging effects, results from the present study were compared with data previously obtained from a group of fifteen 20–25 years old subjects.⁷ Twenty-four-hour means of study parameters and the phase timings and heights of 24-hour rhythms were compared between the two age groups using the Mann-Whitney rank-sum test for unpaired data. The regression lines for the correlation analysis of mean 24-hour CCT versus mean 24-hour corneal hysteresis as well as the correlation analysis of mean 24-hour CCT versus mean 24-hour corneal resistance factor were compared between the two age groups. The null hypothesis was that no significant difference existed in the regression lines between the two age groups with $P < 0.05$.

RESULTS

The 24-hour profiles of CCT, IOP, and corneal hysteresis for the 15 older subjects are presented in Figure 1. There were noticeable 24-hour variations of CCT and IOP. The peak CCT of 555.9 μm appeared at 5:30 AM and the trough CCT of 535.9 μm at 11:30 AM. Mean nocturnal CCT of $550.5 \pm 31.9 \mu\text{m}$ (mean $\pm$ SD) was significantly higher than mean diurnal CCT of $539.0 \pm 30.3 \mu\text{m}$ ($P < 0.001$). The peak IOP was 14.8 mm Hg at 9:30 AM and the trough IOP was 11.8 mm Hg at 11:30 PM. Mean nocturnal IOP of $12.9 \pm 2.1 \text{ mm Hg}$ was not statistically different from the mean diurnal IOP of $13.9 \pm 2.6 \text{ mm Hg}$. Based on the standard deviation of 2.0 mm Hg between the diurnal and nocturnal IOP means and using the paired t-test and the Type I error of 0.05, there was a statistical power of 0.82 to detect a 1.6 mm Hg IOP difference. Linear regression analyses indicated a correlation between CCT and IOP during the diurnal period ($r = 0.581$, $P = 0.023$), but not during the nocturnal period ($P = 0.686$). Comparing the older and the younger groups, differences in the mean 24-hour CCT (10.2 μm) and the mean 24-hour IOP (0.5 mm Hg) were not statistically different. Using the Mann-Whitney rank-sum test and the Type I error of 0.05, the statistical power was 0.80 to detect a 44.0 μm CCT difference and 0.81 to detect a 2.8 mm Hg IOP difference.

Variation in 24-hour corneal hysteresis was not significant (Fig. 1). Mean diurnal corneal hysteresis of $10.4 \pm 1.1 \text{ mm Hg}$ was not statistically different from mean nocturnal corneal

hysteresis of 10.5 ± 1.4 mm Hg. The statistical power was 0.80 to detect a 0.7 mm Hg diurnal-to-nocturnal change of corneal hysteresis. The difference in the mean 24-hour corneal hysteresis between the older subjects and the younger subjects was significant (10.4 ± 1.1 mm Hg versus 11.8 ± 1.6 mm Hg; $P < 0.01$). Corneal resistance factor in the older group also remained relatively constant for 24 hours (data not shown in Fig. 1 because of its overlap with corneal hysteresis). Mean diurnal corneal resistance factor of 9.9 ± 1.3 mm Hg was not statistically different from mean nocturnal corneal resistance factor of 9.7 ± 1.5 mm Hg. The statistical power was 0.85 to detect a 0.5 mm Hg diurnal-to-nocturnal change of corneal resistance factor. There was a significant difference in mean 24-hour corneal resistance factor between the older and the younger subjects (9.8 ± 1.3 mm Hg versus 11.5 ± 1.7 mm Hg; $P = 0.011$).

Cosine-fits of corneal hysteresis, corneal resistance factor, IOP, and CCT collected from all individuals determined the group phase timings and heights of 24-hr rhythms. The Rayleigh test detected synchronized group phase timings for the 24-hour CCT ($P < 0.001$) and the 24-hour IOP ($P < 0.001$), but not for the 24-hour corneal hysteresis and the 24-hour corneal resistance factor. The mean phase timing for CCT was 4:59 AM $\pm$ 156 minutes and the mean height of 24-hour rhythm was 9.0 ± 5.5 μ m. The mean phase timing for IOP was 10:23 AM $\pm$ 209 minutes and the mean height of 24-hour rhythm was 1.8 ± 0.6 mm Hg. Wilcoxon signed-rank test showed that the CCT phase timing was significantly earlier than the IOP phase timing ($P = 0.022$). Compared to the younger group, the phase timings of 24-hour rhythms of IOP and CCT in the older group were significantly delayed ($P < 0.01$, Mann-Whitney rank-sum test) and the heights of 24-hour rhythms were not different.

Central corneal thickness and corneal hysteresis varied among different eyes in the 15 older subjects. Linear regression analysis showed a positive correlation between 15 paired mean CCT and mean corneal hysteresis during the diurnal period ($r = 0.576$, $P = 0.025$), the nocturnal period ($r = 0.656$, $P < 0.01$), and the 24-hour period ($r = 0.645$, $P < 0.01$; Fig. 2). Comparing the two linear regression lines of mean 24-hour CCT versus mean 24-hour corneal hysteresis, one line for each age group, the null hypothesis that the two lines were not different was rejected (Fig. 2). When linear regression was performed among the 12 paired time-dependent CCT and corneal hysteresis collected from the same older individual, there was no consistent correlation; a positive correlation in 2 individuals, a negative correlation in 2 individuals, and no correlation in 11 individuals (Table 1).

Corneal resistance factor also varied among different eyes. Linear regression analysis showed a positive correlation between 15 paired mean CCT and mean corneal resistance factor in the older subjects during the diurnal period ($r = 0.766$, $P < 0.001$), the nocturnal period ($r = 0.572$, $P = 0.026$), and the 24-hour period ($r = 0.719$, $P < 0.01$; Fig. 3). Comparing the two linear regression lines of mean 24-hour CCT versus mean 24-hour corneal resistance factor, one line for each age group, the difference was statistically significant (Fig. 3). When linear regression was performed among the 12 paired time-dependent CCT and corneal resistance factor collected from the same older individual, there was significant intra-individual correlation in only 1 of 15 individuals (Table 2).

There was no significant difference in the sitting mean blood pressure between the diurnal and the nocturnal periods for this group of older subjects. A significant reduction of heart rate was observed during the nocturnal period from the diurnal level ($P < 0.05$).

DISCUSSION

Aging can induce changes in the corneal biomechanical properties,^{2,11,12} which may affect corneal behavior during tonometry. In the present study, three corneal biomechanical

parameters were examined during a 24-hour period. We found that the mean 24-hour corneal hysteresis and corneal resistance factor, but not CCT, were lower in the older group than in the younger group. Aging effects on the corneal hysteresis and corneal resistance factor were consistent for 24 hours, beyond the office-hour period reported by others.¹⁴

Corneal hysteresis and corneal resistance factor were derived from characteristics in central corneal movement during the non-contact IOP measurement using the Ocular Response Analyzer. Although their representing physiologic properties are unclear, corneal hysteresis is thought to be an indicator of corneal viscous dampening and corneal resistance factor is an indicator of overall visco-elastic response of cornea.^{14,15,21} We confirmed the positive correlations between CCT and corneal hysteresis and between CCT and corneal resistance factor.^{5,15,22} One may hypothesize that the lower corneal hysteresis and lower corneal resistance factor in the older subjects can be explained by a thinner CCT. However, the difference in CCT between the older and younger subjects used for comparison in the present study was not statistically significant. In addition, the linear regression lines for the mean 24-hour CCT versus mean 24-hour corneal hysteresis and the mean 24-hour CCT versus mean 24-hour corneal resistance factor were statistically different between the two age groups (Figs. 2 and 3). It indicated that corneal hysteresis and corneal resistance factor were affected by aging, independent from CCT.

In both age groups, 24-hour variations in the corneal hysteresis and corneal resistance factor were not significant. The 24-hour CCT variation of 20 μm in the older group was close to the variation seen in the younger group.⁷ However, the phase timing determined by mathematical approximation was delayed by approximately 3 hours due to aging (2:10 AM vs. 4:59 AM). The phase timing in the 24-hour sitting IOP was affected even more by aging to a delay of 4.5 hours (5:50 AM vs. 10:23 AM). In the older group, the phase timing of 24-hour CCT rhythm appeared much earlier (approximately 5.5 hours) than the phase timing of 24-hour IOP rhythm. As shown in Figure 1, the 24-hour pattern of IOP was significantly out-of-phase with the 24-hour pattern of CCT in the older group. During the period of 5:30 AM to 9:30 AM, changes in CCT and IOP were in the opposite directions. By examining both the 24-hour changes of IOP and CCT and their phase timings of 24-hour rhythm, the time-dependent IOP elevation in this group of older subjects cannot be explained by the time-dependent CCT thickening.

Our data supports a positive correlation between CCT and IOP in this group of older subjects during the diurnal period.² However, this correlation did not appear during the nocturnal period due to the unparallel diurnal-to-nocturnal changes in CCT and IOP. There were positive correlations between CCT and corneal hysteresis as well as between CCT and corneal resistance factor among different eyes (Figs. 2 and 3). However, for the same eye, no consistent correlation between time-dependent data of CCT and corneal hysteresis or corneal resistance factor was found (Tables 1 and 2). When a physiological thickening of CCT occurred in an individual eye, frequently at night due to endogenous change in the corneal hydration state, the corneal hysteresis and corneal resistance factor did not increase accordingly. Others also found that corneal hysteresis was not associated with corneal swelling of 63 μm induced by soft contact lens wear with eye closure.⁵ Influences of corneal hydration state and swelling on the corneal hysteresis and corneal resistance factor are obviously different from the influences of removing real material of corneal stroma by laser in situ keratomileusis (LASIK).^{21,23}

Interpretation of our experimental results has several limitations. The sample size of 15 is relatively small and the participants are primarily Caucasians and female. Caution is needed to extrapolate the results to general aging population. The corneal hysteresis and corneal resistance factor are specific parameters generated by the non-contact Ocular Response Analyzer. When using the Goldmann applanation tonometer, which is widely considered the gold standard in the clinic, the comparable corneal biomechanical characteristics are not

known. The Ocular Response Analyzer can be used only in the sitting position. It is known that a postural change from sitting to supine elevates IOP and an acute IOP elevation has no impact on the corneal hysteresis determined in the sitting position.^{8,15} What the corneal hysteresis and corneal resistance factor are in a recumbent body position and whether or not these parameters stay unchanged in habitual body positions remain to be determined.

In summary, we found that aging can cause significant changes in corneal hysteresis and corneal resistance factor for 24 hours, beyond the office-hour period. Aging can also shift the 24-hour rhythms of CCT and IOP. However, the 24-hour IOP pattern in this group of older subjects is not associated with an endogenous variation in corneal hysteresis, corneal resistance factor, or CCT. Therefore, change patterns of 24-hour IOP observed most likely represent the true IOP change patterns inside the globe. Since changes in corneal hysteresis, corneal resistance factor, and CCT do not account for the 24-hour IOP variation, concomitant measurements of these parameters with IOP may have limited values in clinical evaluations of diurnal IOP variation in older adults with healthy eyes. Whether this observation can be applied to the changes of corneal biomechanical properties and IOP in untreated and treated glaucoma patients needs to be verified.

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B. Financial Disclosures: None.

C. Contributions of Authors: Design and conduct of the study (TK, JHKL, RNW); collection, management, analysis, and interpretation of the data (TK, JHKL, RNW); and preparation, review, or approval of the manuscript (TK, JHKL, RNW).

D. Conformity: The study was approved by the Institutional Review Board of University of California, San Diego. Informed consent was obtained from the subjects and the study is in accordance with HIPPA regulations.

Biography

Teruyo Kida, MD, PhD received her medical degree from Osaka Medical College in 1996. She completed a residency in Ophthalmology and a graduate program in 2002. She had further clinical and research training at Yodogawa Christian Hospital in Japan (2002–2005) and completed a research fellowship at University of California, San Diego (2005–2007). Her areas of research interest are on the 24-hour measurements of corneal biomechanical properties, intraocular pressure, and ocular blood flow in humans.

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Figure 1. Profiles of 24-hour change pattern in central corneal thickness (CCT), sitting intraocular pressure (IOP), and corneal hysteresis. Solid symbols represent the older group and open symbols represent the younger group. Error bars, SEM (N = 15).

Figure 2. Correlation between mean 24-hour central corneal thickness and mean 24-hour corneal hysteresis. Linear regression showing a positive correlation in the older subjects (solid circles; N = 15) and in the younger subjects (open circles; N = 15). The two regression lines were statistically different (P = 0.014).

Figure 3. Correlation between mean 24-hour central corneal thickness and mean 24-hour corneal resistance factor. Linear regression showing a positive correlation in the older subjects (solid circles; $N = 15$) and in the younger subjects (open circles; $N = 15$). The two regression lines were statistically different ($P < 0.01$).

Table 1
Strength of the association between central corneal thickness (CCT) and corneal hysteresis in individual older subject.

Subject	CCT range (μm)	Corneal hysteresis range (mmHg)	Regression coefficient (slope)	Correlation coefficient (r)	P
1*	555–572	9.1–14.8	0.301	0.696	0.012
2	470–491	6.7–10.8	0.013	0.081	0.803
3	530–564	7.0–11.7	0.068	0.568	0.054
4*	532–560	7.9–11.4	–0.086	–0.603	0.038
5	520–535	7.9–11.8	0.065	0.323	0.306
6	505–531	9.6–11.5	–0.039	–0.518	0.085
7	539–594	8.5–11.8	0.020	0.383	0.219
8	519–559	8.8–10.5	0.006	0.112	0.728
9	578–618	11.0–14.0	0.002	0.040	0.902
10	536–552	7.2–8.8	0.054	0.532	0.075
11*	586–601	9.9–12.8	0.108	0.597	0.040
12*	535–561	10.1–11.5	–0.032	–0.671	0.017
13	554–589	8.7–11.1	0.003	0.035	0.913
14	489–521	7.6–11.5	–0.067	–0.455	0.138
15	517–562	8.5–11.9	–0.038	–0.529	0.077

* A significant correlation between 12 paired CCT and corneal hysteresis in this subject.

Table 2
Strength of the association between central corneal thickness (CCT) and corneal resistance factor in individual older subject.

Subject	CCT range (μm)	Corneal resistance factor range (mmHg)	Regression coefficient (slope)	Correlation coefficient (r)	P
1	555–572	8.6–14.9	0.167	0.472	0.121
2	470–491	6.4–8.7	0.011	0.103	0.751
3	530–564	8.9–12.2	0.045	0.496	0.101
4	532–560	7.8–10.4	–0.049	–0.519	0.084
5	520–535	7.8–10.9	0.073	0.462	0.130
6	505–531	8.7–10.9	0.016	0.213	0.506
7	539–594	8.3–10.8	–0.000	–0.002	0.995
8	519–559	7.6–10.0	0.000	0.006	0.985
9	578–618	11.9–13.4	0.002	0.059	0.857
10	536–552	7.9–9.5	0.011	0.093	0.774
11	586–601	10.6–12.0	–0.016	–0.181	0.575
12	535–561	9.8–11.1	–0.015	–0.367	0.240
13	554–589	8.2–10.0	0.029	0.508	0.092
14	489–521	7.1–10.2	–0.037	–0.337	0.284
15*	517–562	6.5–10.0	–0.054	–0.711	0.010

* A significant correlation between 12 paired CCT and corneal resistance factor in this subject.