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Relationship between Diurnal Variation in Intraocular Pressure and Central Corneal Power

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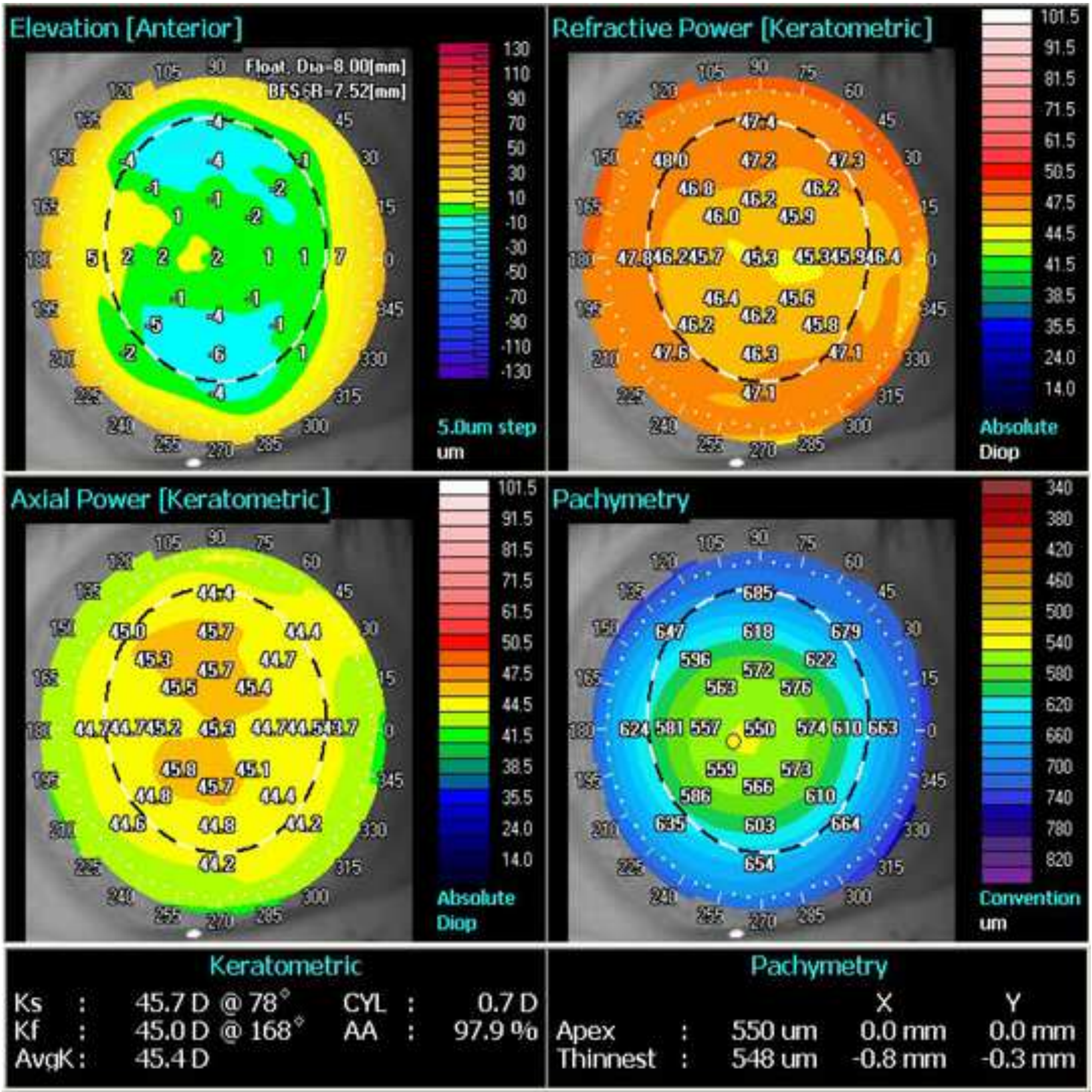
Abstract:	SIGNIFICANCE: Relationship between intraocular pressure (IOP) change and central corneal curvature is complicated by measurement techniques and corneal biomechanical parameters. Findings from this study indicate that it is worthwhile to observe the association between diurnal change in IOP and corneal power. PURPOSE: To investigate the relationship between the diurnal change in IOP and central corneal power among eyes with and without myopia. METHODS: Sixty healthy eyes of 24 emmetropes and 36 myopes were recruited for this cross-sectional study. Both anterior and posterior central corneal powers of the steep (Ks), flat (Kf), mean meridian (Km), best-fit spheres, and central corneal thickness (CCT), were recorded followed by the IOP (Goldmann-correlated [IOPg] and corneal-compensated [IOPcc]) and corneal biomechanics (corneal hysteresis and corneal resistance factor). Measurements were obtained every 3 hours from 9.30AM till 6.30PM. Linear mixed model was used to determine the relationship between the change in IOP and the associated change in corneal measurements (adjusted for age, sex, refractive error, CCT, and biomechanics) among the myopic and non-myopic eyes. RESULTS: Group mean, amplitude of change, and the diurnal change in IOPg were (mean±SD) 15.14±2.50, 3.33±1.44 and 1.81±1.25 mmHg respectively. Overall, an IOP increase was associated with a decrease in the adjusted anterior corneal powers. Myopic eyes were associated with a decrease of 0.04D (95%CI: 0.07-0.01, P=.02) in Ks and 0.03D (95%CI: 0.06-0.001, P=.047) in Kf per mmHg increase in IOP. Whereas for emmetropes, per mmHg increase in IOP only flattened the Kf by 0.03D (95% CI: 0.06-0.004, P=.02). CONCLUSIONS: Change in anterior corneal power was inversely related to the change in IOPg, with myopic and non-myopic eyes reporting a significant but differential impact of IOP. Clinicians must keep in mind the impact of large intraocular pressure fluctuation on the anterior corneal power.


Elevation [Anterior]
Float, Dia=8.00[mm]
BFS R=7.52[mm]
5.0um step
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Refractive Power [Keratometric]
Absolute
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Axial Power [Keratometric]
Absolute
Diop
Pachymetry
Convention
um
Keratometric
Ks : 45.7 D @ 78° CYL : 0.7 D
Kf : 45.0 D @ 168° AA : 97.9 %
AvgK : 45.4 D
Pachymetry
X Y
Apex : 550 um 0.0 mm 0.0 mm
Thinnest : 548 um -0.8 mm -0.3 mm

ORIGINAL INVESTIGATION

Relationship between Diurnal Variation in Intraocular Pressure and Central Corneal Power

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ABSTRACT

Significance: Relationship between intraocular pressure (IOP) change and central corneal curvature is complicated by measurement techniques and corneal biomechanical parameters. Findings from this study indicate that it is worthwhile to observe the association between diurnal change in IOP and corneal power. **Purpose:** To investigate the relationship between the diurnal change in IOP and central corneal power among eyes with and without myopia. **Methods:** Sixty healthy eyes of 24 emmetropes and 36 myopes were recruited for this cross-sectional study. Both anterior and posterior central corneal powers of the steep (Ks), flat (Kf), mean meridian (Km), best-fit spheres, and central corneal thickness (CCT), were recorded followed by the IOP (Goldmann-correlated [IOPg] and corneal-compensated [IOPcc]) and corneal biomechanics (corneal hysteresis and corneal resistance factor). Measurements were obtained every 3 hours from 9.30 AM till 6.30 PM. Linear mixed model was used to determine the relationship between the change in IOP and the associated change in corneal measurements (adjusted for age, sex, refractive error, CCT, and biomechanics) among the myopic and non-myopic eyes. **Results:** Group mean, amplitude of change, and the diurnal change in IOPg were (mean±SD) 15.14±2.50, 3.33±1.44 and 1.81±1.25 mmHg respectively. Overall, an IOP increase was associated with a decrease in the adjusted anterior corneal powers. Myopic eyes were associated with a decrease of 0.04D (95%CI: 0.07-0.01, *P*=.02) in Ks and 0.03D (95%CI: 0.06-0.001, *P*=.047) in Kf per mmHg increase in IOP. Whereas for emmetropes, per mmHg increase in IOP only flattened the Kf by 0.03D (95% CI: 0.06-0.004, *P*=.02). **Conclusions:** Change in anterior corneal power was inversely related to the change in IOPg, with myopic and non-myopic eyes reporting a significant but differential impact of IOP. Clinicians must keep in mind the impact of large intraocular pressure fluctuation on the anterior corneal power.

Intraocular pressure is the only modifiable risk factor for the development and progression of glaucoma.[1] However, a single visit office intraocular pressure measurement every 4-6 months is insufficient to determine the intraocular pressure profile of the eye[2] as it undergoes cyclical diurnal variation throughout and across days.[3] Routine intraocular pressure measurement during office hours misses the peak intraocular pressure in 22.5-62% of glaucoma patients.[4,5] Notwithstanding inconsistent literature[6], intraocular pressure fluctuation may be a risk factor for glaucoma progression.[7] Hence, intraocular pressure needs closer monitoring, preferably the 24-hour behavior.[5]

Wireless ocular telemetry sensor, commercially known as Sensimed Triggerfish, is a silicone contact lens that monitors corneal curvature change and indirectly measures intraocular pressure fluctuation over 24 hours. The strain gauge in the contact lens is based on the assumption that intraocular pressure and central corneal curvature are inversely related as it continuously records the changes in corneal curvature and acquires measurements in millivolts.[8] A clinical and an ex-vivo study on enucleated human eyes found the change in corneal curvature to be associated with a change in intraocular pressure,[9,10] while a clinical study reported no related change.[11] On the contrary, by artificially raising intraocular pressure in pre-surgical patient eyes, Kohlhass et al[12] showed that only central corneal thickness and not corneal curvature is significantly related to intraocular pressure. However, these studies[9,10,12] are limited by the low reliability of manual keratometers[13,14] in measuring the corneal curvature and non-adjustment of corneal biomechanical properties and central corneal curvature which affects intraocular pressure measurement.[15] To our knowledge, there are no reports demonstrating the association between the change in intraocular pressure and corneal curvature after adjusting for corneal biomechanical properties and thickness in a clinical setting.

Swept-source optical coherence tomography (SS-OCT, Casia SS-1000; Tomey, Nagoya, Japan) produces high-quality image of the anterior and posterior surface of the cornea using a fast-scan (axial resolution <10 µm). Casia renders extremely fast and reliable measurements of central corneal thickness, corneal curvatures, power, and best-fit sphere.[16,17] On the other hand, an Ocular Response Analyzer (ORA, Reichert Inc, Depew, NY) is a non-contact tonometer that not only measures corneal-compensated intraocular pressure (IOPcc) and Goldmann-correlated intraocular pressure (IOPg) but also provides corneal biomechanical properties like corneal hysteresis and corneal resistance factor.[18] Briefly, corneal hysteresis is the ability to dampen energy (intraocular pressure fluctuations) and is influenced by the biomechanical/viscoelastic properties of the cornea. The corneal resistance factor is a measurement of the overall resistance of the cornea. We used swept-source OCT (SS-OCT) and the Ocular Response Analyzer (ORA), to estimate the relationship between diurnal change in IOPg and IOPcc of healthy myopic and emmetropic eyes (adjusted for central corneal thickness and biomechanical properties) with the corneal power in dioptres, which is a proxy for corneal curvature.

METHODS

Subjects and Procedure

The study was approved by the local ethics committee and adhered to the tenets of the 1964 Declaration of Helsinki. Informed consent was obtained from all the participants of the study. This cross-sectional study was conducted on a cohort of 60 healthy ethnic Indian subjects at the corneal refractive surgery clinic of the B.B. Eye Foundation between September 1, 2020 and November 30, 2021. The subjects were aged between 24 and 45 years (mean±SD, 30.01±5.09 years) out of whom twenty were male. Subjects had spherical equivalent refraction between 0.00 to -6.00 D (mean±SD, -1.63±1.57 D). All participants underwent complete ophthalmic examination and had no ocular abnormality except myopia <6.0 D, myopic astigmatism ≤1.0 D of cylinder, or anisometropia <1.0 D with a corrected distance visual acuity of 6/6 (logMAR 0.00) or better in both eyes. Subjects had stable refraction for the past 1 year with no sign or symptom of corneal ectasia or abnormality. The examinations included documenting their past medical and ocular history, followed by objective and subjective refraction, anterior and posterior segment examination of both eyes under slit-lamp biomicroscopy, and intraocular pressure with Goldmann applanation tonometer. Subjects did not have any history of contact lens use within the preceding 30 days of examination or any history of intraocular pressure spike >21 mmHg, family history of glaucoma, use of intraocular pressure lowering medication, or any topical and systemic steroid use, ocular surgery, disease or injury. The following day, subjects sequentially underwent SS-OCT followed by ORA after an interval of 5 minutes, every 3 hours from 9.30 AM till 6.30 PM (session 1: 9.30 AM, session 2: 12.30 PM, session 3: 3.30 PM, session 4: 6.30 PM). Subjects were asked to report before the examination session and sit for at least 10 minutes (washout period) to reduce the effect of physical activity or posture on intraocular pressure.[19] The first ocular measurement was collected 2 hours after waking up to avoid any changes in anterior eye parameters induced by overnight eye closure.[20] Participants were asked to refrain from consuming alcoholic,[21] caffeinated beverages[22] and vigorous physical activity[23] from the day before and on the day of the study as they were found to influence intraocular pressure.

Both eyes of the subjects were measured by the same observer and testing was conducted under dim room illumination. Calibration of all the devices was checked and maintained yearly by the manufacturer. For SS-OCT, two readings per eye were recorded and averaged for every session. Corneal parameters included for analysis were central corneal thickness and both anterior and posterior central corneal power of the steep, flat, mean meridian, and best fit sphere. Keratometry values were collected in diopters on all subjects. The corneal fit zone diameter applied was 8 mm and both anterior and posterior elevation analyses were done on a central 3.0 mm corneal zone. Non-contact tonometer was used to obtain the corneal hysteresis, corneal resistance factor, IOPcc, and IOPg as described elsewhere.[18] IOPg readings from ORA are found to correlate well with Goldmann applanation tonometry readings.[24] Three ORA readings were obtained during every session for each eye with a waveform score >6.5 and their average was taken for analysis. Data from the left eyes of all participants were used for analysis.

Statistical Analysis

Data were analyzed using STATA version 12.0 (StataCorp LP, College Station, TX). The group mean (average of all sessions), the amplitude of change (difference between the maximum and minimum), and the diurnal change (average of the differences between one session to the next session) for all the ocular parameters were calculated. Welch's t-test was used to compare means between two groups of unequal sample sizes. Myopia was defined as spherical equivalent less than -0.5 D and emmetropia as spherical equivalent between -0.5 D and +0.5 D. A mixed-design analysis of variance model with one within-subject factor (time of day) was used to determine diurnal changes in the ocular parameters and one between-subject factor (spherical equivalent) to find differences among the refractive error groups. Bonferroni correction was applied for multiple comparisons to reduce the risk of type I error. To investigate the association between change in intraocular pressure and corresponding changes in corneal power, a linear mixed model was utilized. Linear mixed models of corneal power were fitted with fixed coefficients (fixed effects) on age, sex, spherical equivalent, intraocular pressure, corneal hysteresis or resistance factor, central corneal thickness, and with random intercepts and coefficients (random effects) at the subject level for the effect of time (repeated testing). Corneal hysteresis and resistance factors were analyzed in separate models as they were highly correlated (Pearson correlation=0.81, $P<.001$). Central corneal thickness was moderately correlated to the corneal hysteresis (Pearson correlation=0.27, $P<.001$) and resistance factor (Pearson correlation=0.36, $P<.001$) in this study. The rate of change of corneal power was estimated in relation to the change in IOPg and IOPcc. A P value <.05 was considered statistically significant. Power calculation revealed that current sample sizes (24 in emmetropia and 36 in the myopia group) had powers of 0.81 and 0.93 respectively at an α level of 0.05 to detect a minimum change of 0.008±0.024 mm[9] in corneal curvature from 1 baseline and 3 repeated measurements.

RESULTS

Sixty eyes of 60 normal subjects (24 emmetropic and 36 myopic) were included in the analysis. The demographics and ocular parameters are presented in Table 1. Eyes with emmetropia and myopia had similar corneal biometrics and intraocular pressure estimates. The range of IOPg was 7-21 mmHg and central corneal thickness was between 475-619 µm among the participants. IOPg and Goldmann applanation tonometry were strongly correlated (Pearson correlation=0.90, $P<.001$) in our study.

Diurnal Variation in Intraocular Pressure

The group mean, the amplitude of change, and the diurnal change in IOPg (mean±SD) were 15.14±2.50 mmHg (range, 8-21), 3.33±1.44 mm Hg (range, 1.1-6.2) and 1.81±1.25 mmHg (range, 0-6.1) respectively, for all eyes. Emmetropes and myopes had a similar group mean (15.11±2.67 vs 15.16±2.40 mmHg; P=.92) and amplitude of change (3.65±1.41 vs 3.12±1.46 mmHg; P=.33) in IOPg. Although of borderline statistical significance, the intersession change in IOPg was higher in emmetropic eyes than in the myopic ones (2.15±1.51 vs 1.57±0.99 mmHg, P=.048) (Tables 1-2, Appendix Table A1, available at **[LWW insert link]**). Mixed-design analysis of variance model demonstrated significant (P<.05) diurnal variation (within-subject effect of time) in central corneal thickness, anterior and posterior corneal parameters (flat meridian, mean meridian, best fit sphere), corneal resistance factor along with IOPg. There was no significant refractive error or time-refractive error interaction among any of the ocular biometrics or intraocular pressures (Table 2). This indicates that both the emmetropic and myopic eyes had a similar degree and amplitude of diurnal variation among the measured variables.

Diurnal variation in IOPg was significant across the day (mixed-design analysis of variance; F (3,83)=5.42, P=.002). The highest and lowest IOPs were recorded during sessions 1 (9.30 AM) and 3 (3.30 PM). Intrasession IOPg varied significantly (repeated measures ANOVA; F (3,86)=5.66, P=.001). IOPg recordings for sessions 1 (15.98±2.32 mmHg) and 2 (15.43±2.89 mmHg) were significantly higher (Bonferroni corrected P<.05) than sessions 3 (14.55±2.02 mmHg) and 4 (14.58±2.52 mmHg). There was no significant difference in intrasession intraocular pressure among the emmetropes and myopes (P>.05).

Change in Anterior and Posterior Corneal Power in Relation to the Goldmann-correlated Intraocular Pressure

Anterior corneal steep meridian power was inversely related to the increase in IOPg after adjusting for age, sex, spherical equivalent, central corneal thickness, and corneal hysteresis. Every 1 mmHg increase in IOPg resulted in a 0.03 D decrease in the steep meridian power (P=.02). Myopic eyes were significantly related, with a 0.03 D decrease in their steep meridian powers with a unit increase in IOPg (P=.03), which had a further decrease to 0.04 D after additional adjustment for corneal hysteresis (P=.02). Emmetropes had an insignificant relation between steep meridian power and IOPg.

Anterior flat meridian power on the other hand had a stronger association with the IOPg exhibiting a 0.02 to 0.03 D decrease for every mmHg increase in IOPg (P<.05) both with and without adjustment of any factors. Unlike the steep meridian, additional adjustment of corneal hysteresis resulted in a significant relationship between the flat meridian power and IOPg (0.03 D decrease per mmHg) among both emmetropes (P=.02) and myopes (P=.047, borderline statistical significance).

Mean meridian power and IOPg were significantly related before and after adjusting for age, sex, spherical equivalent, central corneal thickness, and corneal hysteresis or resistance factor. With every 1 mm Hg increase in IOPg, there was a 0.02 to 0.03 D decrease in anterior mean meridian power (P<.001) when adjusted for corneal resistance factor and corneal hysteresis along with other variables. The relationship was significant at 0.03 D of decrease in mean meridian power for only myopic eyes (P=.01). When adjusted for corneal resistance factor, the 0.03 D decrease in mean meridian power was borderline significant (*P*=.05) for myopic eyes (Table 3, Appendix Table A2, available at **[LWW insert link]**).

Similar to the anterior steep meridian power, the anterior best fit sphere showed a significant change with IOPg only in the myopic eyes (0.003 mm increase per mmHg, *P*=.01). Although the unadjusted posterior best fit sphere showed an inverse relationship with IOPg, after adjustment for corneal hysteresis and other factors, it remained significant only for emmetropic eyes (*P*=.01).

None of the posterior corneal power showed a significant relation with the IOPg after adjusting for the variables (Table 3). The scatterplots show the weak association between IOPg and anterior corneal steep, flat, and mean meridian powers (Fig. 1 A-C).

Change in Anterior and Posterior Corneal Curvatures in Relation to the Corneal-compensated Intraocular Pressure

The anterior corneal steep, flat, mean meridian power, and the best fit sphere had a non-significant relationship with IOPcc. Similarly, the posterior corneal power also did not have a significant relationship with the IOPcc. Only in eyes with myopia, the posterior best fit sphere was significantly related to the IOPcc (0.002 mm decrease per mmHg, *P*=.04) after age, sex, and refractive error adjustment. The weak association of IOPcc with the anterior steep, flat, and mean meridian power are shown in the scatterplots (Fig. 1 D-F). (Table 4, Appendix Table A3, available at **[LWW insert link]**).

There were minimal changes (<5 degrees) in the astigmatic axes or the angles of both the anterior and posterior corneal steep and flat meridian power across the day (*P*>.05).

DISCUSSION

In this study, the diurnal change in anterior and posterior corneal powers was recorded in diopters from all participants along with the Goldmann correlated and corneal compensated intraocular pressure. A reduction in dioptric power indicated a flattening of the radius of curvature. We demonstrated that diurnal change in intraocular pressure is inversely related to the curvature change in the anterior cornea: where an increase in IOPg significantly flattened the anterior corneal curvatures. Diurnal variation in IOPg observed was comparable to the previous findings of peak intraocular pressure ranging around 9 AM.[25,26] We found the peak IOPg to be during session 1 (9.30 AM) which decreased over the day and maximum intersession difference was observed between sessions 2 (12.30 PM) and 3 (3.30 PM). IOPg fluctuation among myopic and emmetropic eyes observed was similar to that reported by Read et al.[25] The group mean, mean amplitude of change, and intersession change in the IOPg and ocular biometric parameters were similar among the two refractive error groups. Although central corneal thickness and the IOPg both displayed change over time, they had a low correlation (Pearson correlation=0.25, *P*=.006).

Reliability and Accuracy of the Findings

The findings are in agreement with the previous studies done on human donor eyes and animals which similarly recorded flattening of corneal curvature with an increase in intraocular pressure.[9,10,27] by artificially elevating intraocular pressure in enucleated porcine eyes, Leonardi et al[27,28] showed a 3 µm change (equivalent to 0.01-0.02 D) in the corneal curvature for every mmHg change in intraocular pressure. Hjortal et al[10] studied the effect of artificially elevated intraocular pressure by 20 mmHg in enucleated donor eyes and reported 0.02 D decrease of the corneal power per mmHg intraocular pressure. Similarly, Lam et al[9] found intraocular pressure elevation by posture change among healthy individuals results in 0.01 D reduction of horizontal meridian power per mmHg increase. These are comparable to the findings reported here (0.02-0.04 D per mmHg, Table 3). A limitation of this assessment would be comparing studies using in-vivo as well as ex-vivo eyeballs. In addition, the cornea is viscoelastic, rendering the corneal stress-strain relationship non-linear. This means that the cornea may respond differently to different levels of change in IOPg. By artificially inducing elevated intraocular pressure in pre-surgical eyes, Goldmann applanation tonometry intraocular pressure was found to be significantly associated with only central corneal thickness, but not corneal curvature.[12] However, their study participants were much older than in this study (72.9±13.2 vs 30.02±5.09 years) and the cornea tends to stiffen with age[29], altering its biomechanics. Consequently, non-adjustment of corneal biomechanical properties is an issue in clinical studies using Goldmann applanation tonometry, as the intraocular pressure measurements might get affected,[15] especially when comparing differently aged sample populations.[29] Moreover, they are limited by the use of a manual keratometer to measure the corneal curvature which has lower reliability than modern computerized topographers and optical coherence tomography.[13] Additionally, the studies were conducted either in-vitro[10] or in animals.[27] It should be noted that comparing animal models of ocular biomechanics to living human subjects should be done with extreme caution, because of the differences in size and composition/properties between non-human and human eyes. None of the studies mentioned above adjusted for corneal parameters while estimating the relationship between intraocular pressure and corneal curvature. Nevertheless, their findings are close to ours, which probably indicates that the impact of corneal estimates might not be large (something that may be statistically significant is not necessarily clinically significant) on the change in corneal curvature in this study population with normal IOPg. It is likely that changes in central corneal thickness and biomechanics are likely to have a much more significant effect on intraocular pressure measurements than the small changes in corneal curvature, that is, the change in corneal curvature with IOPg may be statistically significant but is unlikely to be clinically significant in a population with normal intraocular pressure.

Impact of Refractive Error

We found corneal curvature among emmetropic and myopic eyes to be differently related to the IOPg, with a change observed in both steep and flat meridian curvatures in myopic eyes, whereas, the flatter meridian had a stronger relationship in the emmetropic eyes. Mean meridian was associated with the IOPg in all eyes when adjusted for corneal hysteresis but not the corneal resistance factor. A different approach of using digital pressure on the temporal sclera examined the effect of increased intraocular pressure on the corneal curvature. They found a mixed effect on the steep and flat meridian power, with significant changes of 0.14-0.2 D (P<.01) observed only in the steep meridian power corresponding to an increase in intraocular pressure by 9.8-37 mmHg.[30] However, this technique is limited by the unpredictable nature and variability of the palpation technique as this potentially induces mechanical deformation of the globe, which would be reflected in a change in keratometry values. No change was observed among myopic, hyperopic, and emmetropic subjects when studying the effect of refractive error and Valsalva maneuver on corneal curvature.[31] But, the authors did not measure actual intraocular pressure, but assumed an increase in intraocular pressure. Ocular axial length is known to undergo significant diurnal variation and they are different among myopes and emmetropes.[19,25] COMET study reported the longitudinal flattening of the flat meridian and no change in the steep meridian over 5 years of myopia progression.[32] Corneal astigmatism and/or axial length variation across the day might be responsible for the differential impact of intraocular pressure on the corneal curvatures among eyes with myopia (longer) and emmetropia (shorter). Although more astigmatism is reported in shorter and longer eyes (Enthoven, et al. IOVS 2017; ARVO E-ABSTRACT 2399) participants of our study had astigmatism ≤1.0 D. There was a non-significant change in astigmatic axes (angle change <5 degrees) of the steep and flat meridians in this study. To compensate for the lack of axial length data from the study subjects, we used the refractive error of the participants as a surrogate. Nevertheless, the axial length is a better predictor of myopia than the spherical equivalent,[33] which is a limitation of this study. Limitations of this study which includes the applicability/generalizability of the conclusions to other ethnic groups and/or states of eye/general health and others were noted throughout the body of the manuscript.

Reliability and Accuracy of the Measurement Devices

This study investigated the diurnal intraocular pressure changes in healthy eyes which was relatively lower than the intraocular pressure change observed in glaucomatous eyes. Likewise, Read et al[11] studied the relationship between diurnal variation in intraocular pressure (using a dynamic contour tonometer) and corneal curvature (using Scheimpflug imaging) among normal subjects. They failed to find any significant change in the corneal curvature associated with 3.12 mmHg mean amplitude of intraocular pressure change. While SS-OCT is faster and has higher repeatability, it can be used interchangeably with Scheimpflug imaging to measure corneal thickness and radius of curvature in healthy eyes.[16] For intraocular pressure measurement, both dynamic contour tonometer and ORA compensate for the corneal biomechanics, but unlike IOPcc, IOPg remains uncompensated. In addition, the intraocular pressure derived from dynamic contour tonometer and ORA (IOPg) has a controversial relationship, with reports of both good agreement[34] as well as differences.[35] There might be differences (over or underestimation) in the relative accuracy and precision of the two intraocular pressure measurement techniques as much as true differences in the populations studied. Studying the effect of intraocular pressure on the corneal curvature of eyes with greater fluctuation is germane to further validate this relationship. IOPcc fluctuation was not related to the change in corneal curvature probably because it was central corneal thickness and biomechanics compensated.[18] Noticeably, the corneal hysteresis was only slightly lower in myopes compared to the emmetropes (Table 1). Previous studies had reported lower corneal hysteresis among eyes with myopia, especially highly myopic eyes (spherical equivalent >-6.00 D)[36] compared to the controls. This was not demonstrated in this population probably because of the limited degree of myopic individuals recruited (low to moderate), which is an additional limitation of this study. The corneal resistance factor as expected was similar among the emmetropic and myopic study participants. Although we recorded both the ORA and Goldmann applanation tonometry for the study subjects, we chose IOPg and IOPcc from the ORA for analysis over Goldmann applanation tonometry to account for the corneal biomechanical properties. Besides, IOPg and Goldmann applanation tonometry is known to be strongly correlated.[24]

Clinical Relevance

Given, that the IOPg recorded in this study is during a typical office working hour, the IOPg fluctuation data may add relevance to the practicing clinician trying to schedule intraocular pressure and/or corneal curvature/power assessment and compare values acquired at different times of the day. A 0.04 D change in anterior corneal power may not have an impact on clinical decision-making, but 5 mmHg or 10 mmHg corresponding to ~0.25 D or ~0.5 D respectively, does. Although not always consistent, previous studies have noted significantly higher intraocular pressure[37] and greater intraocular pressure fluctuation[38] among myopic eyes compared to non-myopic eyes, especially after heavy exercise. Besides, myopia is strongly associated with the risk of developing glaucoma and glaucoma progression.[39] Even a 1.6 mmHg mean intraocular pressure fluctuation is related to faster visual field progression in myopic normal tension glaucoma eyes compared to the non-myopic ones.[40] Likewise, 1 mm Hg higher intraocular pressure fluctuation has been shown to be associated with a 31% higher risk of glaucomatous visual field loss progression.[41] Equally, intraocular pressure diurnal fluctuation tends to play an important role in axial elongation.[25]

Future Directions

The basis of the Goldmann tonometer is Imbert-Fick's law, which assumes the cornea to be infinitely thin, perfectly elastic, perfectly flexible, and corneal curvature to be fixed. However, these assumptions are incorrect. Corneal steepening or flattening associated with an increase or decrease in intraocular pressure changes the area of applanation and force required to achieve the standard area of contact (3.06 mm^2). This results in either underestimation or overestimation of intraocular pressure (statistically significant).[42] Therefore, clinically validating Goldmann applanation tonometry against a myriad of steep and flat meridian curvatures is important to obtain the corrected or true intraocular pressure readings.[43] Previously, authors reported a non-clinically significant effect of corneal curvature on the intraocular pressure readings,[44,45] factors like the central corneal thickness, corneal hysteresis, and corneal resistance factor need to be considered when estimating the relationship between Goldmann applanation tonometry and corneal curvature. Although the effect of intraocular pressure is small for this population with normal intraocular pressure fluctuation, a greater change in intraocular pressure may result in a clinically significant variation.

CONCLUSIONS

Using this sample of a healthy ethnic Indian population, the study found the diurnal change in IOPg associated with a small, yet statistically significant change in anterior corneal curvatures. Although this relatively small change in corneal curvature is measurable[17] using modern corneal imaging techniques, the values were not likely to have a clinical impact. To date, this is the first report demonstrating the inverse association between increasing intraocular pressure and corneal curvature after adjusting for corneal biomechanical properties and thickness in a clinical setting. This relationship was dissimilar among eyes with and without myopia. Increasing IOPg flattened both the anterior steep and flat meridian curvature in myopes, while, for emmetropes, it was only the flat meridian. With the rising prevalence of myopia[46] and glaucoma worldwide[47] and the growing need to measure intraocular pressure, this data can be applied to design, validate and improvise devices for accurate measurement of intraocular pressure and its fluctuation. This association needs to be further validated in eyes with a greater fluctuation in intraocular pressure and a higher degree of myopia.

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APPENDICES

Appendix Table A1, available at **[LWW insert link]**: diurnal change of the ocular biometric parameters and intraocular pressure.

Appendix Table A2, available at **[LWW insert link]**: estimated change in unadjusted ocular biometric parameters in relation to the goldmann-correlated intraocular pressure calculated from the linear mixed models.

Appendix Table A3, available at **[LWW insert link]**: estimated change in unadjusted ocular biometric parameters in relation to the corneal-compensated intraocular pressure calculated from the linear mixed models.

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Table 1. Summary of Group Means among All, Emmetropic and Myopic Eyes for Age, Ocular Biometrics, and Intraocular Pressure.

Demographic	All		Emmetropes		Myopes		*P*†
	Group mean±SD	95% CI	Group mean±SD	95% CI	Group mean±SD	95% CI	
Eyes/Participants	60/60		24/24		36/36		-
Age (years)	30±5	29, 31	29±6	28, 31	31±5	29, 32	.19
Sex, Number							
Male	20		10		10		-
Female	40		20		20		-
SE, diopter	-1.63±1.57	-1.91, -1.35	-0.08±0.19	-0.14, -0.03	-2.68±1.17	-2.95, -2.40	<.001
CCT, μm	547±29	541, 552	551±33	541, 560	544±25	538, 550	.23
Anterior cornea							
Ks, diopter	44.17±1.52	43.90, 44.45	44.02±1.59	43.55, 44.48	44.27±1.46	43.93, 44.62	.37
Kf, diopter	43.16±1.37	42.91, 43.41	43.11±1.31	42.73, 43.50	43.19±1.41	42.86, 43.52	.77
Km, diopter	43.67±1.42	43.41, 43.93	43.57±1.43	43.16, 43.99	43.73±1.41	43.40, 44.07	.54
BFS, mm	7.81±0.24	7.77, 7.86	7.83±0.25	7.75, 7.90	7.80±0.23	7.75, 7.86	.62
Posterior cornea							
Ks, diopter	-6.35±0.22	-6.39, -6.31	-6.32±0.21	-6.38, -6.26	-6.38±0.23	-6.43, -6.32	.16
Kf, diopter	-6.06±0.20	-6.09, -6.02	-6.07±0.18	-6.12, -6.02	-6.05±0.21	-6.10, -6.00	.62
Km, diopter	-6.21±0.20	-6.24, -6.17	-6.20±0.19	-6.25, -6.14	-6.21±0.21	-6.26, -6.16	.66
BFS, mm	6.55±0.21	6.51, 6.59	6.56±0.21	6.50, 6.62	6.55±0.21	6.50, 6.60	.78
Corneal biomechanics							
CH	10.91±1.37	10.66, 11.16	11.01±1.20	10.62, 11.39	10.86±1.46	10.54, 11.19	.57
CRF	10.73±1.24	10.51, 10.96	10.72±1.13	10.39, 11.05	10.74±1.32	10.43, 11.05	.93
Intraocular pressure							
IOPcc, mm Hg	15.13±2.85	14.61, 15.64	15.11±2.95	14.25, 15.97	15.14±2.81	14.47, 15.80	.96
IOPg, mm Hg	15.14±2.50	14.69, 15.59	15.11±2.67	14.33, 15.89	15.16±2.40	14.59, 15.73	.92

†Welch's t-test. SE = spherical equivalent, CCT = central corneal thickness, Ks = central corneal curvature of the steep meridian, Kf = central corneal curvature of the flat meridian, Km = mean central corneal curvature, BFS = best-fit sphere, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal-compensated intraocular pressure, IOPg = Goldmann-correlated intraocular pressure

Table 2. Amplitude of Variation in the Ocular Biometric Parameters and Intraocular Pressure.

Variable	Amplitude of Change						$P^{†}$	*P* (Time)	*P* (Refractive error)	*P* (Time-refractive error)
	All (mean±SD)	95% CI	Emmetrope (mean±SD)	95% CI	Myope (mean±SD)	95% CI				
CCT, µm	6.60±3.76	5.20, 8.00	7.00±3.81	4.58, 9.42	6.33±3.80	4.44, 8.23	.64	**<.001**	.53	.35
Anterior cornea										
Ks, diopter	0.36±0.24	0.27, 0.45	0.41±0.33	0.20, 0.62	0.33±0.16	0.25, 0.41	.45	.39	.64	.14
Kf, diopter	0.30±0.16	0.24, 0.36	0.30±0.14	0.21, 0.39	0.29±0.18	0.21, 0.38	.93	**.01**	.86	.29
Km, diopter	0.28±0.19	0.21, 0.35	0.31±0.22	0.17, 0.45	0.26±0.17	0.18, 0.34	.53	**.046**	.74	.06
BFS, mm	0.02±0.02	0.01, 0.03	0.03±0.01	0.01, 0.04	0.02±0.03	0.01, 0.03	.13	**.003**	.78	.26
Posterior cornea										
Ks, diopter	0.02±0.04	0.01, 0.04	0.03±0.05	0.01, 0.05	0.02±0.04	0.001, 0.04	.61	.11	.47	.45
Kf, diopter	0.03±0.04	0.01, 0.04	0.04±0.05	0.01, 0.07	0.02±0.04	0.001, 0.04	.17	**.009**	.86	.24
Km, diopter	0.03±0.04	0.01, 0.04	0.04±0.05	0.01, 0.07	0.02±0.04	0.001, 0.04	.17	**.004**	.79	.29
BFS, mm	0.02±0.01	0.02, 0.03	0.03±0.01	0.02, 0.03	0.02±0.01	0.02, 0.02	.07	**<.001**	.79	.47
Corneal biomechanics										
CH	1.96±1.18	1.52, 2.40	1.92±1.41	1.02, 2.81	1.99±1.05	1.47, 2.52	.87	.68	.93	.82
CRF	1.85±1.01	1.47, 2.23	1.76±1.09	1.07, 2.45	1.91±0.98	1.42, 2.40	.69	.103	.90	.82
Intraocular pressure										
IOPcc, mm Hg	3.98±1.76	3.33, 4.64	4.56±1.92	3.34, 5.78	3.60±1.58	2.82, 4.38	.16	.05	.98	.64
IOPg, mm Hg	3.33±1.44	2.79, 3.87	3.65±1.41	2.75, 4.55	3.12±1.46	2.39, 3.84	.33	**.002**	.93	.59

†Welch's t-test. Summary data of the amplitude of change and P values from mixed-design analysis of variance model examined the within-subject effect of time, between-subject effect of refractive error, and the time-refractive error interaction for the ocular biometric parameters. *P* values that are significant ($P<.05$) are highlighted in bold. CCT = central corneal thickness, Ks = central corneal curvature of the steep meridian, Kf = central corneal curvature of the flat meridian, Km = mean central corneal curvature, BFS = best-fit sphere, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal-compensated intraocular pressure, IOPg = Goldmann-correlated intraocular pressure

Table 3. Estimated Change in Adjusted Ocular Biometric Parameters in Relation to the Goldmann-correlated Intraocular Pressure (IOPg) Calculated from the Linear Mixed Models.

Variable	Add adj	All			Emmetropes			Myopes		
		Coefficient	95% CI	P	Coefficient	95% CI	P	Coefficient	95% CI	P
Anterior cornea										
Adjusted change of Ks, diopter	CH	-0.03	-0.05, -0.004	**.02**	-0.03	-0.07, 0.01	.16	-0.04	-0.07, -0.01	**.02**
	CRF	-0.02	-0.05, 0.003	.08	-0.02	-0.05, 0.02	.45	-0.03	-0.06, 0.001	.05
Adjusted change of Kf, diopter	CH	-0.03	-0.05, -0.01	**.002**	-0.03	-0.06, -0.004	**.02**	-0.03	-0.06, -0.001	**.047**
	CRF	-0.02	-0.04, -0.003	**.03**	-0.03	-0.05, 0.0004	.05	-0.02	-0.05, 0.01	.19
Adjusted change of Km, diopter	CH	-0.03	-0.05, -0.01	**.003**	-0.03	-0.06, 0.0001	.05	-0.03	-0.06, -0.01	**.01**
	CRF	-0.02	-0.04, -0.002	**.03**	-0.02	-0.05, 0.01	.23	-0.03	-0.06, 0.0003	.05
Adjusted change of BFS, mm	CH	0.002	0.0004, 0.004	**.01**	0.001	-0.001, 0.004	.35	0.003	0.001, 0.006	**.01**
	CRF	0.002	-0.0003, 0.004	.10	0.001	-0.002, 0.004	.49	0.002	-0.0003, 0.005	.08
Posterior cornea										
Adjusted change of Ks, diopter	CH	-0.002	-0.005, 0.001	.23	-0.002	-0.006, 0.002	.37	-0.002	-0.006, 0.002	.41
	CRF	-0.001	-0.004, 0.002	.38	-0.002	-0.004, 0.004	.93	-0.002	-0.01, 0.002	.28
Adjusted change of Kf, diopter	CH	0.001	-0.002, 0.005	.47	0.0001	-0.006, 0.006	.98	0.002	-0.002, 0.01	.39
	CRF	0.003	-0.001, 0.006	.18	0.003	-0.003, 0.01	.31	0.002	-0.002, 0.006	.41
Adjusted change of Km, diopter	CH	-0.001	-0.004, 0.003	.77	-0.005	-0.01, 0.001	.09	0.004	0.0002, 0.008	**.04**
	CRF	-0.001	-0.005, 0.003	.59	-0.004	-0.01, 0.002	.15	0.003	-0.001, 0.007	.14
Adjusted change of BFS, mm	CH	-0.002	-0.003, -0.0005	**.007**	-0.003	-0.005, -0.001	**.01**	-0.001	-0.002, 0.0005	.19
	CRF	-0.002	-0.003, -0.0002	**.03**	-0.002	-0.004, 0.003	.09	-0.001	-0.003, 0.001	.22

Adjusted for age, sex, spherical equivalent refraction, central corneal thickness, corneal hysteresis, or corneal resistance factor. *P* values that are significant (*P*<.05) are highlighted in bold. Add adj = Additionally adjusted for, CH = corneal hysteresis, CRF = corneal resistance factor, Ks = central corneal radius of the steep meridian, Kf = central corneal radius of the flat meridian, Km = mean central corneal radius, BFS = best-fit sphere.

Table 4. Estimated Change in Adjusted Ocular Biometric Parameters in Relation to the Corneal-compensated Intraocular Pressure (IOPcc) Calculated from the Linear Mixed Models.

Variable	All			Emmetropes			Myopes		
	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Anterior cornea									
Adjusted change of Ks, diopter	-0.01	-0.03, 0.01	.28	-0.004	-0.04, 0.03	.82	-0.02	-0.04, 0.01	.14
Adjusted change of Kf, diopter	-0.02	-0.03, 0.001	.07	-0.02	-0.04, 0.002	.07	-0.01	-0.04, 0.01	.42
Adjusted change of Km, diopter	-0.01	-0.03, 0.003	.11	-0.01	-0.03, 0.02	.47	-0.02	-0.04, 0.005	.12
Adjusted change of BFS, mm	0.001	-0.001, 0.003	.20	0.001	-0.001, 0.003	.51	0.001	-0.001, 0.003	.26
Posterior cornea									
Adjusted change of Ks, diopter	-0.002	-0.004, 0.001	.19	-0.001	-0.005, 0.003	.72	-0.003	-0.006, 0.001	.09
Adjusted change of Kf, diopter	0.002	-0.001, 0.005	.28	0.003	-0.002, 0.008	.25	0.0001	-0.003, 0.003	.96
Adjusted change of Km, diopter	-0.001	-0.004, 0.001	.34	-0.003	-0.01, 0.002	.19	0.0005	-0.003, 0.004	.77
Adjusted change of BFS, mm	-0.001	-0.003, -0.0003	**.01**	-0.001	-0.003, 0.0005	.15	-0.002	-0.003, -0.0001	**.04**

Adjusted for age, sex, and spherical equivalent refraction. *P* values that are significant (*P*<.05) are highlighted in bold. Ks = central corneal radius of the steep meridian, Kf = central corneal radius of the flat meridian, Km = mean central corneal radius, BFS = best-fit sphere

FIGURE LEGENDS

Figure 1. Scatterplot illustrating the association between anterior corneal meridians with the Goldmann correlated and corneal compensated intraocular pressures. Ks = central corneal curvature of the steep meridian, Kf = central corneal curvature of the flat meridian, Km = mean central corneal curvature, IOPcc = corneal-compensated intraocular pressure, IOPg = Goldmann-correlated intraocular pressure.

Figure 1A-F color final

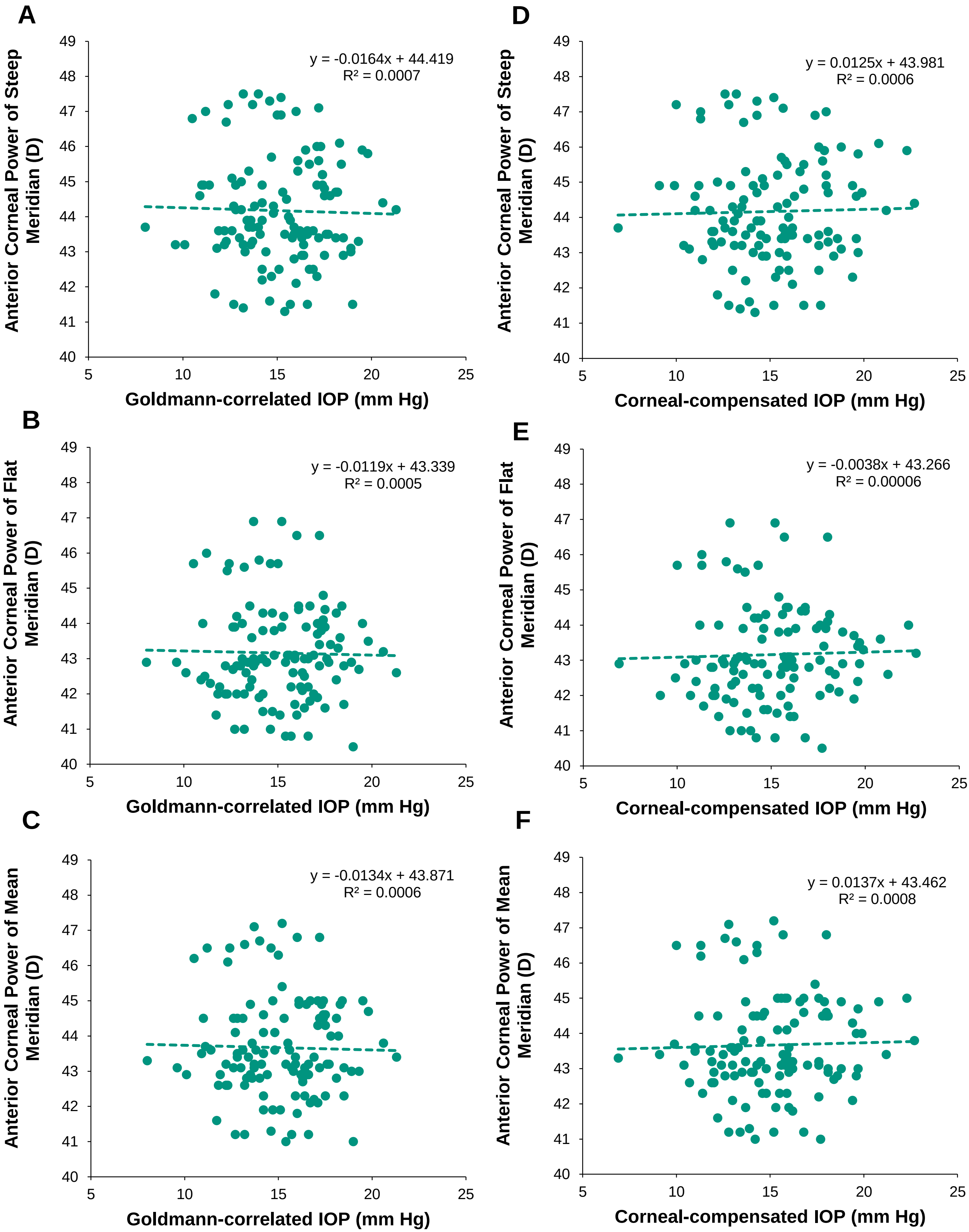

Figure 1A-F reformattedKAZ

Appendix Table A1. Diurnal Change of the Ocular Biometric Parameters and Intraocular Pressure.

Variable	Intersession Change						$P^{\dagger}$
	All		Emmetrope		Myope		
	Mean±SD	95% CI	Mean±SD	95% CI	Mean±SD	95% CI	
CCT, µm	3.01±2.70	2.44, 3.58	3.50±2.93	2.51, 4.49	2.68±2.51	1.99, 3.37	.17
Anterior cornea							
Ks, diopter	0.19±0.18	0.15, 0.22	0.22±0.24	0.14, 0.30	0.16±0.13	0.13, 0.20	.21
Kf, diopter	0.15±0.14	0.12, 0.18	0.15±0.12	0.11, 0.19	0.16±0.16	0.11, 0.20	.75
Km, diopter	0.14±0.15	0.11, 0.17	0.16±0.17	0.11, 0.22	0.12±0.14	0.08, 0.16	.23
BFS, mm	0.01±0.01	0.01, 0.02	0.02±0.01	0.01, 0.02	0.01±0.01	0.01, 0.02	.30
Posterior cornea							
Ks, diopter	0.01±0.03	0.005, 0.02	0.01±0.04	0.002, 0.03	0.01±0.03	0.001, 0.02	.53
Kf, diopter	0.01±0.03	0.005, 0.02	0.02±0.04	0.01, 0.03	0.01±0.02	-0.001, 0.01	.07
Km, diopter	0.01±0.03	0.005, 0.02	0.02±0.04	0.004, 0.03	0.01±0.03	0.0002, 0.01	.22
BFS, mm	0.01±0.01	0.01, 0.01	0.01±0.01	0.01, 0.01	0.01±0.01	0.01, 0.01	.21
Corneal biomechanics							
CH	1.03±0.90	0.84, 1.22	0.96±0.93	0.65, 1.27	1.07±0.89	0.83, 1.32	.58
CRF	0.93±0.80	0.77, 1.10	0.82±0.76	0.56, 1.07	1.01±0.82	0.79, 1.24	.25
Intraocular pressure							
IOPcc, mm Hg	2.09±1.52	1.77, 2.41	2.63±1.63	2.07, 3.18	1.72±1.34	1.36, 2.09	**.008**
IOPg, mm Hg	1.81±1.25	1.54, 2.07	2.15±1.51	1.64, 2.66	1.57±0.99	1.30, 1.85	**.048**

†Welch's t-test between emmetropic and myopic eyes. *P* values that are significant ($P < .05$) are highlighted in bold.
CCT = central corneal thickness, Ks = central corneal curvature of the steep meridian, Kf = central corneal curvature of the flat meridian, Km = mean central corneal curvature, BFS = best-fit sphere, CH = corneal hysteresis, CRF = corneal resistance factor, IOPcc = corneal-compensated intraocular pressure, IOPg = Goldmann-correlated intraocular pressure

Appendix Table A2. Estimated Change in Unadjusted Ocular Biometric Parameters in Relation to the Goldmann-correlated Intraocular Pressure (IOPg) Calculated from the Linear Mixed Models.

Variable	All			Emmetropes			Myopes		
	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Anterior cornea									
Unadjusted change of Ks, diopter	-0.02	-0.04, 0.004	.09	-0.01	-0.05, 0.03	.62	-0.03	-0.06, -0.004	**.03**
Unadjusted change of Kf, diopter	-0.03	-0.05, -0.01	**.002**	-0.03	-0.05, -0.01	**.01**	-0.03	-0.06, 0.0002	.05
Unadjusted change of Km, diopter	-0.03	-0.04, -0.01	**.007**	-0.02	-0.05, 0.01	.20	-0.03	-0.06, -0.01	**.008**
Unadjusted change of BFS, mm	0.002	0.0004, 0.004	**.01**	0.001	-0.001, 0.004	.28	0.003	0.001, 0.005	**.01**
Posterior cornea									
Unadjusted change of Ks, diopter	-0.003	-0.01, -0.0004	**.03**	-0.003	-0.01, 0.001	.16	-0.003	-0.007, 0.0004	.08
Unadjusted change of Kf, diopter	0.001	-0.003, 0.004	.77	0.001	-0.005, 0.01	.64	-0.0003	-0.004, 0.004	.89
Unadjusted change of Km, diopter	-0.002	-0.005, 0.002	.35	-0.004	-0.01, 0.001	.11	0.002	-0.002, 0.005	.37
Unadjusted change of BFS, mm	-0.003	-0.004, -0.001	**<.001**	-0.003	-0.005, -0.001	**.01**	-0.002	-0.004, -0.001	**.003**

P values that are significant (*P*<.05) are highlighted in bold. CH = corneal hysteresis, CRF = corneal resistance factor, Ks = central corneal radius of the steep meridian, Kf = central corneal radius of the flat meridian, Km = mean central corneal radius, BFS = best-fit sphere.

Appendix Table A3. Estimated Change in Unadjusted Ocular Biometric Parameters in Relation to the Corneal-compensated Intraocular Pressure (IOPcc) Calculated from the Linear Mixed Models.

Variable	All			Emmetropes			Myopes		
	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Anterior cornea									
Unadjusted change of Ks, diopter	-0.01	-0.03, 0.01	.29	-0.004	-0.04, 0.03	.81	-0.02	-0.04, 0.01	.13
Unadjusted change of Kf, diopter	-0.02	-0.03, 0.001	.07	-0.02	-0.04, 0.001	.06	-0.01	-0.04, 0.01	.39
Unadjusted change of Km, diopter	-0.01	-0.03, 0.003	.11	-0.01	-0.03, 0.02	.45	-0.02	-0.04, 0.004	.12
Unadjusted change of BFS, mm	0.001	-0.001, 0.003	.20	0.001	-0.001, 0.003	.50	0.001	-0.001, 0.003	.25
Posterior cornea									
Unadjusted change of Ks, diopter	-0.002	-0.004, 0.001	.19	-0.001	-0.005, 0.003	.73	-0.003	-0.006, 0.001	.09
Unadjusted change of Kf, diopter	0.002	-0.001, 0.005	.27	0.003	-0.002, 0.008	.22	0.0001	-0.003, 0.004	.94
Unadjusted change of Km, diopter	-0.001	-0.004, 0.001	.35	-0.003	-0.01, 0.002	.21	0.001	-0.003, 0.004	.75
Unadjusted change of BFS, mm	-0.001	-0.003, -0.0003	**.01**	-0.001	-0.003, 0.001	.15	-0.002	-0.003, 0.0001	**.04**

P values that are significant (*P*<.05) are highlighted in bold. Ks = central corneal radius of the steep meridian, Kf = central corneal radius of the flat meridian, Km = mean central corneal radius, BFS = best-fit sphere