Relationship Between Nocturnal Intraocular Pressure Elevation and Diurnal Intraocular Pressure Level in Normal-Tension Glaucoma Patients

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Purpose. We studied the relationship between nocturnal habitual position IOP elevation and diurnal IOP level in normal-tension glaucoma (NTG) patients.

Methods. A total of 70 young NTG patients with a low diurnal IOP level (mean diurnal seated IOP $<$ 15.0 mm Hg; low IOP group) and 79 age-, axial length–, and disease severity–matched NTG patients with a high diurnal IOP level (mean diurnal seated IOP $\geq$ 15.0 mm Hg; high IOP group) were recruited prospectively. Intraocular pressure was recorded 11 times over a 24-hour period by a single, well-trained ophthalmology resident using a hand-held tonometer.

Results. The mean habitual position IOP during nighttime (14.2 mm Hg) was significantly higher than that of daytime (12.8 mm Hg) in the low IOP group ($P < 0.001$), whereas no such difference was found in the high IOP group (16.4 vs. 16.3 mm Hg, $P = 0.706$). The low IOP group showed an overall nocturnal acrophase in habitual-position IOP, with 11 patients (15.7%) having a diurnal, 30 (42.8%) a nocturnal, and 29 (41.4%) no evident acrophase. By contrast, the high IOP group showed no evident peak in habitual-position IOP, with 28 patients (35.4%) having a diurnal, 12 (15.2%) a nocturnal, and 39 (49.4%) no evident acrophase.

Conclusions. In NTG eyes with a low diurnal IOP, there are significant IOP increases at nighttime in the habitual position, whereas there is no significant nocturnal IOP elevation in NTG eyes with a high diurnal IOP.

Keywords: nocturnal intraocular pressure elevation, diurnal intraocular pressure level, normal-tension glaucoma

Untreated open-angle glaucoma (OAG) patients have a higher nocturnal (supine) IOP than diurnal (seated) IOP.[1–3] Studies have suggested that elevated nocturnal IOP in the supine position may be a risk factor for glaucomatous optic nerve head and/or visual field (VF) damage or progression in patients with normal-tension glaucoma (NTG).[2,3] Consequently, these findings may highlight the importance of nocturnal IOP elevation in the management of NTG, and emphasize the clinical relevance and usefulness of 24-hour habitual position IOP measurements in NTG patients or suspects.

Increased incidence of NTG in relatively young Asian patients has been reported recently in the ophthalmic literature.[2,4–7] Some of these young Asian patients are found incidentally to have glaucomatous optic nerve head changes and/or VF defects during routine eye examination or work-up for keratorefractive surgery for myopic refractive error.[7,8] At present, however, there is little information on the pattern of the 24-hour habitual position IOP and nocturnal IOP elevation in NTG subjects, including these young patients.

Recent studies, including our own reports,[9–13] have suggested that there might be differences in the mechanism of glaucomatous damage that are related to the baseline diurnal IOP level in NTG patients. For example, glaucomatous VF progression has been significantly associated with nocturnal events, such as low nocturnal ocular perfusion pressure due to low systemic blood pressure and/or elevated nocturnal IOP or disc hemorrhage in some NTG subjects that had diurnal IOP levels in the low teens (IOP $<$ 15.0 mm Hg).[9,10,12,13] In contrast, the mean diurnal IOP value was a significant predictor of VF progression in those with baseline diurnal IOP levels in the high teens (IOP $\geq$ 15.0 mm Hg) during follow-up, suggesting the importance of the peak IOP time and nocturnal IOP elevation in terms of glaucomatous damage in NTG eyes with low baseline diurnal IOP levels.[13,14] We hypothesized that NTG eyes with low diurnal IOP levels might have greater nocturnal habitual position IOP elevation than those with high diurnal IOP levels because disease onset or progression in these low IOP NTG eyes may be related more closely to IOP peak or elevation outside the diurnal period.

With this in mind, we measured the time course of habitual position IOP changes in a large group of newly diagnosed NTG subjects, including young patients (age $\geq$ 21 years). The purpose of the current study was to (1) report the amount of nocturnal IOP elevation based on a 24-hour habitual position IOP study as well as peak IOP time (acrophase) over a 24-hour period in NTG subjects with a low baseline diurnal IOP level (mean diurnal IOP $<$ 15.0 mm Hg; low IOP group); (2) compare the data from the low IOP group to those of age-, axial

length (AL)–, and disease severity–matched (based on mean deviation) NTG subjects with a high baseline diurnal IOP level (mean diurnal IOP $\geq$ 15.0 mm Hg; high IOP group); and (3) study the relationship between a nocturnal habitual position IOP elevation and the diurnal seated IOP level using regression analyses.

Patients and Methods

Subjects

We prospectively recruited consecutive NTG patients examined by a single glaucoma specialist (MSK) from March 2011 to June 2014 in the glaucoma clinic of Asan Medical Center, Seoul, Korea. At initial evaluation, each subject underwent a complete ophthalmologic examination, including medical, ocular, and family history; visual acuity testing; the Humphrey field analyzer (HFA) Swedish Interactive Threshold Algorithm 24-2 test (Carl Zeiss Meditec, Dublin, CA, USA); multiple IOP measurements using Goldmann applanation tonometry (GAT); stereoscopic optic nerve photography; and Cirrus-HD spectral-domain optical coherence tomography (Carl Zeiss Meditec) scanning. All patients had more than one experience of HFA testing. To minimize the learning effect, the second HFA test was performed when the first VF test indicated glaucomatous VF.

For inclusion in the study, all eligible NTG patients were healthy, nonsmoking individuals, 21 years or older, of both sexes, and newly diagnosed. There had also been no previous treatment. In our current study, the age cutoff values ($\geq$21 years) were chosen because there is an increased incidence of NTG in young Asian patients.[2,4–7] Eyes with NTG were defined as those showing a maximum bilateral IOP of less than 22 mm Hg on GAT measurements in at least three outpatient clinic visits as well as those showing a maximum bilateral IOP of less than 22 mm Hg on hand-held tonometer (TonoPenXL; Mentor Ophthalmics, Santa Barbara, CA, USA) measurements during in-hospital 24-hour IOP monitoring before any antiglaucoma therapy. Additionally, all NTG patients had best-corrected visual acuity greater than 20/40; a normal anterior segment, anterior chamber, and open-angle based on slit-lamp and gonioscopic examination; optic nerves that appeared to be glaucomatous based on increased cupping (a vertical cup/disc ratio $>$ 0.7), a difference in the vertical cup/disc ratio of $>$0.2 between eyes not explained by differences in disc size, diffuse or focal neural rim thinning, disc hemorrhage, or retinal nerve fiber layer defects; and glaucomatous VF defects as confirmed by at least two reliable VF examinations with a false-positive error $<$ 15%, a false-negative error $<$ 15%, and a fixation loss $<$ 20%. Eyes with glaucomatous VF defects were defined as those with a cluster of three points with probabilities of $<$5% on the pattern deviation map in at least one hemifield, including at least one point with a probability of $<$1%; or a cluster of two points with a probability of $<$1%, and a glaucoma hemifield test result outside the 99% age-specific normal limits; or a pattern SD outside the 95% normal limits.

Patients were excluded if they had one or more of the following: severe myopic disc and fundus changes impairing adequate optic nerve/VF evaluation for glaucoma, evidence of an intracranial or otolaryngological lesion, history of massive hemorrhage or hemodynamic crisis, previous or current use of antiglaucoma medications or systemic or topical steroids, presence of any other ophthalmic disease that could result in optic nerve and VF defects, and/or a history of diabetes mellitus. Individuals who smoked or had an irregular daily sleep schedule also were excluded. Finally, patients who had previous ocular laser procedures or surgeries including keratorefractive surgery, or had corneal abnormalities that prevented reliable IOP measurements also were excluded.

Central corneal thickness (CCT) was measured three times by ultrasonic pachymetry (DGH-550; DGH Technology, Inc., Exton, PA, USA) at the initial visit, and the average was calculated. Axial length was measured using IOL Master (Carl Zeiss Meditec) at the initial visit. All procedures conformed to the Declaration of Helsinki, and the study was approved by the Institutional Review Board of Asan Medical Center. All patients provided informed consent.

Measurement of In-Hospital IOP Over 24 Hours

All IOP measurements were performed by a single, well-trained, ophthalmology resident (DWJ). First, a separate study[7] was performed by DWJ to test the accuracy of the TonoPenXL against GAT: We compared the TonoPenXL and GAT readings by performing a cross-sectional study of 52 consecutive patients (104 eyes) with glaucoma or suspected glaucoma. There was an excellent correlation between the IOP readings obtained by the TonoPenXL and GAT ($r = 0.93$, $P < 0.001$). The difference between the GAT and TonoPenXL readings was less than 2 mm Hg in 95% of the measurements.

All eligible patients in our main study were instructed to abstain from alcohol and caffeine for 3 days before hospital admission. The length and times of diurnal/nocturnal periods at home may have differed among enrolled patients. All measurements of IOP were obtained with the TonoPenXL at 8 and 10 AM, and 12, 2, 4, 6, 8, and 10 PM (diurnal IOP), and at 12, 3, and 6 AM (nocturnal IOP) in both eyes of each patient. This schedule has been used in our previous studies[2,7] and was chosen to provide the best trade-off between the maximum number of IOP readings over 24 hours and minimal non-physiological responses during in-hospital IOP measurement. One or two drops of 0.5% proparacaine were administered as topical anesthetic before each IOP measurement at each time points. Three measurements were taken at each time point, and the average value was used for analysis in the sitting and supine positions. Subjects were instructed to continue normal indoor activities during the diurnal period, and diurnal IOP was measured when patients were seated. During the nocturnal period, lights in individual rooms were turned off by the nurse at 10 PM, and patients were instructed to sleep with their head at the same level as their body. Subjects were awakened (if necessary) and IOP measurements were taken with the TonoPenXL under dim light, with patients in the supine position (because activation of the sympathetic nervous system by changing body position at night could be nonphysiological) to measure long-term habitual position-induced IOP changes during 24 hours. Following a 10-minute resting period in the upright position, nocturnal IOP was measured while the patient was seated to measure short-term posture-induced IOP changes. Intraocular pressure obtained with the TonoPenXL was used in the data analysis without correction for CCT. We measured the IOP of both eyes in all enrolled NTG patients. If both eyes were eligible for the study, the right eye was arbitrarily selected for analysis.

Classification of the Two Study Groups

Patients with NTG were consecutively divided into two groups based on the mean IOP level from eight diurnal TonoPenXL measurements during the 24-hour in-hospital stay. The low IOP group had a mean in-hospital diurnal IOP $<$ 15 mm Hg, whereas the high IOP group had a mean in-hospital diurnal IOP $\geq$ 15 mm Hg. This cutoff IOP value (15 mm Hg) was based on previous studies on the relationship between mechanisms of glaucomatous damage and different baseline IOP levels.[9–14]

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The mean nocturnal IOP level was based on the average IOP value from three nocturnal measurements (12, 3, and 6 AM) in each patient during the 24-hour in-hospital stay.

Statistical Analysis

Our previous study showed that OAG eyes had a significant nocturnal IOP elevation of approximately 2.0 mm Hg with a SD of 1.75 mm Hg in the supine position.[2] Therefore, assuming that low IOP NTG eyes show significantly greater nocturnal IOP elevation (>1.0 mm Hg) than the high IOP group, a sample size calculation was performed to acquire 80% power to detect differences in nocturnal IOP changes between the two groups of greater than 1.0 mm Hg by controlling the probability of a type I error at 0.05 in a 2-tailed test. A sample size of at least 51 subjects or greater was needed to meet these conditions with a SD of 1.75 mm Hg.

First, mean habitual position IOP measurements obtained at different time points for the overall group and each subgroup were compared using paired *t*-tests. Second, two IOP calculations were made following the body posture change. These included short-term posture-induced changes (supine to sitting) in the mean IOP at 10 minutes during nighttime and long-term habitual position-induced changes (sitting to supine) in the mean IOP during 24 hours. Various habitual position IOP parameters, separated by different time periods (diurnal versus nocturnal), were compared between the two groups using unpaired *t*-tests. Finally, we calculated the 24-hour mean IOP flow for seated and habitual position IOP measurements in the overall group and each subgroup.

Least-squares cosinor rhythmometry has been used to describe the pattern of the 24-hour habitual position IOP and acrophase recording.[2,7,15,16] This model has been proven useful for fitting symmetric and stationary rhythmic patterns, such as in 24-hour IOP behavior. Briefly, the cosinor model uses sine and cosine terms to describe a diurnal variation, and is expressed as $Y(t) = b0 + b1 \times \mathrm{Cos}[(2\pi/24) \times t] + b2 \times \mathrm{Sin}[(2\pi/24) \times t]$, where Y is the observed IOP at time t after the IOP measurement is initiated, and $b0$, $b1$, and $b2$ are regression coefficients. The constant $(2\pi/24)$ and the coefficient $b0$ represent the 24-hour periodicity of IOP and the 24-hour rhythm-adjusted mean IOP, respectively. Thus, the amplitude (A) that represents half of the extent of rhythmic change in a cycle can be given as $A = \sqrt{b_1^2 + b_2^2}$. The 24-hour pattern was analyzed using this cosinor model for the overall patient group and all patients in each group. Individual analysis also was performed and classified based on the acrophase in each group. The distributions of the different acrophases were compared between the two groups using the χ^2 test.

The relationships between various clinical variables and a nocturnal habitual IOP elevation were assessed by univariate linear regression models. The following formula was used to represent nocturnal habitual IOP elevation: nighttime supine average IOP minus daytime sitting average IOP. All clinical variables with a P value less than or equal to 0.20 in the univariate analyses were included as candidate variables for the multivariate regression analysis. The model for each outcome variable was reduced using backward elimination until it contained only significant predictors. Clinical variables for analysis were age, CCT, AL, mean deviation, pattern SD, office IOP, mean diurnal IOP, mean diurnal systolic blood pressure, mean diurnal diastolic blood pressure, and body mass index.

A scatterplot was constructed to show the correlation between the daytime IOP level and a nocturnal habitual IOP elevation using Pearson's correlation analysis. All statistical tests were performed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). The criterion for statistical significance was $P < 0.05$.

Table 1. Demographic Characteristics of the Low and High IOP Groups

Demographic	Low IOP Group, $n = 70$	High IOP Group, $n = 79$	*P* Value
Age, y			
Mean ± SD	45.69 ± 7.19	45.56 ± 8.82	0.18
Range	21 to 65	21 to 62	
Sex, M/F	34/36	47/32	0.192
Axial length, mm			
Mean ± SD	24.12 ± 1.92	24.57 ± 1.79	0.143
Range	22.45 to 31.54	22.67 to 29.27	
SE, D			
Mean ± SD	−2.88 ± 3.51	−2.41 ± 3.29	0.167
Range	−10.25 to 0.50	−10.13 to 0.38	
CCT, μm			
Mean ± SD	541.39 ± 39.03	549.31 ± 41.15	0.231
Range	452.67 to 638.67	441.67 to 651.33	
Humphrey VF, MD			
Mean ± SD	−2.26 ± 2.84	−2.17 ± 2.35	0.819
Range	−14.20 to 3.43	−14.96 to 1.74	
Humphrey VF, PSD			
Mean ± SD	2.93 ± 2.75	2.67 ± 2.16	0.516
Range	0.91 to 15.66	1.10 to 11.86	
Mean clinic IOP, GAT			
Mean ± SD	13.18 ± 2.16	17.11 ± 2.19	0.001
Range	9 to 16	15 to 20	

M, male; F, female; SE, spherical error; MD, mean deviation; PSD, pattern SD.

Results

A total of 149 eyes of 149 patients with NTG meeting the inclusion criteria was analyzed in this prospective study. Of these, 70 NTG patients were enrolled in the low IOP group. Of the 70 low IOP subjects, 34 were men, 36 were women, and all were native Koreans. The remaining 79 NTG patients (47 men and 32 women) comprised the high IOP group. The demographic and clinical characteristics of both groups are summarized in Table 1.

Regarding nocturnal IOP changes in the overall group, the mean habitual position IOP during sleeping hours was significantly higher than that of waking hours (15.27 vs. 14.57 mm Hg, $P < 0.001$). In subgroup analysis, the mean habitual position IOP during sleeping hours also was significantly higher than that of waking hours in the low IOP group ($P < 0.001$, Table 2), whereas no such difference was found in the high IOP group ($P = 0.706$, Table 2). When different IOP cutoff values (14 and 16 mm Hg, respectively) were used (data not shown), similar findings also were found in that the mean

Table 2. Comparison of the Mean Habitual Position IOP (Measured by a Hand-Held Tonometer) During Daytime and Nighttime Within Each Group and Between the Two Groups

	Mean Diurnal IOP	Mean Nocturnal IOP	*P* Value
Low IOP group	12.80	14.21	<0.001
High IOP group	16.33	16.40	0.706
P value	<0.001	<0.001	

Table 3. Comparison of the Short- and Long-Term Mean Habitual Position IOP Changes (Measured by a Hand-Held Tonometer) Between the Two Groups

	Low IOP Group	High IOP Group	*P* Value
Nocturnal supine minus nocturnal sitting IOP	1.63	1.25	0.072
Nocturnal supine minus diurnal sitting IOP	1.42	0.07	<0.001

habitual position IOP during sleeping hours (mean IOP = 14.21 and 14.70 mm Hg, respectively) was significantly higher than that of waking hours (12.53 and 13.72 mm Hg, respectively) in the low IOP group ($P < 0.001$). However, in the high IOP group, the mean habitual position IOP during sleeping hours (mean IOP = 16.33 and 17.50 mm Hg, respectively) showed similar IOP level compared to that of waking hours (16.07 and 17.65 mm Hg, respectively; $P = 0.155$ and 0.641, respectively).

In intergroup comparisons, the mean habitual position IOP in the high IOP group was significantly higher than that of the low IOP group during waking and sleeping hours ($P < 0.01$, Table 2). However, short- and long-term nocturnal IOP changes were greater in the low than in the high IOP group ($P = 0.072$ and $P < 0.001$, respectively, Table 3).

The overall group showed an IOP peak during sleeping hours (3–6 AM) in the habitual body position, whereas it showed an IOP peak during waking hours (6–10 AM) in the sitting position (Fig. 1A). Regarding subgroup patterns, the low IOP group showed an IOP peak during sleeping hours (3–6 AM), whereas the high IOP group showed an IOP peak during waking hours (6–10 AM) in the habitual body position (Fig. 1B). In the sitting position, however, the low and high IOP groups showed an IOP peak during waking hours (6–10 AM, Fig. 1B).

An analysis of the overall group based on the cosinor model showed no evident peak (acrophase) in habitual position IOP measurements during the 24-hour period (Fig. 2A). However, further analysis of individual patients indicated that 39 (26.2%) had a diurnal acrophase (Fig. 2B), 68 (45.6%) had no evident acrophase (Fig. 2C), and 42 (28.2%) had a nocturnal acrophase (Fig. 2D). When analyzing the low IOP group, a nocturnal peak (acrophase) of habitual position IOP was found in the overall patient group at approximately 3 to 6 AM (Fig. 3A), whereas in an analysis of individual patients, 11 (15.7%) had a diurnal acrophase (Fig. 3B), 29 (41.4%) had no evident acrophase (Fig. 3C), and 30 (42.8%) had a nocturnal acrophase (Fig. 3D). In contrast, no evident peak (acrophase) was found in the overall high IOP group (Fig. 4A), whereas in an analysis of individual patients, 28 patients (35.4%) had a diurnal acrophase (Fig. 4B), 39 (49.4%) had no evident acrophase (Fig. 4C), and 12 (15.2%) had a nocturnal acrophase (Fig. 4D). There were significant

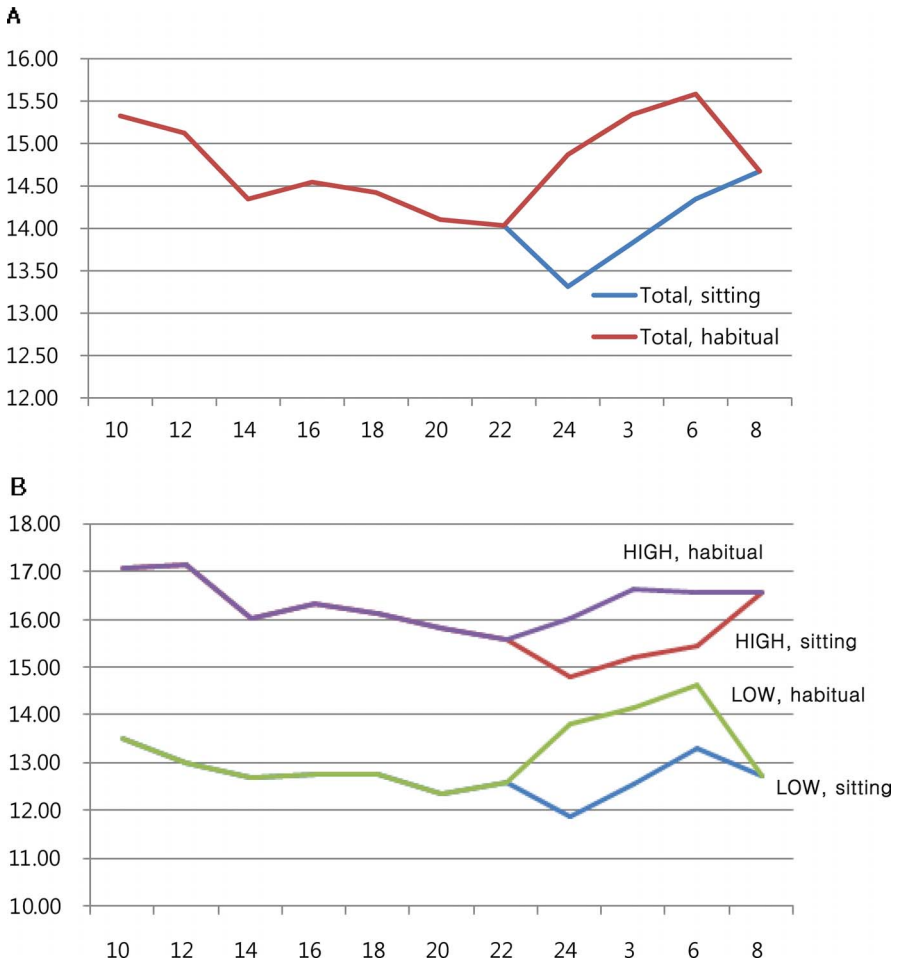

Figure 1. Twenty-four hour mean IOP flow, and IOP peak time analysis at sitting and habitual positions: (**A**) in all patients ($n = 149$), and (**B**) in the low ($N = 70$) and high ($N = 79$) IOP groups.

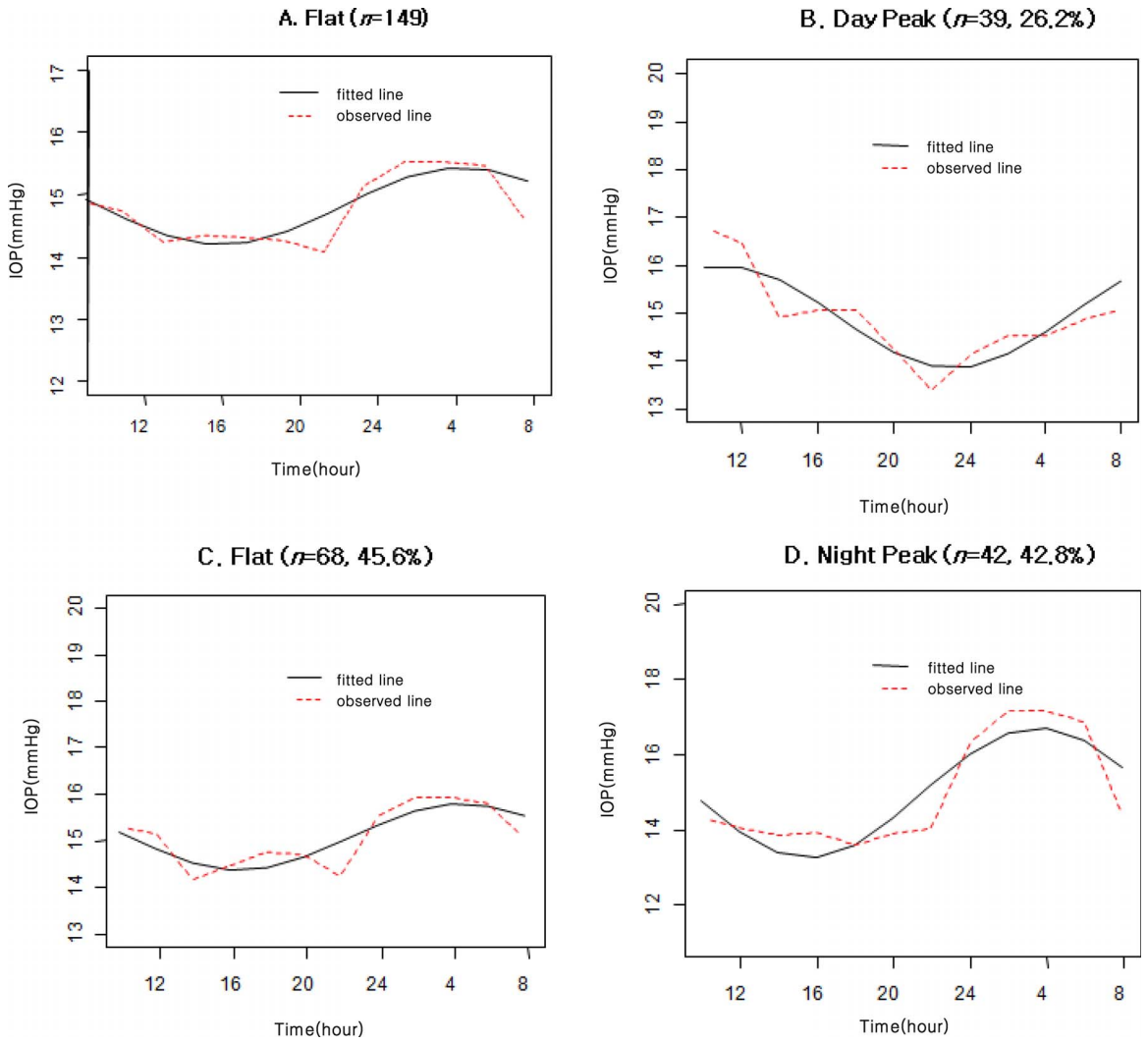

Figure 2. Average 24-hour rhythms of habitual position IOP in the overall patient group (**A**) and in three subgroups of patients (**B–D**) based on the cosinor model (mean ± SE) in the overall patient group.

differences in the distribution of the diurnal and nocturnal acrophases between the two groups ($P < 0.05$, χ^2 test, Table 4).

The results of univariate and multivariate modeling of the ability of various clinical variables to predict nocturnal habitual IOP elevation (nocturnal supine average IOP minus diurnal sitting average IOP) are presented in Table 5. In univariate modeling, among various clinical parameters, the mean daytime IOP level and AL significantly correlated with nocturnal habitual IOP elevation. In multivariate modeling, the mean daytime IOP level and AL remained as significant predictors of nocturnal habitual IOP elevation. A statistically significant correlation was found between nocturnal habitual IOP changes and daytime IOP level in the same eye using Pearson's correlation analysis ($P < 0.001$, Fig. 5).

Discussion

In the current study, we found a statistically significant nocturnal elevation in habitual position IOP in NTG subjects, including relatively young patients. Therefore, this finding is in agreement with those of previous studies that investigated relatively older NTG subjects (mean age > 50 years).[2,3] Thus, ageing seems to have a limited impact on the overall 24-hour IOP rhythms in NTG subjects. In subgroup analysis, there also was a statistically significant nocturnal elevation in habitual position IOP in the low IOP group. In contrast, no such nocturnal elevation in IOP was seen in the NTG subjects with high diurnal IOP levels. To our knowledge, this is the first study to evaluate the relationship between the baseline diurnal IOP level and the nocturnal IOP elevation in the habitual body position in a large number of NTG subjects who have undergone 24-hour IOP study. We believe that our study is clinically important given that a significant percentage of an individual's life is spent in the supine position, and nocturnal IOP elevation may be associated with the onset and progression of vision loss in some NTG patients.[2,3]

As expected, the mean diurnal and nocturnal IOPs of the high IOP group were significantly higher than those of the low IOP group in the habitual body position. Interestingly, in the recumbent position, the long-term mean nocturnal IOP change of the low IOP group was significantly greater than that of the high IOP group. Therefore, our results suggested that a high baseline IOP level during daytime may result in blunting of the nocturnal IOP elevation in NTG subjects, thereby making the supine IOP change in the high IOP group significantly lower than that of an age-, AL-, and disease severity–matched low IOP group at nighttime. Another possible explanation is that eyes

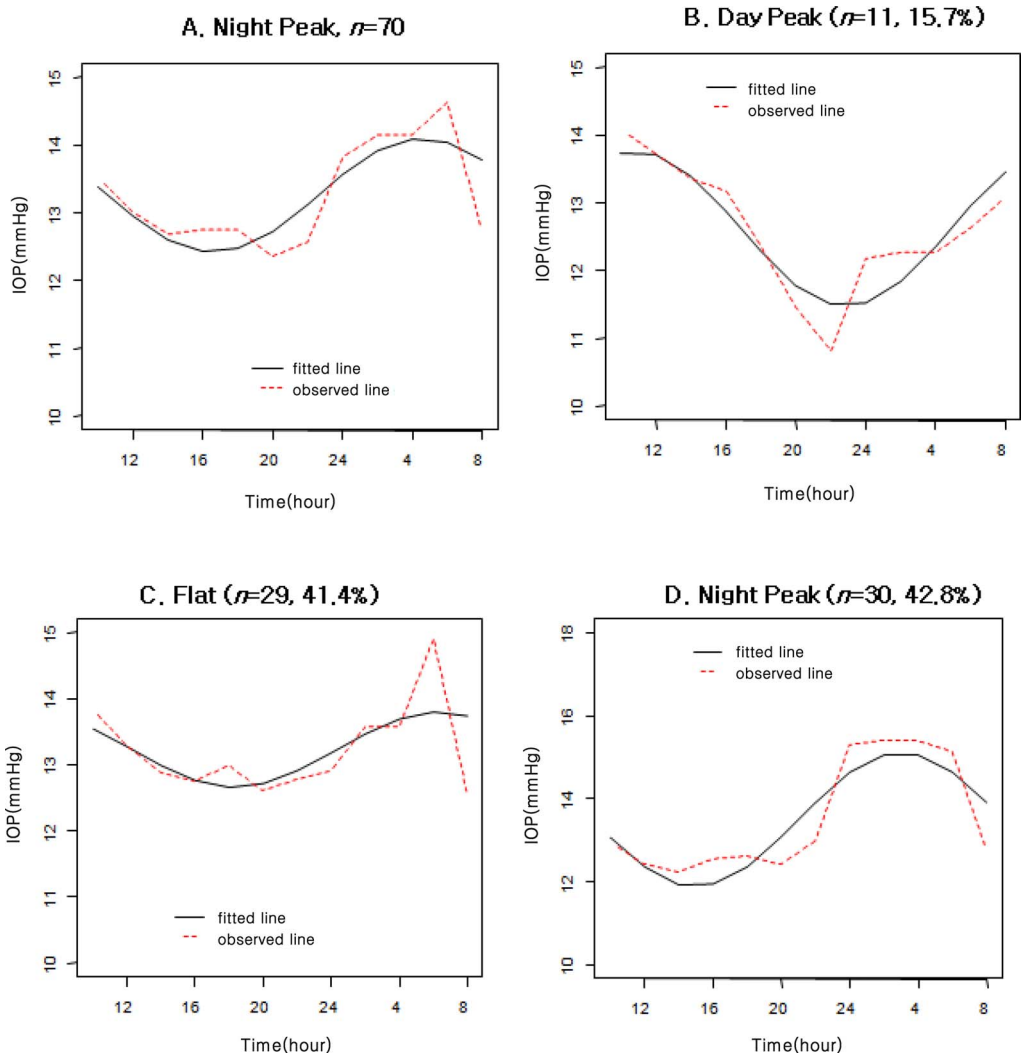

FIGURE 3. Average 24-hour rhythms of habitual position IOP in all low IOP group patients (**A**) and in three subgroups of patients (**B–D**) based on the cosinor model (mean ± SE) in the low IOP group.

with high baseline IOP level do not have IOP decrease during daytime and have consistently higher IOP level throughout 24 hours compared to the low IOP group without significant IOP elevation at night. Consequently, nocturnal mean IOP changes were greater in the low than in the high IOP group during the 24-hour study period, as well as at 10 minutes after posture change during sleeping hours.

How nocturnal IOP responds differently to postural changes between the low and high IOP NTG groups remains uncertain. Sit et al.,[17] who measured the diurnal and nocturnal aqueous humor flow rate, IOP, and outflow facility in young healthy adults, found that the outflow facility did not decrease enough to compensate for the significant reduction in aqueous humor inflow rate at nighttime, suggesting that the nocturnal IOP pattern could be explained by changes in episcleral venous pressure (EVP) and/or uveoscleral outflow. Although the patients in the current study had glaucoma, an increase in the EVP along with a decreased uveoscleral outflow at night might compensate for the decreased aqueous humor inflow and could explain the elevated nocturnal IOP observed in the low IOP group. The smaller nocturnal IOP elevation in the high than in the low IOP group might be attributable to different EVP responses or a combination of the EVP and uveoscleral outflow rate occurring at nighttime between the groups.

In addition, the observed differences in nocturnal IOP elevation between the two diurnal IOP groups may not accurately reflect the true IOP variation occurring in the sleeping state. For example, hand-held tonometer readings can be influenced by corneal biomechanical properties that may change over 24 hours, such as CCT.[18,19] Kida et al.[20] showed that the CCT was thicker and IOP was higher during the nocturnal period than during the diurnal period. Despite similar baseline pachymetry values between the groups, different 24-hour variations in CCT between the groups also may give rise to different nocturnal IOP readings between the groups. Future aqueous humor dynamic studies with use of implantable intraocular IOP sensors are needed to further elucidate the mechanisms of the 24-hour IOP rhythm and nocturnal IOP elevation in NTG eyes with different baseline IOP levels.

Previous studies showed higher nocturnal IOP than diurnal IOP in the habitual position among primary open-angle glaucoma (POAG) patients of different ages and disease stage.[1,21–23] The explanations for observing differences in nocturnal IOP elevation between the high IOP group in the current study and POAG patients in the published studies are not clear, but may be attributed to multiple factors. One of them may be related to differences in the disease entity (NTG versus POAG) between different studies. Racial differences across the

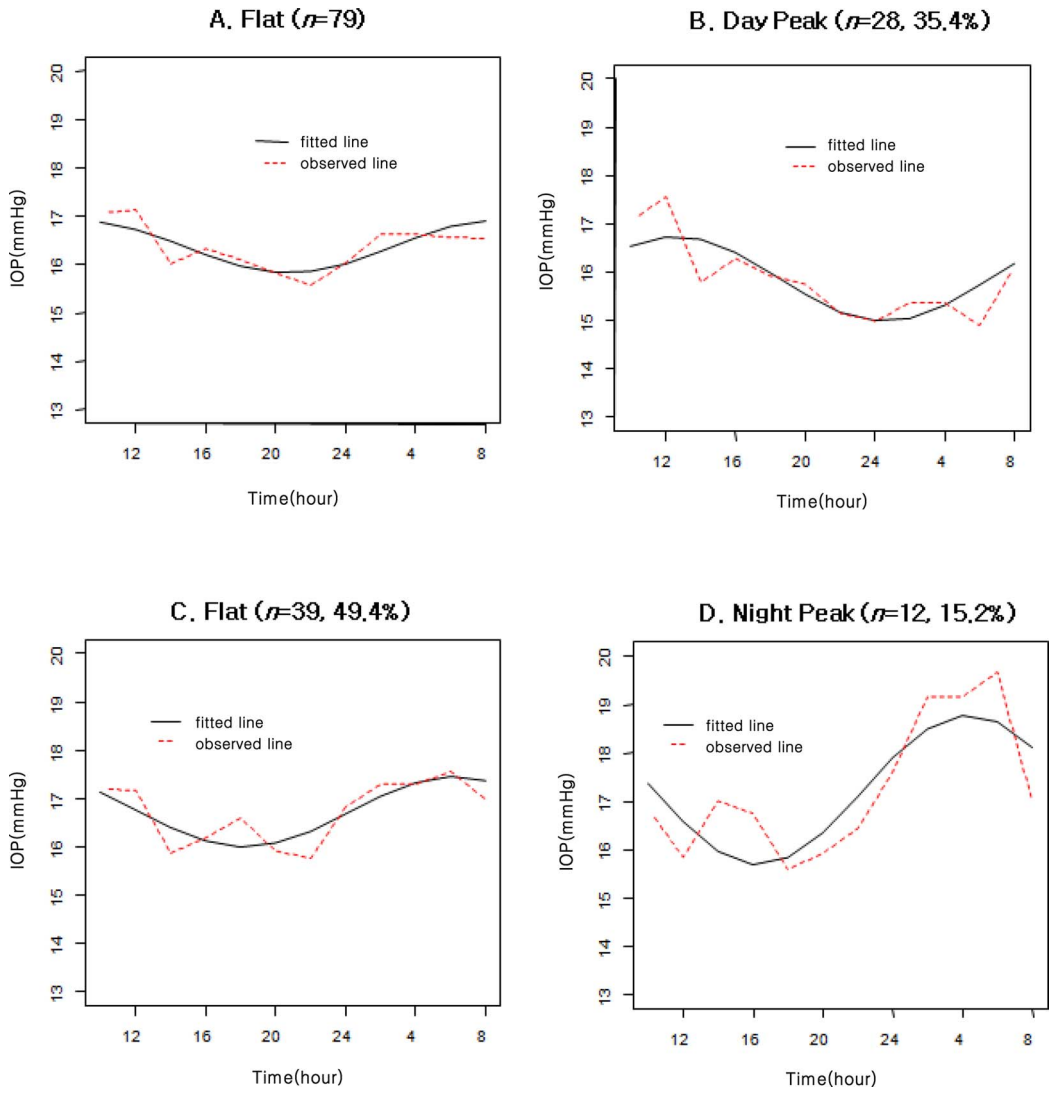

Figure 4. Average 24-hour rhythms of habitual position IOP in all high IOP group patients (**A**) and in three subgroups of patients (**B–D**) based on the cosinor model (mean ± SE) in the high IOP group.

studies also may contribute to the different nocturnal IOP responses between the high IOP NTG group and POAG patients. The observed differences in nocturnal IOP elevation between the high IOP NTG group and POAG patients also may reflect artifacts in IOP measurement related to different biomechanical properties between the groups. Kim et al.[24] showed that the CCT was thinner in NTG eyes than ocular hypertension or POAG patients. Since hand-held tonometer readings can be influenced by corneal biomechanical properties, such as CCT,[18,19] different CCT between the groups also may give rise to different nocturnal IOP readings between the groups.

Data are limited on the daily IOP pattern in NTG subjects with different baseline diurnal IOP levels. Using least-squares cosinor rhythmometry[2,7,15,16] to describe the 24-hour pattern of IOP, analysis of the low IOP group indicated that the mean IOP was highest at nighttime (peak at 3–6 AM) when patients were supine. In individual analysis, we also identified three major IOP rhythms among our 70 patients: diurnal (15.7%), nocturnal (42.8%), and no (41.4%) acrophase. This finding is in agreement with previous studies[2,3] that analyzed older NTG subjects. In contrast, no acrophase in IOP was found in an analysis of the overall high IOP group. In individual analysis, three significantly different acrophase patterns were found in the high compared to the low IOP group. That is, we identified three major habitual position IOP patterns among the 79 high IOP patients: diurnal (35.8%), nocturnal (15.2%), and no identifiable (49.4%) acrophase. One of the important clinical implications of this finding is that, although the disease severity is similar, the mechanisms for glaucomatous damage may be different in the two groups classified by different diurnal IOP levels. In other words, nocturnal IOP elevation may have an important role in the NTG eyes with low diurnal IOP levels, whereas those eyes with high diurnal IOP levels may have less pronounced or minimal

Table 4. Comparison of the 24-Hour IOP Pattern Based on the Cosinor Model

	Low IOP Group	High IOP Group	*P* Value
Day peak	11 (15.7%)	39 (49.4%)	<0.001
Flat	29 (41.4%)	28 (35.4%)	0.453
Night peak	30 (42.9%)	12 (15.2%)	<0.001
Total	70	79	

Table 5. Probabilities of the Tests of Significance of Variables Predicting the Nocturnal IOP Elevation: Univariate and Multivariate Models

	Univariate Modeling		Multivariate Modeling			
	Pearson's *r* Correlation	*P* Value	Estimated Coefficient	95% CI		*P* Value
Age	0.128	0.120	−0.018	0.053	0.017	0.303
CCT	0.015	0.161	0.004	0.003	0.011	0.232
AL	−0.395	<0.001	−0.372	0.510	0.233	<0.001
MD	−0.005	0.952				
PSD	0.025	0.762				
Office IOP	−0.080	0.331				
Diurnal mean IOP	−0.324	<0.001	−0.285	0.405	0.164	<0.001
SBP	0.030	0.716				
DBP	0.085	0.303				
MAP	0.074	0.368				
BMI	0.057	0.494				

SBP, mean diurnal systolic blood pressure; DBP, mean diurnal diastolic blood pressure; BMI, body mass index.

nocturnal IOP elevation, and the persistently high 24-hour IOP may be linked to glaucomatous damage.

Renard et al.[25] identified two major IOP rhythms in 22 NTG subjects, diurnal (54.5%) and nocturnal (36.4%) acrophase, when IOP was measured every hour, with patients in a physiological posture, using an electronic tonometer. In contrast to our findings, this study showed a significantly greater proportion of eyes with a diurnal ($n = 12$, 54.5%) than nocturnal ($n = 8$, 36.4%) acrophase. However, direct comparison of different studies may be problematic due to differences in the IOP levels in NTG populations, number of enrolled subjects, study designs, and the definition of NTG. In addition, ethnic differences in IOP nyctohermeral rhythms also may explain the different results between two studies. Nonetheless, different 24-hour IOP patterns among NTG patients with different diurnal IOP levels can potentially influence the selection of the optimal dosing and choice of medical therapy based on individualized 24-hour IOP patterns.

Axial length and diurnal IOP levels were the most important predictor variables for nocturnal habitual position IOP elevation in our series of NTG subjects (Table 5). In our previous study of OAG eyes with a wide range of ALs (22–32 mm),[7] we found that eyes with a longer AL had smaller nocturnal IOP increases (mean nocturnal supine IOP minus mean diurnal sitting IOP) as well as a smaller range of 24-hour IOP fluctuations (peak nocturnal supine IOP minus trough diurnal sitting IOP). In line with our previous findings, our current study also showed that the nocturnal IOP elevation (mean nocturnal supine IOP minus mean diurnal sitting IOP) in habitual position IOP measurements correlated negatively with AL. Moreover, diurnal IOP level remained as another significant independent predictor of nocturnal IOP elevation. Therefore, our findings may underscore the importance of paying attention to the diurnal IOP level as well as AL as possible clinical variables affecting nocturnal IOP elevation in NTG. Based on linear regression, Figure 5 shows a statistically significant negative correlation between the diurnal IOP level and nocturnal habitual position IOP elevation in NTG patients.

Our study suggests that NTG eyes with low diurnal IOP may have different nocturnal IOP elevation pattern from those with higher diurnal IOP. However, these results should be interpreted with caution in that NTG eyes should not be divided into two groups according to baseline diurnal IOP level using an arbitrary IOP cutoff value. Further, NTG eyes with different diurnal IOP levels should not be regarded as having different diseases as NTG is likely part of a continuum of OAG with different risk factors. However, knowledge of 24-hour IOP pattern in NTG patients is helpful not only in understanding its pathogenesis, but also in managing glaucoma patients with certain IOP elevation pattern during 24 hours. It is important to keep in mind that nocturnal IOP elevation is most likely affected by a variety of ocular elements, including aqueous humor dynamics as well as posture in the habitual body position.

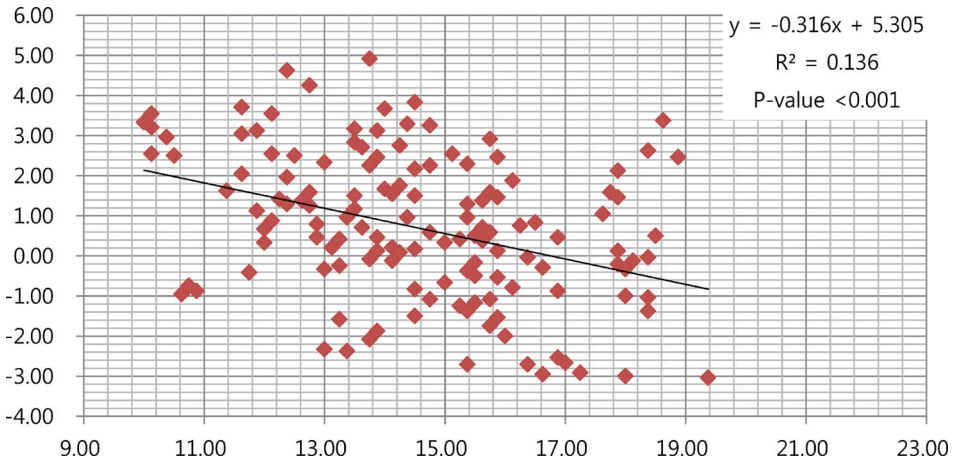

Figure 5. Pearson correlation plot showing a correlation between the mean diurnal IOP level and nocturnal habitual position IOP elevation (night supine average minus day seated average). *x*-axis, mean diurnal IOP level; *y*-axis, night supine average IOP minus day seated average IOP.

Our study had some limitations. First, measurements of the habitual position IOP using a hand-held tonometer in the hospital may not provide the best physiological 24-hour ocular tension data because our habitual position IOP measurements were based on a theoretical assumption (sitting during the day and supine at night). The use of a continuous implantable IOP sensor at home in the habitual body position may provide the most ideal measure of physiological IOP. A second limitation of our study may be an inability to generalize our findings to high-tension glaucoma classified by an IOP level $>$ 21 mm Hg and non-Asian individuals, because only Korean NTG patients were included in our current analyses. The number of 24-hour IOP measurements can affect IOP nyctohemeral rhythm. The greater the number of IOP measurement time points, the higher the probability to find a significant IOP nyctohemeral rhythm. In the current study, the number of IOP measurements was few (n = 11) during 24 hours, while IOP was measured in every hour in other study.[25] Finally, our NTG patients had relatively early-stage glaucoma based on VF criterion (average mean deviation = −2.65 dB). Therefore, it is important to keep in mind that the results of the current study may not be generalized to NTG or OAG patients at more advanced glaucomatous stage.

In conclusion, our current study data indicated a significant nocturnal mean IOP elevation in NTG patients with a low baseline daytime IOP level when IOP was measured in patients' habitual positions. This is in contrast to the high IOP group, which showed no significant nocturnal habitual position IOP elevation. In addition, individual analysis revealed three distinct acrophase patterns among the NTG subjects with a low daytime IOP that differed from those of the high IOP group. The nocturnal habitual position IOP elevation was significantly associated with the daytime IOP level and AL in our series of NTG patients. Further studies are needed to identify other clinical variables that may influence the 24-hour IOP pattern, as this may provide clinicians with a better understanding of the mechanisms of glaucomatous damage and aid determination of the optimal individualized IOP-lowering treatment strategy.

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References

1. Liu JH, Zhang X, Kripke DF, Weinreb RN. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Invest Ophthalmol Vis Sci*. 2003;44:1586–1590.
2. Lee YR, Kook MS, Joe SG, et al. Circadian (24-hour) pattern of intraocular pressure and visual field damage in eyes with normal-tension glaucoma. *Invest Ophthalmol Vis Sci*. 2012;53:881–887.
3. Sakata R, Aihara M, Murata H, et al. Intraocular pressure change over a habitual 24-hour period after changing posture or drinking water and related factors in normal tension glaucoma. *Invest Ophthalmol Vis Sci*. 2013;54:5313–5320.
4. Xu LA, Wang YX, Wang SA, Wang Y, Jonas JB. High myopia and glaucoma susceptibility – The Beijing Eye Study. *Ophthalmology*. 2007;114:216–220.
5. Casson RJ, Gupta A, Newland HS, et al. Risk factors for primary open-angle glaucoma in a burmese population: the Meiktila Eye Study. *Clin Exp Ophthalmol*. 2007;35:739–744.
6. Perera SA, Wong TY, Tay WT, Foster PJ, Saw SM, Aung T. Refractive error, axial dimensions, and primary open-angle glaucoma: the Singapore Malay Eye Study. *Arch Ophthalmol*. 2010;128:900–905.
7. Jeong DW, Kook MS, Lee KS, Lee JR, Han S. Circadian pattern of intraocular pressure in young myopic eyes with open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2014;55:2148–2156.
8. Lee KS, Lee JR, Kook MS. Optic disc torsion presenting as unilateral glaucomatous-appearing visual field defect in young myopic Korean eyes. *Ophthalmology*. 2014;121:1013–1019.
9. Choi J, Jeong J, Cho HS, Kook MS. Effect of nocturnal blood pressure reduction on circadian fluctuation of mean ocular perfusion pressure: a risk factor for normal tension glaucoma. *Invest Ophthalmol Vis Sci*. 2006;47:831–836.
10. Choi J, Kim KH, Jeong J, Cho HS, Lee CH, Kook MS. Circadian fluctuation of mean ocular perfusion pressure is a consistent risk factor for normal-tension glaucoma. *Invest Ophthalmol Vis Sci*. 2007;48:104–111.
11. Kim DM, Seo JH, Kim SH, et al. Comparison of localized retinal nerve fiber layer defects between a low-teen intraocular pressure group and a high-teen intraocular pressure group in normal-tension glaucoma patients. *J Glaucoma*. 2007;16:293–296.
12. Sung KR, Lee S, Park SB, et al. Twenty-four hour ocular perfusion pressure fluctuation and risk of normal-tension glaucoma progression. *Invest Ophthalmol Vis Sci*. 2009;50:5266–5274.
13. Lee J, Kong M, Kim J, Kee C. Comparison of visual field progression between relatively low and high intraocular pressure groups in normal-tension glaucoma patients. *J Glaucoma*. 2014;23:553–560.
14. Leske MC, Heijl A, Hyman L, et al. Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology*. 2007;114:1965–1972.
15. Yamagami J, Araie M, Aihara M, Yamamoto S. Diurnal variation in intraocular pressure of normal-tension glaucoma eyes. *Ophthalmology*. 1993;100:643–650.
16. Liu JHK, Weinreb RN. Asymmetry of habitual 24-hour intraocular pressure rhythm in glaucoma patients. *Invest Ophthalmol Vis Sci*. 2014;55:7398–7402.
17. Sit AJ, Nau CB, McLaren JW, Johnson DH, Hodge D. Circadian variation of aqueous dynamics in young healthy adults. *Invest Ophthalmol Vis Sci*. 2008;49:1473–1479.
18. Bhan A, Browning AC, Shah S, Hamilton R, Dave D, Dua HS. Effect of corneal thickness on intraocular pressure measurements with the pneumotonometer, Goldmann Applanation Tonometer, and Tono-Pen. *Invest Ophthalmol Vis Sci*. 2002;43:1389–1392.
19. Liu J, Roberts CJ. Influence of corneal biomechanical properties on intraocular pressure measurement: quantitative analysis. *J Cataract Refract Surg*. 2005;31:146–155.
20. Kida T, Liu JHK, Weinreb RN. Effect of 24-hour corneal biomechanical changes on intraocular pressure measurement. *Invest Ophthalmol Vis Sci*. 2006;47:4422–4426.
21. Liu JHK, Kripke DF, Hoffman RE, et al. Nocturnal elevation of intraocular pressure in young adults. *Invest Ophthalmol Vis Sci*. 1998;39:2707–2712.
22. Liu JHK, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. *Invest Ophthalmol Vis Sci*. 1999;40:2912–2717.
23. Lee AC, Mosaed S, Weinreb RN, Kripke DF, Liu JHK. Effect of laser trabeculoplasty on nocturnal intraocular pressure in medically treated glaucoma patients. *Invest Ophthalmol Vis Sci*. 2007;114:666–670.
24. Lee ES, Kim CY, Ha SJ, Seong GJ, Hong YJ. Central corneal thickness of Korean patients with glaucoma. *Ophthalmology*. 2007;114:927–930.
25. Renard E, Palombi K, Gronfier C, et al. Twenty-four hour (Nyctohemeral) rhythm of intraocular pressure and ocular perfusion pressure in normal-tension glaucoma. *Invest Ophthalmol Vis Sci*. 2010;51:882–889.