Baseline Diurnal Intraocular Pressure Can Predict Progression Rate of Visual Field Loss in Normal-tension Glaucoma

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Purpose: To determine if baseline diurnal intraocular pressure (D-IOP) can predict the progression rate of visual field (VF) loss in normal-tension glaucoma (NTG).

Methods: NTG eyes (n = 73) with D-IOP (measured from 8 AM to 4 PM at 90-minute intervals), which had been followed-up for more than 10 years were enrolled in this study. Eyes were categorized into a low-teen NTG group (n = 30, D-IOP = 12.2 ± 1.5 mmHg) and a high-teen NTG group (n = 43, D-IOP = 15.7 ± 1.4 mmHg). In each group, multiple linear regression was used to find factors (including maximum D-IOP parameter and IOP reduction after treatment) associated with visual field index progression rate based on Humphrey VF tests.

Results: In the low-teen NTG group, VF progression rate was significantly associated with age (p < 0.001), IOP reduction after treatment (p = 0.01), and maximum D-IOP (p = 0.02) after adjustment for multiple confounding factors. However, in the high-teen NTG group, age (p = 0.04) and IOP reduction after treatment (p = 0.02), but none of the D-IOP or follow-up IOP parameters, were significantly associated with VF progression rate.

Conclusions: D-IOP measurement could be helpful in predicting long-term VF progression, especially in low-teen NTG eyes.

Key words: Diurnal intraocular pressure; Normal-tension glaucoma

Introduction

Normal-tension glaucoma (NTG) is a disease presenting with glaucomatous optic nerve head and visual field (VF) defect, despite an open, normal-appearing anterior chamber angle and intraocular pressure (IOP) that never rises above 21 mmHg.¹² In two previous reports from the Japanese Tajimi study and Korean Namill study, the prevalence of primary open-angle glaucoma (POAG) was 3.9% and 3.5%, respectively.¹⁴ Among them, POAG with an IOP of 21 mmHg or less accounted for 92% and 77%, respectively.

Several other studies have further classified NTG into two groups: low-teen NTG with IOP of 15 mmHg or less, and high-teen NTG with IOP of more than 15 mmHg.⁵⁻¹⁰ These studies have shown that low-teen and high-teen NTG may have differing pathophysiologies with regard to the development of glaucoma. Low-teen NTG may be more affected by a history of vascular factors, whereas high-teen NTG may be more affected by IOP.

However, other studies have reported an association of low-teen NTG progression with IOP. Caprioli and Coleman¹¹ determined that long-term IOP fluctuation is related to disease progression in low-pressure glaucoma patients. Baek et al.¹² demonstrated that diurnal IOP (D-IOP) is associated with low-
teen glaucoma progression along with disc hemorrhage and diastolic blood pressure fluctuation. Yet, the factors that may influence glaucoma progression in both low-teen and high-teen NTG patients remain unknown. The present study is a minimum-10-year follow-up longitudinal study that aimed to determine if factors including D-IOP parameters are associated with progression rate of VF loss in both low-teen and high-teen NTG.

Materials and Methods

This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: 2107-154-1237) and adhered to the tenets of the Declaration of Helsinki.

Study subjects

We retrospectively reviewed the medical records of 315 NTG patients from the Glaucoma Clinic at Seoul National University Hospital from January 1999 to April, 2020. We included NTG patients who had been followed-up regularly for more than 10 years. We excluded patients without baseline D-IOP measurement, those who had undergone intraocular surgeries other than cataract operation, who had failed the VF test, and who had comorbid ocular diseases that could interfere with visual function.

D-IOP measurements

A calibrated Goldmann applanation tonometer was used to measure untreated IOP (before initiation of topical medication). D-IOPs were measured by Goldmann applanation tonometry at 90-minute intervals from 08:30 to 16:00, for a total six measurements. Each measurement was taken three times by experienced physicians using the same tonometer.

Data collection

Medical records were assessed for age, sex, history of systemic diseases (diabetic mellitus [DM], hypertension [HTN], cardiovascular disease [CVD]), and number of topical anti-glaucoma medications. Patients were evaluated by ophthalmic examinations: visual acuity, central corneal thickness, axial length, cup-to-disc ratio, occurrence of disc hemorrhage, VF indexes (number of tests, mean deviation, pattern standard deviation, visual field index [VFI]), IOP (baseline D-IOP, IOP at every visit after medication), and follow-up duration.

VF examination

VF tests were evaluated by Swedish interactive thresholding algorithm 24-2 perimetry (Humphrey Field Analyzer II, Carl Zeiss Meditec, Jena, Germany). The VF defect progression was assessed in event- and trend-based analysis by Guided Progression Analysis software from the Humphrey Visual Field Analyzer.13 The software compares follow-up VF tests with initial two reliable VF tests and assess whether significant decrease in VFI occurred at three or more of the same test points on at least two consecutive VF tests. Also, the VF progression rate was evaluated using global trend-based analysis of VFI.

Data analysis

Clinical characteristics were compared between low-teen and high-teen NTG groups. We grouped eyes as “low-teen NTG” when none of the measured baseline D-IOPs were over 15 mmHg, and as “high-teen NTG” when any of them were over 15 mmHg. Continuous variables were compared between the groups by student’s t-test, and categorical variables were compared using the chi-square test. Data were presented as the mean ± standard deviation (SD). Multiple linear regression analysis was performed, first with a univariate model and then with a multivariate model that included variables from the univariate model with \( p < 0.10 \) to identify significant factors associated with VF progression rate in trend-based analysis by the Humphrey VF test. The Kaplan-Meier survival analysis and the log-rank test were conducted to compare the VF progression in event-based analysis between the low-teen and high-teen NTG groups. Except where stated otherwise, statistical significance was defined as \( p < 0.05 \). Statistical analysis was conducted by R software (R version 3.6.1., available at: http://www.r-project.org; accessed July 2019).

Results

Subject demographics

Among the 315 NTG patients who had been followed-up
Figure 1. Flow diagram of study population. IOP = intraocular pressure; VF = visual field.

Table 1. Patient and ocular characteristics of total subjects and comparison between low-teen NTG group and high-teen NTG group

| Variable                        | Total (n = 73) | Low-teen NTG group (n = 30) | High-teen NTG group (n = 43) | p-value |
|---------------------------------|---------------|-----------------------------|-------------------------------|---------|
| Age (years)                     | 67.6 ± 13.7   | 68.3 ± 16.3                 | 67.0 ± 11.8                   | 0.69*   |
| Sex                             |               |                             |                               |         |
| Male                            | 41 (56.2)     | 14 (46.7)                   | 27 (62.8)                     | 0.17†   |
| Female                          | 32 (43.8)     | 16 (53.3)                   | 16 (37.2)                     |         |
| HTN                             |               |                             |                               | 0.89†   |
| No                              | 48 (65.8)     | 20 (66.7)                   | 28 (65.1)                     |         |
| Yes                             | 25 (34.3)     | 10 (33.3)                   | 15 (34.9)                     |         |
| DM                              |               |                             |                               | 0.15†   |
| No                              | 60 (82.2)     | 27 (90.0)                   | 33 (76.7)                     |         |
| Yes                             | 13 (17.8)     | 3 (10.0)                    | 10 (23.3)                     |         |
| CVD                             |               |                             |                               | 0.59†   |
| No                              | 65 (89.0)     | 26 (86.7)                   | 39 (90.7)                     |         |
| Yes                             | 8 (11.0)      | 4 (13.3)                    | 4 (9.3)                       |         |
| CCT (μm)                        | 531.3 ± 34.1  | 523.9 ± 30.8                | 536.4 ± 35.7                  | 0.12‡   |
| CDR                             | 0.62 ± 0.2    | 0.60 ± 0.2                  | 0.63 ± 0.2                    | 0.50*   |
| Disc hemorrhage                 | 10 (13.7)     | 3 (10.0)                    | 7 (16.3)                      | 0.44†   |
| Baseline VFI                    | 93.2 ± 10.2   | 94.2 ± 10.1                 | 92.6 ± 10.4                   | 0.50†   |
| Progression                     | 33 (45.2)     | 10 (33.3)                   | 23 (53.5)                     | 0.09†   |
| Progression duration (years)    | 4.0 ± 5.2     | 3.0 ± 4.6                   | 4.6 ± 5.6                     | 0.19†   |
| Number of medication            | 1.5 ± 0.9     | 1.1 ± 0.8                   | 1.8 ± 0.9                     | <0.001‡ |
| Number of visual field test     | 11.3 ± 2.9    | 10.3 ± 2.8                  | 12.0 ± 2.9                    | 0.02‡   |
| Follow up duration (years)      | 13.3 ± 2.2    | 13.0 ± 2.2                  | 13.6 ± 2.2                    | 0.24‡   |

Values are presented as mean ± standard deviation or number (%).
NTG = normal-tension glaucoma; HTN = hypertension; DM = diabetic mellitus; CVD = cardiovascular disease; CCT = central corneal thickness; CDR = cup-to-disc ratio; VFI = visual field index.
*Comparison was performed using student’s t-test; †Comparison was performed using chi-square test; ‡Statistically significant values (p < 0.05).
for more than 10 years, a total of 73 eyes of 73 subjects were included in this study (Fig. 1). The baseline demographic and clinical characteristics are described in Table 1. The subjects’ mean age was 67.6 years; 44% were female, 34% had HTN, 18% had DM, and 11% had CVD. The mean follow-up duration was 13.3 years (range, 10.0-20.9).

Comparing characteristics between the two groups, there were no statistical differences in age, sex ratio, underlying diseases (HTN, DM, CVD), central corneal thickness, cup-to-disc ratio, incidence of disc hemorrhage, baseline VFI, proportion of progression, progression duration, or follow-up duration (all \( p > 0.05 \)). The number of anti-glaucoma agents and the number of VF tests were significantly lower in the low-teen NTG group than in the high-teen NTG group (\( p < 0.05 \)). All

### Table 2. Intraocular pressure parameters of total subjects and comparison between low-teen NTG group and high-teen NTG group

| Variable                              | Total (n = 73) | Low-teen NTG group (n = 30) | High-teen NTG group (n = 43) | p-value* |
|---------------------------------------|---------------|-----------------------------|-------------------------------|----------|
| Mean D-IOP before treatment           | 14.3 ± 2.2    | 12.2 ± 1.5                  | 15.7 ± 1.4                   | <0.001   |
| Range of D-IOP before treatment       | 3.0 ± 1.5     | 2.5 ± 1.3                   | 3.4 ± 1.5                    | 0.01     |
| Peak D-IOP before treatment           | 15.8 ± 1.5    | 13.5 ± 1.4                  | 17.5 ± 1.5                   | <0.001   |
| Trough D-IOP before treatment         | 12.8 ± 2.3    | 11.0 ± 1.6                  | 14.1 ± 1.8                   | <0.001   |
| Mean IOP during treatment             | 12.1 ± 1.6    | 11.0 ± 1.1                  | 12.8 ± 1.5                   | <0.001   |
| SD of IOP during treatment            | 1.5 ± 0.4     | 1.4 ± 0.3                   | 1.7 ± 0.4                    | <0.001   |
| Peak IOP during treatment             | 15.7 ± 2.4    | 14.1 ± 1.7                  | 16.7 ± 2.2                   | <0.001   |
| Trough IOP during treatment           | 9.3 ± 1.6     | 8.6 ± 1.1                   | 9.7 ± 1.7                    | 0.002    |
| Reduction of IOP after treatment      | 3.6 ± 1.3     | 3.1 ± 1.2                   | 3.9 ± 1.3                    | 0.01     |

Values are presented as mean ± standard deviation.

NTG = normal-tension glaucoma; D-IOP = diurnal intraocular pressure; IOP = intraocular pressure.

\(^*\)Comparison was performed using student’s t-test, statistically significant values (\( p < 0.05 \)).

### Table 3. Multiple linear regression analysis of factors associated with visual field defect progression in low-teen NTG group

| Variable                             | Low-teen NTG group | Multivariate |
|--------------------------------------|--------------------|--------------|
|                                      | Univariate         |              |
|                                      | \( \beta \)-coefficient | SE | p-value | \( \beta \)-coefficient | SE | p-value |
| Age                                  | -0.02              | 0.01         | 0.09\(^*\) | -0.02              | 0.01         | <0.001\(^*\) |
| Sex                                  | -0.32              | 0.31         | 0.31       | -0.32              | 0.31         | 0.31       |
| Hypertension                         | -0.15              | 0.24         | 0.55       | -0.15              | 0.24         | 0.55       |
| Diabetes mellitus                    | 0.22               | 0.47         | 0.64       | 0.22               | 0.47         | 0.64       |
| Cardiovascular disease               | -0.27              | 0.56         | 0.64       | -0.27              | 0.56         | 0.64       |
| Central corneal thickness            | 0.003              | 0.004        | 0.54       | 0.003              | 0.004        | 0.54       |
| Disc hemorrhage                      | -0.15              | 0.49         | 0.76       | -0.15              | 0.49         | 0.76       |
| Follow up duration (years)           | -0.06              | 0.06         | 0.36       | -0.06              | 0.06         | 0.36       |
| Baseline VFI (%)                     | -0.004             | 0.01         | 0.79       | -0.004             | 0.01         | 0.79       |
| Number of medication                 | -0.14              | 0.16         | 0.40       | -0.14              | 0.16         | 0.40       |
| IOP Reduction after treatment        | -0.28              | 0.11         | 0.02\(^*\) | 0.22               | 0.08         | 0.01\(^*\) |
| Maximum D-IOP before treatment       | -0.17              | 0.09         | 0.07\(^*\) | -0.17              | 0.07         | 0.02\(^*\) |

NTG = normal-tension glaucoma; SE = standard error; VFI = visual field index; IOP = intraocular pressure; D-IOP = diurnal intraocular pressure.

\(^*\)Statistically significant values (\( p < 0.05 \)).
the IOP parameters are shown in Table 2. All parameters of D-IOP before treatment (mean, range, peak, and trough) and all parameters of IOP during treatment (mean, SD, peak, trough, and reduction of IOP) were significantly lower in the low-teen NTG group than in the high-teen NTG group (all \( p < 0.05 \)).

Factors associated with VF defect progression

The factors associated with VF progression rate in trend-based analysis by Humphrey VF tests were analyzed by dividing the subjects into their two groups: low-teen NTG and high-teen NTG (Table 3, 4). In each group, univariate and multivariate linear regression analysis were used. In the low-teen group, VF progression rate was significantly associated with age (\( p < 0.001 \)), IOP reduction after treatment (\( p = 0.01 \)), and maximum D-IOP (\( p = 0.02 \)) after adjustment for multiple confounding factors. In the high-teen group, age (\( p = 0.04 \)) and IOP reduction after treatment (\( p = 0.02 \)) were significantly associated with VF progression rate, while baseline VFI (\( p = 0.05 \)) was marginally associated with VF progression rate. However, none of the D-IOP nor follow-up IOP parameters were significantly associated with VF progression rate.

Survival analysis comparing low-teen and high-teen groups

Kaplan-Meier survival analysis was used to estimate the cumulative probabilities of VF defect progression in event-based analysis, as compared between the low-teen and high-teen NTG groups. Both groups showed gradual progression of VF defect. During a mean (SD) 13.3 (2.1)-year (range, 10.0-20.9 years) follow-up period, 10 of 30 low-teen NTG eyes (33.3%) and 23 of 43 high-teen NTG eyes (53.5%) showed VF defect progression. However, the analysis showed that there was no statistically significant difference between two groups (\( p = 0.19 \), log-rank test) (Fig. 2).

Discussion

Our 10-year longitudinal study investigated D-IOP as a predictive factor for VF defect progression rate in NTG eyes. In the low-teen NTG group, VF progression rate was significantly associated with greater maximum D-IOP after adjustment for multiple confounding factors, along with age and IOP reduction after treatment. However, in the high-teen NTG group, age and IOP reduction after treatment were factors that were

| Table 4. Multiple linear regression analysis of factors associated with visual field defect progression in high-teen NTG group |
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| **Variable** | **High-teen NTG group** | **Univariate** | **Multivariate** |
|  | \( \beta \)-coefficient | SE | \( p \)-value | \( \beta \)-coefficient | SE | \( p \)-value |
| Age | -0.03 | 0.01 | 0.04* | -0.02 | 0.01 | 0.04* |
| Sex | 0.05 | 0.30 | 0.88 |
| Hypertension | 0.45 | 0.30 | 0.14 |
| Diabetes mellitus | 0.08 | 0.30 | 0.79 |
| Cardiovascular disease | 0.16 | 0.44 | 0.72 |
| Central corneal thickness | 0.003 | 0.004 | 0.47 |
| Disc hemorrhage | -0.65 | 0.47 | 0.18 |
| Follow up duration (years) | -0.08 | 0.06 | 0.20 |
| Baseline VFI (%) | 0.03 | 0.01 | 0.03* | 0.02 | 0.01 | 0.05* |
| Number of medication | -0.30 | 0.17 | 0.09* | -0.21 | 0.14 | 0.13 |
| IOP reduction after treatment (mmHg) | 0.21 | 0.10 | 0.04* | 0.23 | 0.09 | 0.02* |
| Maximum D-IOP before treatment (mmHg) | 0.09 | 0.11 | 0.40 |

NTG = normal-tension glaucoma; SE = standard error; VFI = visual field index; IOP = intraocular pressure; D-IOP = diurnal intraocular pressure.

*Statistically significant values (\( p < 0.05 \)).
associated with VF progression rate; D-IOP parameter was not significantly associated with VF progression rate.

Older age and IOP reduction after treatment are well known risk factors for progression in open angle glaucoma eyes.\textsuperscript{14,15} In our study, the two variables were revealed to be risk factors for faster progression rate as well in both low-teen NTG and high-teen NTG groups. Interestingly, D-IOP parameter was associated with VF progression rate in only low-teen NTG group. D-IOP fluctuation as a risk factor for NTG progression has been studied previously. Asrani et al.\textsuperscript{16} and Baek et al.\textsuperscript{12} reported, based on a minimum-5-year follow-up longitudinal study, that D-IOP was significantly associated with progression in low-teen NTG eyes. Our present, minimum-10-year follow-up results corroborate former findings that D-IOP fluctuation may be related to faster VF defect progression rate in low-teen NTG eyes.

In our Kaplan-Meier survival analysis, there was no significant association between D-IOP and VF progression ($p = 0.19$). However, as we can see from Fig. 2, the high-teen D-IOP NTG group was more likely to progress than was the low-teen D-IOP NTG group. In a further study, we will include a larger population in order to validate the association of D-IOP with VF progression time.

There are two hypothetical mechanisms of D-IOP’s effect on glaucoma progression. First, irregular and large IOP fluctuations induce repetitive stress on the lamina cribrosa and ganglion cell axons.\textsuperscript{12} Second, this stress surge disturbs the homeostatic compensatory mechanism, leading to vulnerability.\textsuperscript{17} Regardless, and notwithstanding an opposing report\textsuperscript{18} regarding the influence of D-IOP on glaucoma progression, the issue of controlling IOP fluctuation is generally considered to be important for managing glaucoma patients.\textsuperscript{17}

The strength of the present study is its substantially long follow-up period (>10 years). However, this study has a few limitations. First, the number of included subjects was relatively small. Further studies with a prospective design and a large cohort are warranted. Second, we measured D-IOP by Goldmann applanation tonometry at 90-minute intervals during working hours (from 08:30 to 16:00). However, differences in D-IOP might have arisen if 24-hour IOP readings, including nighttime IOP, had been measured. Third, high-teen NTG group had significantly greater number of VF tests ($12.0 \pm 2.9$) than low-teen NTG group ($10.3 \pm 2.8$) ($p = 0.02$). The differences of number of VF tests between two groups may have attributed to differences of VF progression rate. Lastly, we excluded patients who had undergone intraocular surgeries, including glaucoma.

![Figure 2](image-url)

Figure 2. Kaplan-Meier survival analysis for visual field progression in low-teen normal tension glaucoma (NTG) and high-teen NTG group.
surgeries. This might have had the effect of excluding glaucoma patients with highly fast progression rates from our study population. In conclusion, D-IOP measurement could be helpful in predicting long-term VF progression, especially in low-teen NTG eyes.

Conflicts of Interest
The authors declare no conflicts of interest relevant to this article.

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국문초록

정상안압녹내장에서 기저 일중 안압과 시야결손 진행 속도와의 연관성: 10년 경과 관찰 연구

목적: 정상안압녹내장에서 기저 일중 안압으로 시야결손 진행 속도의 예측이 가능한지 연구해보고자 한다.

대상과 방법: 정상안압녹내장 환자 중 10년 이상 경과 관찰한 73명 73안을 대상으로 후향적 의무기록 분석을 진행하였다. 기저 일중 안압을 기준으로 15 mmHg 이하인 경우를 low-teen 정상안압녹내장 그룹(n=30, 안압=12.2 ± 1.5 mmHg)으로 분류하고, 15 mmHg 초과인 경우를 high-teen 정상안압녹내장 그룹(n=43, D-IOP=15.7 ± 1.4 mmHg)으로 분류하였다. 분석은 다중 선형회귀분석으로 기저 일중 안압을 포함한 변수들과 visual field index (VFI) 진행 속도 간 상관 관계를 분석하였다.

결과: Low-teen 정상안압녹내장 그룹에서 시야 진행 속도는 나이가 많을수록, 치료 후 안압 하강 폭이 클수록, 그리고 최고 일중 안압이 높을수록 더 빨리 진행하였다. 하지만 high-teen 정상안압녹내장 그룹에서는 나이와 치료 후 안압 하강 폭만 VFI 진행 속도와 연관성이 있었고, 기저 일중 안압 수치는 진행 속도와 연관성이 없었다.

결론: 기저 일중 안압 측정이 low-teen 정상안압녹내장 환자에서 정기적인 시야결손 진행 속도 예측에 도움을 줄 수 있다.