Changes in Axial Length and Progression of Visual Field Damage in Glaucoma

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Purpose. To investigate the relationship between axial length (AL) elongation and progression of primary open-angle glaucoma (POAG).

Methods. AL was measured twice over a 5.1 ± 0.76 (mean ± standard deviation: SD) year period in 125 eyes of 72 patients with POAG. The eyes were divided into not long (AL < 26 mm, 80 eyes) and long (>26 mm, 45 eyes) groups. During this period, patients' visual fields (VFs) were measured with the Humphrey Field Analyzer 12.4 ± 7.5 times and intraocular pressure (IOP) was measured with Goldmann applanation tonometry 27.0 ± 7.5 times. The relationship between the mean total deviation (mTD) progression rates in the whole field and superior and inferior hemifield, as well as in 10 VF sectors, and the variables of age, mean IOP, SD of IOP, AL, difference in AL (△AL), and mTD value at baseline was examined.

Results. There was a significant difference between AL at baseline and AL at repeat measurement ($P < 0.0001$). △AL was 0.035 ± 0.10 mm. An increase in △AL was significantly related to AL at baseline ($P = 0.027$), but not to age, mean IOP, and SD of IOP. △AL was related to the progression of mTD in the inferior hemifield (slower mTD progression was associated with increased △AL), but not in the whole field or superior hemifield. Increased △AL was related to slower progression rates in 2 of 10 sectors, both in the inferior hemifield.

Conclusions. The main finding was that an increase in AL was significantly related to slower VF progression in the inferior hemifield.

Keywords: glaucoma, axial length, visual field

Glaucoma is one of the leading causes of irreversible blindness worldwide. The pathophysiology of glaucoma is not fully understood, but the disease causes damage to the optic nerve, which leads to progressive loss of retinal ganglion cells and their axons. The development of glaucoma is closely related to elevated intraocular pressure (IOP); however, the vulnerability of the optic disc is also very important because normal-tension glaucoma (NTG) develops in persons with normal IOP.[1]

In myopia, the optic disc is deformed according to the elongation of the eye,[2] and the prevalence of glaucoma is high in myopic eyes.[3–7] Myopic eyes and glaucomatous eyes share similar features. For instance, peripapillary atrophy (PPA) is associated with the development and progression of glaucoma,[8–15] but PPA is also commonly seen in myopic eyes.[16–18] More specifically, PPA with the presence of Bruch's membrane is related with glaucoma, whereas PPA with the absence of Bruch's membrane is related to myopia.[19] Recently, Yamada et al.[20] reported that, in glaucomatous eyes, PPA with the presence of Bruch's membrane is associated with fast glaucomatous progression, while PPA with the absence of Bruch's membrane is associated with slow progression.

Elongation of the eye can occur in adults. For example, McBrien and Adams[21] investigated refractive error and ocular structure in adult clinical microscopists, demonstrating that 39% of those who were originally emmetropic and 48% of those who were originally myopic had a progression of myopia equal to at least 0.37 diopters following entry into the profession, related to 0.26- and 0.77-mm vitreous chamber length, respectively. To the best of our knowledge, no study has investigated the relationship between elongation of the eye and the progression of glaucoma. This is especially important for Asians, including Japanese, because myopia is very common in these populations.[22–24] Furthermore, we have recently reported that progression rate cannot be explained by the level of IOP control alone in treated glaucoma patients,[25] so it is of huge clinical interest to identify other factors that influence glaucomatous progression.

Methods

The study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at the University of Tokyo. Written consent was given by the patients for their information to be stored in the hospital database and used for research. This study was performed according to the tenets of the Declaration of Helsinki.

Subjects

This study included 125 eyes of 72 patients with primary open-angle glaucoma (mean ± standard deviation [SD] age: 59.2 ± 11.6 years) attending the glaucoma clinic at the University of

Tokyo Hospital, followed since 2008. All of the participants were Japanese.

All patients had axial length (AL) measured twice over a period spanning at least 4 years (5.1 ± 0.76), using the IOL Master (Ver4) (Carl Zeiss Meditec, Dublin, CA, USA), by a well-trained examiner (MY). All patients had a minimum of five reliable visual field (VF) tests with the Humphrey Field Analyzer (Carl Zeiss Meditec) in the interval between the two AL measurements. An unreliable VF was defined as having more than 20% fixation losses or more than 15% false-positive errors; the false-negative rate was not applied as a reliability criterion because it has been shown to be positively correlated with the level of VF damage rather than patient attentiveness.[26] All patients had an experience of the VF test prior to the initial AL measurement. All VFs were recorded using the 24-2 or 30-2 test pattern and the Swedish Interactive Threshold Algorithm (SITA) standard strategy with a Goldmann size III target. When the VF was measured using the 30-2 test pattern, only the 52 test points overlapping with the 24-2 test pattern were used for the analysis; mean total deviation value (mTD) in the whole field was –3.5 ± 4.6 (mean ± SD [range, –23.2 to 2.0]) dB. IOP measurements, with Goldmann applanation tonometry, were recorded over the same period, and the mean and SD were calculated (mean IOP and IOP SD). Mean IOP was 13.6 ± 2.4 [9.0–23.3] mm Hg, and IOP SD was 1.6 ± 0.5 [0.6–4.8] mm Hg.

Inclusion criteria were as follows. (1) Primary open-angle glaucoma was the only disease causing VF damage, and there were no other ocular diseases that could affect VF sensitivity, such as diabetic mellitus retinopathy, corneal opacity, and age-related macular degeneration, or cataract other than clinically insignificant senile cataract. Primary open-angle glaucoma was defined, first, as presence of typical glaucomatous changes in the optic nerve head such as a rim notch with a rim width ≤ 0.1 disc diameters or a vertical cup-to-disc ratio of >0.7 and/or a retinal nerve fiber layer defect with its edge at the optic nerve head margin greater than a major retinal vessel, diverging in an arcuate or wedge shape; secondly, as gonioscopically wide open angles of grade 3 or 4 based on the Shaffer classification. (2) Best-corrected visual acuity was better than or equal to 6/12. (3) No previous ocular surgery (except for cataract extraction) had occurred. (4) No other posterior segment eye diseases were present. Patients who experienced any intraocular surgery, including cataract and glaucoma surgery, during the observation period were not included. Eyes with aberrant disc morphology or anomalies, or signs suggestive of pathologic myopia on dilated funduscopy, were carefully excluded. As patients were recruited from a glaucoma clinic, medication might be changed during the follow up; for example, it might be intensified if IOP was increased or progression of VF damage was suspected.

Statistical Analysis

The rate of VF progression was calculated by regressing the mTD in the whole field, the superior hemifield ($mTD_{superior}$), and the inferior hemifield ($mTD_{inferior}$) against time. The VF was also divided into small sectors following the Garway-Heath map[27]; VF test points corresponding to each of the 12 30° sectors (T, temporal; TS, temporosuperior; ST, superotemporal; S, superior; SN, superonasal; NS, nasosuperior; N, nasal, three sectors; NI, nasoinferior; IN, inferonasal; I, inferior; IT, inferotemporal; TI, temporoinferior) are shown in Figure 1. Because of the small number of test points, the NS, N, and NI sectors were combined (cluster N3). The average TD values were calculated in each sector (mTD_T/mTD_{TS}/mTD_{ST}/mTD_S/mTD_{SN}/mTD_{N3}/mTD_{IN}/mTD_I/mTD_{IT}/mTD_{TI}). Please note that the superior and inferior hemifields are located in the superior and inferior VF, whereas TS, ST, S, SN, and NS reside in the inferior VF, and NI, IN, I, IT, and TI in the superior VF (see Fig. 1).

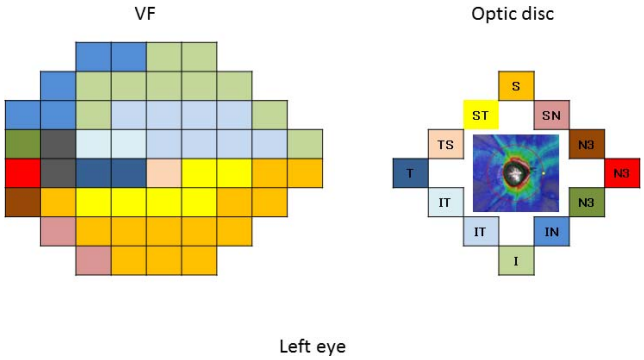

FIGURE 1. Ten VF clusters and corresponding optic disc sectors. Derived from Garway-Heath map.[27] Right eye was mirror imaged.

The relationship between sectorial mTD progression rate and the variables of age, AL at baseline, difference or change in AL (△AL), mean of IOP, IOP SD, and baseline mTD was investigated using the linear mixed model. The linear mixed model was used because both eyes of a patient were included in the analyses; therefore patients were treated as a "random effect" in the model. The linear mixed model is equivalent to ordinary linear regression in that the model describes the relationship between the predictor variables and a single outcome variable. However, the standard linear regression analysis is based on the assumption that all observations are independent of each other. Ignoring the nested structure of the dataset results in underestimation of standard errors of regression coefficients. The linear mixed model adjusts for the hierarchical structure of the data, modeling in a way in which measurements are grouped within subjects.

Subsequently, eyes were divided into a "long AL group" (AL ≥ 26 mm) and a "not long AL group" (AL < 26 mm), and AL was compared between the first and second measurements, using the linear mixed model. Baseline characteristics were compared between long AL and not long AL groups, using the linear mixed model. Also, the effects of age, AL at baseline, △AL, mean of IOP, IOP SD, and baseline mean TD values on the VF progression rate were investigated, using the linear mixed model. In addition, records of the use of a prostaglandin analogue, beta-blocker, topical carbonic anhydrase inhibitor (CAI), or brimonidine throughout the observation period or at least once (single use) were collected, and their relationships to △AL were analyzed in all eyes, the long AL group, or the not long AL group.

All statistical analyses were performed with the statistical programming language R (R version 3.1.3; The Foundation for Statistical Computing, Vienna, Austria).

Results

Subject demographics are described in Table 1. Subjects' average age was 59.2 ± 11.6 (mean ± SD) [range, 32–88] years. The mean interval between the two AL measurements was 5.1 ± 0.76 [4.1–7.6] years. During this period, VFs were measured 12.4 ± 7.5 [5–30] times, whereas IOP measurement was carried out 27.0 ± 7.5 [15–60] times. The mTD progression rates in the whole field, superior hemifield, and inferior hemifield were –0.24 ± 0.35 [–1.7 to 0.51], –0.32 ± 0.51 [–3.2 to 0.52], and –0.15 ± 0.35 [–1.5 to 0.87] dB/year, respectively. Sectorial mTD progression rates are shown in Table 1. Mean IOP was 13.6 ± 2.4 [9.0–23.3] mm Hg and IOP SD was 1.6 ± 0.5 [0.6–4.8] mm Hg.

Table 1. Subject Demographics

Variables	All Eyes, $N = 125$	Long AL Group, $N = 45$	Not Long AL Group, $N = 80$	P Value
Sex, male:female	63:62	29:16	34:46	0.019
Eye, right:left	63:62	22:23	40:40	0.91
Age, y, mean ± SD [range]	59.2 ± 11.6 [32 to 88]	54.2 ± 9.9 [36 to 69]	61.2 ± 11.3 [32 to 88]	0.59
Number of VF measurements, times, mean ± SD [range]	12.4 ± 7.5 [5 to 30]	14.1 ± 8.3 [5 to 30]	11.5 ± 6.8 [5 to 26]	0.88
Number of IOP measurements, times, mean ± SD [range]	27.0 ± 7.5 [15 to 60]	27.6 ± 7.8 [18 to 60]	26.7 ± 7.4 [15 to 50]	0.97
Mean IOP, mm Hg, mean ± SD [range]	13.6 ± 2.4 [9.0 to 23.3]	13.0 ± 1.8 [9.0 to 16.4]	14.0 ± 2.6 [9.8 to 23.3]	0.26
IOP SD, mm Hg, mean ± SD [range]	1.6 ± 0.6 [0.6 to 4.8]	1.5 ± 0.4 [0.6 to 3.3]	1.7 ± 0.7 [0.9 to 4.8]	0.55
AL first measurement, mm, mean ± SD [range]	25.29 ± 1.44[22.55 to 29.02]	26.86 ± 0.60 [26.03 to 29.02]	24.41 ± 0.93 [22.55 to 25.98]	<0.0001
AL second measurement, mm, mean ± SD [range]	25.33 ± 1.43 [22.60 to 29.04]	26.87 ± 0.58 [26.01 to 29.04]	24.45 ± 0.94 [22.60 to 26.04]	<0.0001
△AL, mm, mean ± SD [range]	0.035 ± 0.10 [−0.26 to 0.61]	0.013 ± 0.10 [−0.24 to 0.36]	0.047 ± 0.10 [−0.28 to 0.61]	0.063
Refractive error, diopters, mean ± SD [range]	−3.5 ± 3.1 [−13.0 to 3.25]	−6.3 ± 2.5 [−13.0 to −2.25]	−1.9 ± 2.2 [−6.75 to 3.25]	<0.0001
Used PG throughout the period	71 eyes of 44 patients	27 eyes of 17 patients	44 eyes of 28 patients	0.72
Used PG at least once in the period	91 eyes of 56 patients	35 eyes of 21 patients	56 eyes of 36 patients	0.47
Used beta-blocker throughout the period	23 eyes of 14 patients	11 eyes of 6 patients	12 eyes of 8 patients	0.29
Used beta-blocker at least once in the period	52 eyes of 34 patients	17 eyes of 11 patients	35 eyes of 24 patients	0.64
Used CAI throughout the period	10 eyes of 7 patients	1 eyes of 1 patients	9 eyes of 6 patients	0.15
Used CAI at least once in the period	31 eyes of 22 patients	6 eyes of 6 patients	25 eyes of 16 patients	0.044
Used brimonidine throughout the period	0 eyes of 0 patients	0 eyes of 0 patients	0 eyes of 0 patients	NA
Used brimonidine at least once in the period	22 eyes of 15 patients	7 eyes of 5 patients	15 eyes of 10 patients	0.84
Number of eye drops, mean ± SD [range]	0.94 ± 0.79 [0.0 to 3.6]	0.88 ± 0.75 [0.0 to 3.6]	0.98 ± 0.81 [0.0 to 3.6]	0.72
Base mTD, mean ± SD [range]	−3.5 ± 4.6 [−23.2 to 2.0]	−4.0 ± 5.1 [−21.6 to 1.0]	−3.2 ± 4.3 [−23.2 to 2.0]	0.56
Base $mTD_{superior}$, mean ± SD [range]	−4.9 ± 1.44 [−28.8 to 2.2]	−5.9 ± 7.9 [−28.4 to 1.3]	−4.3 ± 6.2 [−28.8 to 2.2]	0.32
Base $mTD_{inferior}$, mean ± SD [range]	−2.1 ± 4.5 [−24.0 to 2.3]	−2.1 ± 4.7 [−24.0 to 1.5]	−2.1 ± 4.4 [−21.5 to 2.3]	0.81
Base mTD_T, mean ± SD [range]	−0.3 ± 2.5 [−18.0 to 3.5]	−0.4 ± 2.2 [−12.0 to 2.5]	−0.2 ± 2.7 [−18.0 to 3.5]	0.85
Base mTD_{TS}, mean ± SD [range]	−0.7 ± 4.5 [−35.0 to 6.0]	−1.6 ± 6.7 [−35.0 to 2.0]	−0.2 ± 2.6 [−15.0 to 6.0]	0.27
Base mTD_{ST}, mean ± SD [range]	−2.3 ± 6.0 [−33.3 to 2.7]	−2.6 ± 6.9 [−33.3 to 2.5]	−2.2 ± 5.4 [−22.2 to 2.7]	0.92
Base mTD_S, mean ± SD [range]	−2.8 ± 6.0 [−31.5 to 2.2]	−2.7 ± 5.8 [−28.8 to 1.8]	−2.9 ± 6.2 [−31.5 to 2.2]	0.75
Base mTD_{SN}, mean ± SD [range]	−1.2 ± 5.1 [−32.5 to 3.5]	−0.3 ± 1.9 [−7.0 to 3.0]	−1.7 ± 6.1 [−32.5 to 3.5]	0.15
Base mTD_{N3}, mean ± SD [range]	−1.0 ± 2.5 [−13.5 to 2.8]	−1.3 ± 2.6 [−13.0 to 1.8]	−0.9 ± 2.4 [−13.5 to 2.8]	0.56
Base mTD_{IN}, mean ± SD [range]	−2.6 ± 5.4 [−29.2 to 3.0]	−3.3 ± 5.7 [−25.2 to 2.8]	−2.2 ± 5.2 [−29.2 to 3.0]	0.33
Base mTD_I, mean ± SD [range]	−5.8 ± 8.2 [−31.2 to 2.4]	−7.7 ± 9.7 [−31.2 to 1.7]	−4.7 ± 7.1 [−30.0 to 2.4]	0.11
Base mTD_{IT}, mean ± SD [range]	−6.6 ± 9.6 [−33.6 to 2.0]	−7.7 ± 10.5 [−33.6 to 1.1]	−6.0 ± 9.2 [−32.6 to 2.0]	0.46
Base mTD_{TI}, mean ± SD [range]	−4.9 ± 9.6 [−34.5 to 3.0]	−4.0 ± 9.1 [−34.5 to 2.5]	−5.5 ± 10.0 [−32.5 to 3.0]	0.47
mTD progression rate, dB/y, mean ± SD [range]	−0.24 ± 0.35 [−1.72 to 0.51]	−0.24 ± 0.35 [−1.72 to 0.30]	−0.24 ± 0.36 [−1.28 to 0.51]	0.73
$mTD_{superior}$ progression rate, dB/y, mean ± SD [range]	−0.32 ± 0.51 [−3.16 to 0.52]	−0.34 ± 0.56 [−3.16 to 0.41]	−0.32 ± 0.48 [−1.99 to 0.52]	0.94
$mTD_{inferior}$ progression rate, dB/y, mean ± SD [range]	−0.15 ± 0.35 [−1.54 to 0.87]	−0.14 ± 0.23 [−0.74 to 0.14]	−0.16 ± 0.40 [−1.54 to 0.87]	0.38
mTD_T progression rate, dB/y, mean ± SD [range]	−0.12 ± 0.35 [−2.04 to 0.60]	−0.12 ± 0.39 [−2.04 to 0.48]	−0.12 ± 0.33 [−1.52 to 0.60]	0.64
mTD_{TS} progression rate, dB/y, mean ± SD [range]	−0.13 ± 0.33 [−1.57 to 0.66]	−0.15 ± 0.31 [−1.12 to 0.39]	−0.11 ± 0.34 [−1.57 to 0.66]	0.69
mTD_{ST} progression rate, dB/y, mean ± SD [range]	−0.22 ± 0.44 [−2.13 to 0.57]	−0.15 ± 0.31 [−1.11 to 0.28]	−0.25 ± 0.50 [−2.13 to 0.57]	0.28
mTD_S progression rate, dB/y, mean ± SD [range]	−0.17 ± 0.46 [−2.28 to 1.18]	−0.18 ± 0.28 [−1.01 to 0.22]	−0.17 ± 0.53 [−2.28 to 1.18]	0.64

Table 1. Continued

Variables	All Eyes, $N = 125$	Long AL Group, $N = 45$	Not Long AL Group, $N = 80$	P Value
mTD_{SN} progression rate, dB/y, mean ± SD [range]	−0.09 ± 0.46 [−1.98 to 1.58]	−0.14 ± 0.40 [−1.25 to 0.40]	−0.06 ± 0.49 [−1.98 to 1.58]	0.42
mTD_{N3} progression rate, dB/y, mean ± SD [range]	−0.06 ± 0.29 [−1.25 to 0.82]	−0.07 ± 0.29 [−0.81 to 0.69]	−0.05 ± 0.29 [−1.25 to 0.82]	0.83
mTD_{IN} progression rate, dB/y, mean ± SD [range]	−0.28 ± 0.66 [−3.26 to 1.68]	−0.32 ± 0.80 [−3.26 to 0.78]	−0.25 ± 0.57 [−2.30 to 1.68]	0.67
mTD_{I} progression rate, dB/y, mean ± SD [range]	−0.35 ± 0.60 [−3.26 to 1.02]	−0.38 ± 0.66 [−3.26 to 0.66]	−0.34 ± 0.56 [−2.39 to 1.02]	0.72
mTD_{IT} progression rate, dB/y, mean ± SD [range]	−0.39 ± 0.66 [−4.08 to 0.45]	−0.37 ± 0.73 [−4.08 to 0.46]	−0.41 ± 0.62 [−2.53 to 0.44]	0.59
mTD_{TI} progression rate, dB/y, mean ± SD [range]	−0.33 ± 0.90 [−5.46 to 1.94]	−0.35 ± 0.81 [−4.11 to 0.36]	−0.32 ± 0.95 [−5.46 to 1.94]	0.89

P values: comparison between long AL and not long AL groups (linear mixed model for numerical variables and χ^2 test for categorical variables). PG, prostaglandin.

The mean AL was 25.29 ± 1.44 (mean ± SD) [22.55–29.02] mm at baseline and 25.33 ± 1.43 [22.60–29.04] mm at the second measurement (Fig. 2). As shown in Table 2 and Figure 3, AL at baseline was significantly related to age (AL = 27.9 − 0.043 × age, $P = 0.0032$, linear mixed model), but not significantly related to mean IOP and IOP SD ($P = 0.92$ and 0.87, respectively, linear mixed model). AL was not significantly related to baseline mTD, baseline $mTD_{superior}$ (corresponds to inferior hemiretina), baseline $mTD_{inferior}$ (corresponds to superior hemiretina), or any sectorial baseline mTD ($P > 0.05$, linear mixed model). Mean △AL was 0.035 ± 0.10 [−0.26 to 0.61] mm. There was a significant difference between the AL at baseline and AL at the repeated measurement (linear mixed model, $P < 0.0001$, Fig. 2). These AL values were significantly related ($P < 0.001$, linear mixed model). With univariate analyses, △AL was not significantly related to age, mean IOP, and IOP SD ($P = 0.58$, 0.14, and 0.36, respectively, linear mixed model), whereas the increase of △AL value was significantly related to the decrease of AL value (△AL = 0.46 − 0.017 × AL, $P = 0.027$, linear mixed model, Fig. 4).This result was not changed with multivariate analysis using these variables: $P =$ 0.50, 0.0088, 0.10, and 0.66 (linear mixed model) for age, AL, mean IOP, and SD IOP (Table 3). △AL was not significantly related to the interval between the first and second AL measurements ($P = 0.11$, linear mixed model).

The Effects of Medication

A total of 71 eyes of 44 patients used a prostaglandin analogue throughout the observation period (Table 1). There was no significant relationship between the use of a prostaglandin analogue throughout the observation period and △AL in all eyes, the long AL group, or the not long AL group ($P = 0.61$, 0.61, and 0.81, linear mixed model). Ninety-one eyes of 56 patients received a prostaglandin analogue at least once in the observation period (Table 1). There was no significant relationship between the single use of a prostaglandin analogue and △AL in all eyes, the long AL group, or the not long AL group ($P = 0.33$, 0.20, and 0.29, linear mixed model). Similarly, usage (throughout the period or single use) of beta-blocker, CAI, or brimonidine was not significantly related to △AL in any analyses ($P > 0.05$, linear mixed model). No patients used pilocarpine in the observation period.

Relationship Between VF Progression Rates and AL in All Eyes

Figure 5 shows the relationship between △AL and mTD progression rate, $mTD_{superior}$ progression rate, and $mTD_{inferior}$ progression rate. Slower $mTD_{inferior}$ progression rate was significantly related to increased △AL ($P = 0.0062$, linear mixed model); however, a significant relationship was not observed

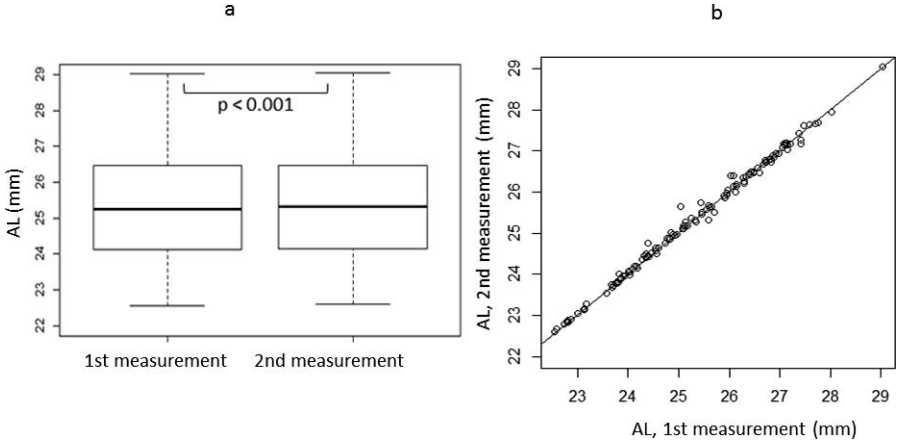

Figure 2. Comparison of ALs in first and second measurements and the relationship between ALs in first and second measurements. (**a**) Comparison of ALs in first and second measurements. AL in second measurement was significantly longer than that of first measurement ($P < 0.001$, linear mixed model). (**b**) Relationship between ALs in first and second measurements. These AL values were significantly related ($P < 0.001$, linear mixed model).

Table 2. Relationship Between Axial Length at Baseline and Various Parameters

Variable	Coefficient	SE	*P* Value
Age	***−0.043***	***0.014***	***0.0032***
Mean IOP	−0.0037	0.039	0.92
IOP SD	0.019	0.12	0.87
Base mTD	0.014	0.011	0.21
Base $mTD_{superior}$	0.0045	0.0065	0.49
Base $mTD_{inferior}$	0.018	0.012	0.13
Base mTD_{T}	−0.032	0.025	0.22
Base mTD_{TS}	−0.0063	0.015	0.68
Base mTD_{ST}	0.0042	0.0093	0.65
Base mTD_{S}	0.014	0.008	0.077
Base mTD_{SN}	0.013	0.0071	0.08
Base mTD_{N3}	−0.008	0.018	0.66
Base mTD_{IN}	0.0023	0.0091	0.8
Base mTD_{I}	0.0014	0.0052	0.8
Base mTD_{IT}	0.005	0.0045	0.27
Base mTD_{TI}	0.0019	0.0044	0.66

AL at baseline was significantly related to age (AL = 27.9 − 0.043 × age, $P = 0.0032$, linear mixed model), but not significantly related to mean IOP and IOP SD ($P = 0.92$ and 0.87, respectively, linear mixed model). SE, standard error. Bold and Italic characters suggest significance.

between mTD progression rate and $mTD_{superior}$ progression rate, and △AL ($P = 0.46$ and 0.94, respectively). Similarly, in the multivariate analysis using age, mTD at baseline, mean IOP, IOP SD, AL, and △AL as independent variables, increased △AL was significantly related with slower progression rate of $mTD_{inferior}$ ($P = 0.0049$, linear mixed model), but there was no significant relationship between the progression rates of mTD and $mTD_{superior}$ and △AL ($P = 0.25$ and 0.71, linear mixed model; see Table 4). Other variables of age, mTD at baseline, mean IOP, IOP SD, and AL were not significantly related to the progression rates of mTD, $mTD_{superior}$, and $mTD_{inferior}$ ($P > 0.05$, linear mixed model).

The relationship between sectorial mTD progression rate and various variables is shown in Table 4. Increased △AL was significantly related to slower progression rates of mTD_{ST} and mTD_{S} ($P = 0.0097$ and 0.00080, respectively, linear mixed model). Also higher baseline mTD_{T} and baseline mTD_{ST} were significantly related to slower progression rates of mTD_{T} and mTD_{ST}, respectively ($P = 0.014$ and 0.0009, linear mixed model), but an inverse relationship was observed between baseline mTD_{SN} and progression rate of mTD_{SN} ($P = 0.035$, linear mixed model), and also mTD_{N3} and progression rate of mTD_{N3} ($P = 0.029$, linear mixed model). Mean IOP was not significantly related to any sectorial mTD progression rates. Older age was significantly related to fast progression rate of mTD_{TI} ($P = 0.0019$, linear mixed model). IOP SD and AL were not significantly related to progression rate at any sector.

Relationship Between VF Progression Rates and AL in Long AL Group

The long AL group consisted of 45 eyes of 26 patients (age: 54.2 ± 9.9 [36–69] years), and the not long AL group consisted of 80 eyes of 48 patients (age: 61.2 ± 11.3 [32–88] years); see Table 1. There was a significant difference in sex between the two groups. There was no significant difference in any baseline mTD value or mTD progression rates in the whole field, superior/inferior hemifield, and each sector between the two groups ($P > 0.05$, linear mixed model). △AL was not significantly different between the two groups; however, it approached significance ($P = 0.063$, linear mixed model).

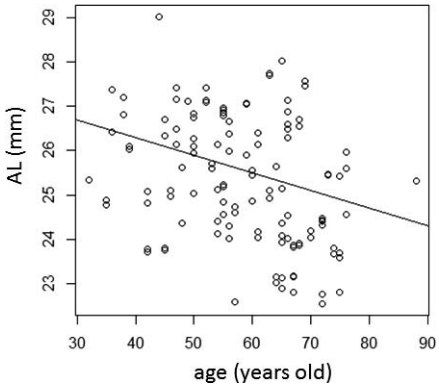

Figure 3. Relationship between axial length at baseline and age. AL at baseline was significantly related to age (AL = 27.9 − 0.043 × age, $P = 0.0032$, linear mixed model).

In the long AL group, △AL was not significantly related to any baseline mTD values or mTD progression rates in the whole field, superior/inferior hemifield, and each sector ($P > 0.05$, linear mixed model); see Table 5. Long AL was significantly correlated with faster progression of mTD_{T} and mTD_{TS} ($P = 0.014$ and 0.046, respectively, linear mixed model). Higher mean IOP was significantly related with slower progression rates of $mTD_{superior}$ and mTD_{I} ($P = 0.042$ and 0.031, respectively, linear mixed model). IOP SD was not significantly related to the progression rate of any mTD values ($P > 0.05$, linear mixed model).

Relationship Between VF Progression Rates and AL in Not Long AL Group

In the not long AL group, increased △AL was significantly related to the progression rates of $mTD_{inferior}$, mTD_{ST}, and mTD_{S} ($P = 0.0021$, 0.0039, and 0.00050, respectively, linear mixed model); see Table 6. AL was not significantly related to the progression rate of any mTD values ($P > 0.05$, linear mixed model). Higher mean IOP was significantly related with faster progression rates of mTD_{N3} and mTD_{I} ($P = 0.020$, linear mixed model). Higher IOP SD was significantly related with faster progression rates of mTD_{N3} and mTD_{I} ($P = 0.049$, linear mixed model).

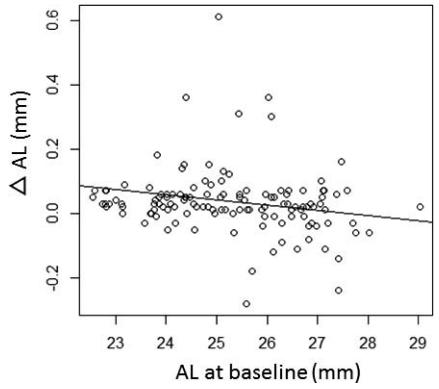

Figure 4. Relationship between change of axial length and axial length at baseline. △AL was significantly related to AL at baseline (△AL = 0.46 − 0.017 × AL, $P = 0.027$, linear mixed model).

Table 3. Relationship Between Various Parameters and Change of Axial Length

	Univariate Analysis			Multivariate Analysis		
Variable	**Coefficient**	**SE**	***P* Value**	**Coefficient**	**SE**	***P* Value**
Age	0.00053	0.00095	0.58	−0.00070	0.0010	0.50
AL	***−0.017***	***0.0073***	***0.027***	***−0.022***	***0.0081***	***0.0088***
Mean IOP	−0.0065	0.0043	0.14	−0.0084	0.0050	0.10
IOP SD	−0.015	0.016	0.36	−0.0083	0.019	0.66

△AL was not significantly related to age, mean IOP, and IOP SD ($P = 0.50$, 0.10, and 0.66, respectively, linear mixed model), whereas the increase of △AL value was significantly related to the decrease of AL value ($P = 0.0088$). SE, standard error. Bold and Italic characters suggest significance.

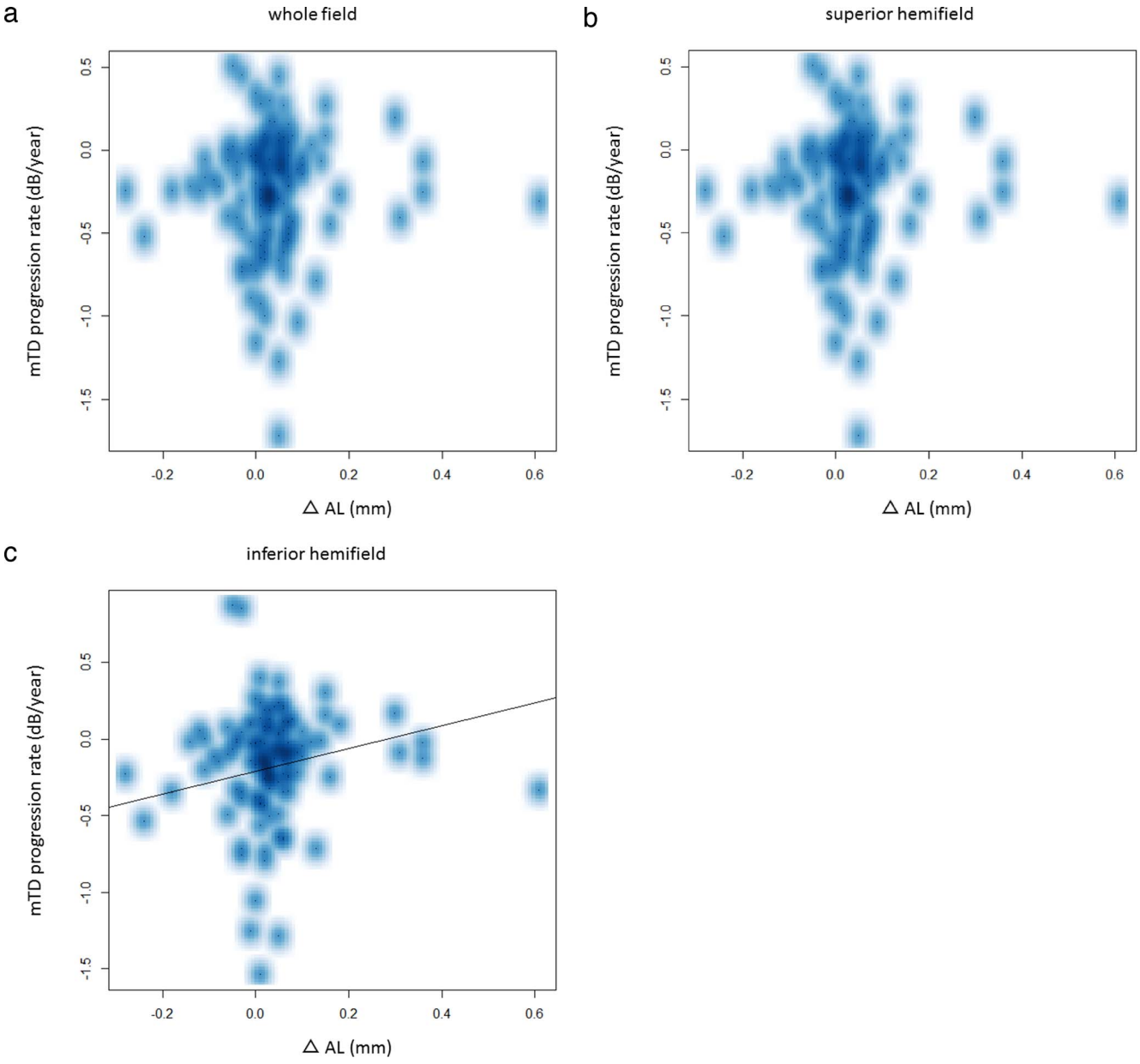

Figure 5. Relationship between change of axial length and visual field progression. (**a**) Whole field. There was no significant relationship between change of axial length and visual field progression ($P = 0.46$, linear mixed model). (**b**) Superior field. There was no significant relationship between change of axial length and visual field progression ($P = 0.94$, linear mixed model). (**c**) Inferior field. There was a significant relationship between change of axial length and visual field progression ($P = 0.0062$, linear mixed model). The results are plotted using the smoothScatter function in the statistical programming language R.

Table 4. Relationship Between Visual Field Progression Rates and Various Parameters (All Eyes, $N = 125$)

Variable	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value
	mTD			$mTD_{superior}$			$mTD_{inferior}$		
Age	−0.0044	0.00038	0.25	−0.0059	0.0050	0.24	−0.0020	0.0040	0.62
AL	0.0073	0.010	0.83	0.022	0.040	0.59	0.0036	0.031	0.91
△AL	0.39	0.34	0.25	0.18	0.48	0.71	***0.92***	***0.31***	***0.0049***
Mean IOP	0.029	0.019	0.12	0.036	0.025	0.16	0.017	0.018	0.37
IOP SD	−0.074	0.067	0.27	−0.1	0.94	0.29	0.0057	0.062	0.93
Corresponding base mTD	0.0053	0.0075	0.49	0.0094	0.0069	0.18	0.0059	0.0078	0.46
	mTD_T			mTD_{TS}			mTD_{ST}		
Age	−0.0064	0.0038	0.099	−0.004	0.0033	0.23	0.00065	0.0054	0.90
AL	−0.022	0.03	0.55	−0.0081	0.027	0.76	0.037	0.042	0.39
△AL	−0.31	0.31	0.27	−0.048	0.32	0.88	***1.03***	***0.38***	***0.0097***
Mean IOP	0.015	0.018	0.40	0.023	0.017	0.17	0.042	0.024	0.094
IOP SD	−0.045	0.064	0.49	−0.048	0.062	0.45	−0.040	0.083	0.63
Corresponding base mTD	***0.034***	***0.013***	***0.014***	−0.0029	0.0078	0.71	***0.026***	***0.0074***	***0.0009***
	mTD_S			mTD_{SN}			mTD_{N3}		
Age	−0.0020	0.0052	0.71	0.00017	0.0054	0.97	−0.0014	0.0030	0.65
AL	−0.0059	0.042	0.89	−0.027	0.043	0.53	−0.0021	0.025	0.93
△AL	***1.56***	***0.44***	***0.0080***	−0.15	0.44	0.72	−0.0079	0.27	0.77
Mean IOP	0.017	0.024	0.49	0.00079	0.025	0.98	−0.016	0.015	0.29
IOP SD	0.035	0.084	0.67	−0.032	0.087	0.72	0.048	0.0054	0.38
Corresponding base mTD	−0.0022	0.0076	0.77	***−0.016***	***0.008***	***0.035***	***−0.023***	***0.010***	***0.029***
	mTD_{IN}			mTD_I			mTD_{IT}		
Age	−0.0011	0.0066	0.87	−0.0063	0.046	0.46	0.046	0.52	0.35
AL	−0.0048	0.053	0.93	0.034	0.046	0.46	0.046	0.52	0.35
△AL	−0.46	0.63	0.47	0.43	0.56	0.45	0.49	0.63	0.38
mean IOP	0.034	0.033	0.31	0.048	0.029	0.10	0.039	0.033	0.23
IOP SD	0.047	0.12	0.71	−0.12	0.11	0.30	−0.14	0.12	0.26
Corresponding base mTD	0.0099	0.011	0.39	0.0083	0.0067	0.22	0.0055	0.0065	0.40
	mTD_{TI}								
Age	***−0.025***	***0.008***	***0.002***						
AL	−0.026	0.062	0.68						
△AL	−0.43	0.81	0.59						
Mean IOP	0.025	0.040	0.54						
IOP SD	−0.094	0.16	0.55						
Corresponding base mTD	−0.11	0.0087	0.19						

△AL was significantly related with slower progression rate of $mTD_{inferior}$, but there was no significant relationship between the progression rates of mTD and $mTD_{superior}$, and △AL. Increased △AL was significantly related to slower progression rates of mTD_{ST} and mTD_S. Bold and italic suggests $P < 0.05$ (linear mixed model). mTD values in superior/inferior hemifield ($mTD_{superior}$/$mTD_{inferior}$) were derived from superior/inferior visual field, whereas sectorial mTD values were derived from corresponding area on optic disc. Corresponding base mTD means baseline mTD in the same sector; for instance, base mTD is base mTD_T for the progression rate of mTD_T. SE, standard error.

Discussion

In the current study, AL was measured twice over an interval of approximately 5 years. A considerable number of VF and IOP measurements were taken during this period, and the influence of age, mean IOP, SD IOP, AL, △AL, and mTD value at baseline on the progression rate was investigated. Results showed that none of these variables were significantly related to the progression rates of mTD (whole VF) or $mTD_{superior}$ (corresponds to inferior hemifield). Only △AL was related to the progression rate of $mTD_{inferior}$ (slow $mTD_{inferior}$ progression with increased △AL). Dividing the VF into 10 sectors, it was observed that increased △AL was related to slow progression rates of mTD_{ST} and mTD_S. AL was not significantly related to any of the sectorial mTD progression rates.

In the current study, AL was significantly longer in the younger population (Fig. 3). This is probably because of the high prevalence of myopia in young Japanese and the younger population worldwide.[28,29] In contrast, AL was not significantly related to mean IOP, IOP SD, or any baseline mTD value. It has been reported that glaucomatous VF change is more pronounced in specific areas in myopic eyes, such as near the central fixation point,[30,31] the superior peripheral area, and near the blind spot[32]; however, this finding was not observed in the current population. Many previous studies have suggested that myopia is a risk factor for the development of glaucoma.[3,5,33–35] On the other hand, it is controversial whether myopia is a risk factor for the progression of glaucoma.[35–37] In the current study, longer AL was significantly related to faster VF progression only for mTD_T, which corresponds to the papillo-macular bundle area. In patholog-

Table 5. Relationship Between Visual Field Progression Rates and Various Parameters (Long Axial Length Eyes, $N = 45$)

	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value
Variable	**mTD**			**$mTD_{superior}$**			**$mTD_{inferior}$**		
Age	0.0069	0.0067	0.31	***0.010***	***0.0980***	***0.30***	0.0058	0.0046	0.23
AL	−0.310	0.098	0.76	0.0550	0.1500	0.72	−0.087	0.064	0.19
△AL	0.53	0.64	0.43	0.760	0.95	0.44	0.39	0.42	0.37
Mean IOP	0.79	0.038	0.057	***0.13***	***0.058***	***0.042***	0.028	0.024	0.26
IOP SD	−0.23	0.130	0.10	−0.40	0.21	0.076	0.042	0.085	0.63
Corresponding base mTD	0.0040	0.012	0.74	−0.00057	0.012	0.96	0.0130	0.0096	0.20
	mTD_T			**mTD_{TS}**			**mTD_{ST}**		
Age	−0.000051	0.0045	0.99	0.0018	0.0053	0.73	0.0082	0.0066	0.22
AL	***−0.20***	***0.073***	***0.014***	***−0.180***	***0.083***	***0.046***	−0.12	0.091	0.20
△AL	0.63	0.48	0.21	−0.41	0.51	0.43	0.47	0.60	0.45
Mean IOP	0.044	0.025	0.098	0.040	0.028	0.17	0.041	0.033	0.24
IOP SD	−0.025	0.10	0.81	−0.043	0.11	0.71	0.047	0.130	0.71
Corresponding base mTD	***0.11***	***0.022***	***0.00020***	0.0017	0.0082	0.84	0.003	0.0095	0.73
	mTD_S			**mTD_{SN}**			**mTD_{N3}**		
Age	0.0089	0.0066	0.19	−0.0029	0.0083	0.72	−0.0077	0.0048	0.12
AL	−0.12	0.084	0.16	−0.10	0.12	0.43	0.034	0.073	0.65
△AL	0.89	0.58	0.14	0.010	0.77	0.99	−0.63	0.46	0.19
Mean IOP	0.0048	0.033	0.89	0.050	0.046	0.29	0.057	0.027	0.053
IOP SD	0.030	0.10	0.77	−0.062	0.16	0.71	−0.073	0.10	0.48
Corresponding base mTD	0.011	0.0096	0.28	***−0.004***	***0.0370***	***0.92***	***−0.037***	***0.016***	***0.04***
	mTD_{IN}			**mTD_I**			**mTD_{IT}**		
Age	0.024	0.0130	0.074	0.016	0.011	0.15	0.005	0.013	0.70
AL	−0.034	0.20	0.12	0.11	0.17	0.55	0.29	0.20	0.17
△AL	−0.49	1.24	0.70	1.18	1.07	0.29	1.38	1.28	0.30
Mean IOP	0.14	0.073	0.074	***0.16***	***0.066***	***0.031***	0.15	0.077	0.073
IOP SD	−0.28	0.28	0.34	−0.51	0.24	0.051	−0.55	0.28	0.064
Corresponding base mTD	0.0073	0.021	0.74	−0.0043	0.011	0.70	−0.0077	0.012	0.52
	mTD_{TI}								
Age	−0.012	0.014	0.37						
AL	−0.22	0.22	0.33						
△AL	0.43	1.30	0.75						
Mean IOP	0.079	0.075	0.31						
IOP SD	−0.14	0.30	0.65						
Corresponding base mTD	0.005	0.014	0.74						

△AL was not significantly related to any baseline mTD values or mTD progression rates in the whole field, superior/inferior hemifield, and each sector. Bold and italic suggests $P < 0.05$ (linear mixed model). SE, standard error.

ically myopic eyes, nerve fibers in the macular area are damaged, due to stretching of the retina and the scleral bulge in the temporal area of the optic disc (see Table 4).[38,39] The current study did not include pathologically myopic eyes; however, there is a possibility that a weak but similar phenomenon is observed in eyes with long AL. As a result, in glaucomatous eyes with long AL, VF damage in the mTD_T area could be the result of both glaucomatous damage and myopic change.

AL was significantly elongated by 0.035 mm over the study period. This elongation was not related to age or the interval between the first and second AL measurements. This suggests that the elongation of AL does not occur universally and homogenously in all eyes. Also, the elongation of AL appears to be independent of IOP control, as suggested by a nonsignificant relationship with mean IOP and IOP SD. However, AL elongation was more pronounced in eyes with a not long AL (Fig. 4). On the other hand, according to McBrien and Adams,[21] progression of myopia was observed more frequently in originally myopic eyes compared to the development of myopia in originally emmetropic eyes (39% and 48%, respectively) with larger magnitude (0.26- and 0.77-mm vitreous chamber length, respectively) in a survey with clinical microscopists. The reason for these contradicting results is not entirely clear; however, it may be attributed to the much older population in the current study compared to that in the previous report (median age: 29.9 years), because progression of myopia has been frequently observed in those of a young age.[21] Nonetheless, △AL was not significantly related to age in the current study. Another possible reason could be ethnicity, because there is a considerable difference in the development of myopia in Caucasians and Asians.[22–24] Another survey with a larger population would be needed to shed light on this issue.

The current study consisted of patients from the "real-world" clinic; however, considerable variations were observed in VF progression rates (from −1.7 to 0.51 with mTD) and mean (from 9.0 to 23.3) and SD (from 0.6 to 4.8) values of IOP during the observation period. Numerous reports have

Table 6. Relationship Between Visual Field Progression Rates and Various Parameters (Not Long Axial Length Eyes, $N = 80$)

	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value	Coefficient	SE	*P* Value
Variable	**mTD**			**$mTD_{superior}$**			**$mTD_{inferior}$**		
Age	−0.0086	0.0047	0.08	***−0.013***	***0.0056***	***0.029***	−0.0038	0.0056	0.50
AL	−0.001	0.055	0.99	0.0580	0.0650	0.39	−0.039	0.063	0.54
△AL	0.47	0.38	0.22	−0.063	0.52	0.90	***1.24***	***0.37***	***0.0021***
Mean IOP	0.014	0.021	0.52	0.0034	0.027	0.90	0.026	0.023	0.26
IOP SD	−0.0063	0.075	0.94	0.0023	0.10	0.98	0.0050	0.075	0.95
Corresponding base mTD	0.0058	0.0097	0.56	0.011	0.0085	0.22	0.0026	0.0097	0.79
	mTD_T			**mTD_{TS}**			**mTD_{ST}**		
Age	−0.0077	0.0047	0.11	−0.0061	0.0042	0.16	−0.0022	0.0072	0.76
AL	−0.03	0.051	0.60	0.051	0.049	0.31	−0.016	0.081	0.85
△AL	−0.37	0.24	0.14	0.0083	0.36	0.98	***1.35***	***0.43***	***0.0039***
Mean IOP	0.0073	0.017	0.68	0.026	0.020	0.22	0.051	0.030	0.10
IOP SD	−0.029	0.058	0.75	−0.067	0.071	0.36	−0.075	0.099	0.46
Corresponding base mTD	0.0045	0.014	0.75	***−0.030***	***−0.014***	***0.0503***	***0.035***	***0.0090***	***0.0006***
	mTD_S			**mTD_{SN}**			**mTD_{N3}**		
Age	−0.0051	0.0074	0.49	0.0051	0.0074	0.49	−0.00024	0.015	0.34
AL	−0.090	0.084	0.29	−0.0055	0.082	0.95	0.0046	0.047	0.92
△AL	***2.09***	***0.53***	***0.00050***	−0.54	0.51	0.30	0.03	0.27	0.92
Mean IOP	0.028	0.031	0.38	−0.0054	0.030	0.86	***−0.043***	***0.017***	***0.020***
IOP SD	0.043	0.10	0.68	0.0046	0.10	0.96	***0.12***	***0.060***	***0.049***
Corresponding base mTD	−0.0049	0.0094	0.61	***−0.024***	***0.0078***	***0.0045***	−0.015	0.015	0.34
	mTD_{IN}			**mTD_I**			**mTD_{IT}**		
Age	−0.0099	0.0071	0.17	***−0.016***	***0.006***	***0.013***	−0.011	0.0073	0.15
AL	0.10	0.082	0.22	0.091	0.073	0.22	0.0080	0.085	0.93
△AL	−0.56	0.59	0.35	0.082	0.62	0.89	0.25	0.71	0.72
Mean IOP	−0.016	0.033	0.64	0.0076	0.030	0.80	0.0094	0.035	0.79
IOP SD	0.098	0.12	0.41	0.014	0.11	0.90	−0.049	0.13	0.71
Corresponding base mTD	0.0067	0.012	0.59	0.011	0.0084	0.20	0.011	0.0079	0.18
	mTD_{TI}								
Age	***−0.029***	***0.01***	***0.0042***						
AL	0.15	0.11	0.20						
△AL	−1.25	1.03	0.24						
Mean IOP	−0.0054	0.049	0.91						
IOP SD	−0.067	0.18	0.71						
Corresponding base mTD	−0.019	0.011	0.094						

Increased △AL was significantly related to the progression rates of $mTD_{inferior}$, mTD_{ST}, and mTD_S. Bold and italic suggests $P < 0.05$ (linear mixed model). SE, standard error.

suggested the importance of IOP in the progression of glaucoma.[40–50] Nonetheless, in the current study, an accelerating effect of increased mean IOP on the progression of glaucoma was observed only for mTD_{N3} in the not long AL group (Table 6). In addition, in the long AL group, increased mean IOP was significantly related to slow progression of $mTD_{superior}$ and mTD_I (Table 6). This may be because clinicians may not intensify IOP reduction treatments when IOP is high unless VF progression is fast in this area. The effect of SD of IOP on glaucoma progression is controversial.[51–54] In the current study, SD IOP was not related to the progression of any mTD progression rates, except for mTD_{N3} in the not long AL group (Table 6). In contrast, increased △AL was significantly related to VF progression in the inferior hemifield. In other words, in the current studied population, the wide variation in the rates of progressions of mTD, $mTD_{superior}$, and $mTD_{inferior}$ cannot be explained by age, baseline mTD, AL, mean IOP, and IOP SD. Only $mTD_{inferior}$ was explained by the magnitude of △AL, at least partially. The slower $mTD_{inferior}$ progression in eyes with increased △AL may be in agreement with the results of Yamada et al.,[20] which suggested that larger PPA not accompanied by Bruch's membrane is associated with slower progression of glaucoma; this may suggest that extension of PPA not accompanied by Bruch's membrane may reduce the stress to the lamina cribrosa when elongation of AL occurs with increasing myopia. It should be noted that these results do not deny the efficacy of IOP reduction on preventing the progression of glaucoma, because the patients studied were already being given treatments for IOP reduction. The weak influence of IOP level on glaucoma progression observed in eyes from real-world clinics is in agreement with our recent study.[25] In contrast, △AL was not significantly related to the progression of $mTD_{superior}$. The reason for a null relationship between △AL and the progression of $mTD_{superior}$ is not entirely clear, but could be because typical myopic retinal change, such as chorioretinal atrophy and conus, is usually predominantly observed in inferior retina, and thus the suppressive effect of the increase of △AL on VF progression was canceled out by

the accelerating direct effect of structural myopic change on VF progression.

A significant relationship between increased △AL and slow progression rate in the superior VF was observed in the analyses of all eyes and eyes in the not long AL group, but not eyes in the long AL group. Combined with the result that an increase of △AL was significantly negatively related to AL, and also that an increase of △AL was significant only in the not long AL group, it appears that elongation of AL may have a protective effect on the progression of the superior VF in eyes with not long AL. This phenomenon was independent from IOP control and also age. This is not only important clinically, but also in understanding the mechanism of glaucoma, because stretching of the eye (and retina) due to elongation of the eyeball may be related to changes in the structure of the optic disc, and this kind of structural change may be related to the development and progression of glaucoma.

A limitation of the current study is that the analysis was carried out over a relatively short period (approximately 5 years). Further study should be performed following patients for a longer period. Also, a possible caveat is the exclusion of central corneal thickness (CCT) as a clinical parameter. CCT is closely related to IOP measured with Goldmann tonometry[55–59] and also the progression of glaucoma.[60,61] Further efforts should be made to collect data with accompanying CCT measurements.

In conclusion, it is suggested that AL was elongated in glaucomatous eyes in an observation period of approximately 5 years. This elongation of AL was independent of age and IOP level. Increased AL was significantly related to slower progression of the VF in the inferior hemifield.

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