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Glaucoma Structural and Functional Progression in American and Korean Cohorts

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Abstract

Objective—To compare the rate of glaucoma structural and functional progression in American and Korean cohorts.

Design—Retrospective longitudinal study.

Participants—313 eyes from 189 glaucoma and glaucoma suspects, followed for an average of 38 months.

Methods—All subjects were examined semiannually with visual field (VF) testing and spectral-domain optical coherence tomography. All subjects had 5 reliable visits.

Main Outcome Measurements—The rates of change of retinal nerve fiber layer (RNFL) thickness, cup-to-disc (C/D) ratios, and VF mean deviation (MD) were compared between the cohorts. Variables affecting the rate of change for each parameter were determined, including ethnicity, refraction, baseline age and severity, disease subtype (high vs. normal tension glaucoma), clinical diagnosis (glaucoma vs. glaucoma suspect), and the interactions between variables.

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Results—The Korean cohort was predominantly normal tension glaucoma, while the American cohort was high tension glaucoma. Cohorts had similar VF parameters at baseline, but the Korean eyes had significantly thinner mean RNFL and larger cups. Korean glaucoma eyes showed a faster thinning of mean RNFL (mean: -0.71 vs. $-0.24\mu\text{m}/\text{year}$, $p<0.01$). There was no detectable difference in the rate of change between the glaucoma cohorts for C/D ratios and VF MD and for all parameters in glaucoma suspect eyes. Different combinations of the tested variables significantly impacted the rate of change.

Conclusion—Ethnicity, baseline severity, disease subtype, and clinical diagnosis should be considered when comparing glaucoma progression studies.

Glaucoma is a multi-factorial optic neuropathy characterized by the progressive loss of retinal ganglion cells and optic nerve damage, associated with visual field defect. Determining the rate of glaucomatous changes over time has an important impact on the management of patients, and dictates clinical intervention. The introduction of ocular imaging into the routine clinical management of glaucoma subjects allows for the detection of micron scale structural changes, and it has ignited widespread interest in glaucoma progression detection. While these studies provide important insight into the disease mechanism and clinical detection, the effect of the diversity of the populations participating in these studies has not been thoroughly considered. Ethnicity, refractive error, disease subtype prevalence, treatment approach, and other variables might have an important effect on glaucomatous rate of change, thus putting into question the generality of the reported information. For example, high tension glaucoma has been reported to be most prevalent in African-Americans and Caucasians, while normal tension glaucoma is prevalent in east Asian.^{1,2} Furthermore, African-American tend to have more aggressive glaucoma compare with Caucasians.³⁻⁵ It has been reported that variability in progression rates has also been related to age groups and disease types.⁶⁻⁸ However, a rigorous comparison between cohorts with similar baseline characteristics but different population compositions has not been performed to assess the effect on the progression rate and determine which variables impact the rate. We hypothesis that the composition of the participating populations in longitudinal glaucoma studies has a significant effect on the rate of structural and functional progression. The purpose of this longitudinal study was to compare glaucoma structural and functional rates of change in two similar cohorts enrolled in discrete geographical locations that differ significantly in ethnic composition and type of glaucoma.

Methods

Subjects

Glaucoma subjects and glaucoma suspects from the Pittsburgh Imaging Technology Trial (PITT) and the glaucoma clinic of the Asan Medical Center, Seoul, Korea were included in the study. The PITT study is an ongoing prospective longitudinal study designed to assess ocular structure over time carried out at the University of Pittsburgh Medical Center (UPMC) Eye Center. Consecutive subjects that qualified for the study were enrolled at both sites. The institutional review boards and ethics committees of both institutions approved this study. This study followed the tenets of the Declaration of Helsinki and was conducted

in compliance with the Health Insurance Portability and Accountability Act. Informed consent was obtained from all subjects.

Study Protocol

All participants had full comprehensive ocular examinations, including a review of medical history, measurement of best-corrected visual acuity, refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, visual field (VF) testing (HFA, Zeiss, Dublin, California, USA), and spectral domain optical coherence tomography (SD-OCT; Cirrus HD-OCT, Zeiss) at baseline and every 6 months afterward, unless otherwise medically indicated. Subjects were 40 years, had a visual acuity of 20/60 or better, a spherical equivalent refractive error between -6.00 and $+6.00$ D, and 5 visits with reliable testing. Subjects were excluded from the study if they had a history of diabetes, any macular pathology, any conditions affecting VF and retinal thickness other than glaucoma, a history of ocular trauma or surgery other than uncomplicated glaucoma interventions, or cataract extraction. Additionally, subjects were excluded for the use of any medication known to affect the retina. Both eyes were included in the study if they were eligible. For subjects that underwent a cataract extraction surgery, their refraction was recorded from the visits prior to the surgery.

Clinical diagnosis

Eyes were defined as high tension glaucoma (HTG) if there was a glaucomatous VF defect at baseline, records of IOP >21 mmHg and optic nerve head (ONH) cupping >0.6 , or the clinical detection of a retinal nerve fiber layer (RNFL) defect. Normal tension glaucoma (NTG) eyes were included if they exhibited the same optic disc and VF criteria as the HTG patients, with the exception that their IOP was ≤ 21 mmHg at any time point.

Glaucoma suspect eyes were defined as those with an IOP of 22 – 30 mmHg, asymmetric ONH cupping (difference in vertical cup / disc ratio greater than 0.2 between eyes), abnormal appearance of the ONH as described above, or the contralateral eye of unilateral glaucoma, all in the presence of normal VF testing. Glaucoma suspects had no history of retinal pathology, laser therapy, or intra-ocular surgery.

Visual Field Testing

All subjects underwent Swedish interactive thresholding algorithm 24-2 perimetry (SITA standard; Humphrey Field Analyzer; Zeiss) testing. Qualified VF examinations had less than 30% fixation losses, false-positive, or false-negative responses. Mean deviation (MD) was used for the analysis.

SD-OCT

All subjects were scanned with SD-OCT using the Optic Disc Cube 200 $\times$ 200 scan protocol to obtain the circumpapillary RNFL thickness measurements. Scans with signal strength <7 , motion artifacts (assessed subjectively as a medium size vessel diameter discontinuity of blood vessels), or scans with segmentation errors were excluded. Mean RNFL and two ONH parameters (average and vertical cup-to-disc ratio) were used in the analysis.

Definition of Progression

Structural progression, as detected by OCT, was defined by two independent methods: 1. Guided progression analysis (GPA) – the progression analysis provided by the device's commercial software. "Likely" and "possible progression" were considered as progression when detected in the RNFL thickness map, RNFL profile average RNFL thickness, or average C/D ratio progression analyses. 2. Linear mixed effect (LME) model – A statistically significant negative slope ($p < 0.05$) computed by the LME model while accounting for baseline age was considered progression.

Functional (VF) progression was determined by the event analysis of the GPA report, with "likely" and "possible progression" considered as progression when these designations appeared in the final visit. The trend analysis was determined for the VF MD by computing the rate of change using a LME model. A statistically significant negative slope was considered as progression.

Statistical Analysis

Baseline characteristics were compared between Korean and American cohorts using generalized estimating equation (GEE) to take into account the correlations between both eyes of a given subject. Linear mixed effect models accounting for baseline age were used to determine the rates of change over time of analyzed parameters. To determine what variables impacted the rate of change of the investigated parameters in the entire population, an ANCOVA model accounting for ethnicity, refraction (reported as spherical equivalent), baseline age and disease severity (as reflected by the baseline level of the individual tested parameter), disease subtype (HTG or NTG), clinical diagnosis (glaucoma or glaucoma suspect), and the interactions between these potential confounders was used. A $p < 0.05$ was considered as statistically significant. R Language and Environment for Statistical Computing program (version 3.1.1) with geepack and lme4 packages, was used for the statistical analysis.⁹

Results

The characteristics of the study population are summarized in Table 1. The American cohort included 81 glaucoma and 45 glaucoma suspect eyes from 69 subjects; the Korean cohort included 91 glaucoma and 96 glaucoma suspect eyes from 120 subjects. The American cohort included Caucasians (84%) and African Americans (16%) with high tension glaucoma (96%), while the Korean cohort included subjects with exclusively Korean origin and predominantly normal tension glaucoma (87%). At baseline, the Korean cohort was significantly younger than the American cohort, with thicker RNFL and larger cup to disc ratio measurements. There was no difference in VF MD and refractive error (reported as the spherical equivalent) between the cohorts. The mean length of follow-up in the American cohort was 37.5 months with a mean of 7 visits per eye (range: 5 – 14). In the Korean cohort, the mean follow-up was 37.7 months with a mean of 6 visits per eye (range: 5 – 8). There was no difference in follow up duration between the two cohorts.

GPA

The VF GPA event analysis in the American cohort identified 17 progressing eyes from the glaucoma group and 2 eyes from the glaucoma suspects (7 eyes were not available for the progression analysis because they exhibited advanced damage). In the Korean cohort, 22 progressing eyes were detected in the glaucoma group and 6 eyes were detected in the glaucoma suspects. There was no significant difference in the number of progressing eyes between the cohorts.

Thirty-two eyes in the Korean cohort progressed by the RNFL thickness map progression analysis, 18 by RNFL thickness profile progression analysis, 52 by average RNFL thickness progression analysis, and 3 by the average C/D ratio progression analysis. In the American cohort, the number of progressing eyes was 85, 5, 10, and 3, respectively. No progression was detected by any of the four parameters in 66.3% of the Korean eyes, while only 32.5% did not progress by any of the parameters among the American eyes.

LME model

Figure 1 demonstrates the individual rate of RNFL change for all participants for mean RNFL and the four quadrants as a dependent on baseline RNFL measurement. A statistically significant rate of change was detected for all parameters (VF, RNFL and C/D ratios) in both cohorts in glaucoma subjects (Table 2). In glaucoma suspects, both cohorts demonstrated statistically significant rates of change for mean RNFL thickness only (Table 3). The American cohort also exhibited a significant rate of change for VF MD.

Comparing rate of change between the two glaucoma cohorts demonstrated a significantly faster rate of mean RNFL thinning in the Korean cohort (Table 2). No difference was detected in the rate of change for VF and C/D ratio parameters between the two glaucoma cohorts. The comparison of rate of change between the two cohorts for the glaucoma suspects did not yield any statistically significant difference (Table 3).

Table 4 summarizes the variables influencing the rate of change for each given parameter for the entire study population. For mean RNFL, ethnicity and baseline severity (baseline mean RNFL thickness) significantly influenced the rate of change, along with the interaction between diagnosis and ethnicity. This means that the rate of change difference between glaucoma and glaucoma suspects varies for Asians, African Americans, and Caucasians. The rate of change for both C/D ratio parameters was affected by the clinical diagnosis and the interaction term between diagnosis and ethnicity. For the functional assessment, as reflected by VF MD, the rate of change was affected by ethnicity, disease subtype, clinical diagnosis, and several interactions. Refraction affected the rate of change only in the interaction term with ethnicity for Average C/D ratio. Age did not show a significant impact on the rate of change for any of the investigated parameters.

Discussion

This longitudinal study was designed to compare structural and functional progression rates between two cohorts that were assembled using identical inclusion and exclusion criteria typical of that which is often used in longitudinal glaucoma studies, but differ

geographically, ethnically, and in glaucoma type. The follow-up duration was identical, and at baseline functional performance and refractive error were similar between the cohorts. However, longitudinally Korean glaucoma eyes had a steeper rate of change in mean RNFL thickness in comparison with the American cohort. In glaucoma suspect eyes the rate of change was similar between the cohorts for all structural and functional parameters.

The study was designed to simulate typical glaucoma longitudinal studies with commonly used inclusion and exclusion criteria performed in two distinct geographic locations. As expected, this led to a substantial difference in the ethnic composition of the cohorts and the prevalence of glaucoma types (Table 1). The percentage of women was higher in the American cohort, but numerous studies have already determined that gender is unlikely to affect the glaucomatous process.^{10–14} The American cohort was also significantly older than the Korean cohort, and therefore age was included in the statistical modeling that we used. The strength of our study is the similar follow-up period (approximately 3 years), number of visits (6 – 7 visits) for both cohorts and refractive error between the cohorts.

Even though the functional parameter was similar at baseline between the cohorts, the American cohort had significantly thinner RNFL and smaller optic nerve head cupping in comparison with the Korean eyes. These differences are similar to those reported previously in Caucasian and Asian populations.^{15–19}

The VF GPA method showed a similar number of eyes that progressed over the course of the follow-up period in the two cohorts when accounting for the difference in the number of participants at each site. Similarly, no significant difference was noted for the rate of change for VF MD between the two cohorts for both glaucoma and glaucoma suspect eyes. However, when considering the OCT GPA method, there was a substantially higher prevalence of progression by at least one of the four parameters in the American cohort compared with the Korean cohort. Furthermore, the prevalence of the parameters that detected progression were markedly different with substantially higher prevalence of eyes detected as progressing by RNFL thickness map progression analysis in the American eyes while the Korean eyes had higher prevalence of progression detected by the average RNFL thickness analysis in comparison to their counterpart. These differences highlight the disparity between the modes of glaucomatous change in the two populations.

The RNFL rate of change we report, as computed by the LME modeling, is similar to those previously reported that varied from -0.33 to -1.26 $\mu\text{m}/\text{year}$ for NTG^{20–21}, and from -1.18 to -2.12 $\mu\text{m}/\text{year}$ in HTG.²² We detected similar rate of change for glaucoma suspect eyes between the two cohorts using all structural parameters (Table 3). However, a significantly steeper rate of change was detected in Korean **glaucomatous** eyes for mean RNFL thickness (Table 2). The refractive error does not explain the difference in the rate of change between the cohorts, detected in our study, because the refractive error term in the models was not significant.

The difference in the structure and function rate of change between the cohorts during the same follow-up period should be also noted. In the **glaucomatous** eyes there was a significant difference in the structural rate of change between the American and Korean

cohorts without a detectable functional difference. In glaucoma suspects eyes there was no statistically significant difference for any of the parameters. Discrepancies between structural and functional status over the spectrum of glaucoma severity were previously reported²³ but they only partially explain the findings in our study.

When assessing the factors that impact the rate of change of the various parameters in our entire study group we determined that ethnicity, baseline severity, disease subtype, and clinical diagnosis in different combinations had a significant effect (Table 4). Furthermore, the effect is often complex as an interaction term between variables is commonly present. Surprisingly, age and refraction had limited effects on the rates of change in our cohorts. However, it should be remembered that we included only subjects with a refractive error within the range of -6.00 to $+6.00$ diopters, and therefore the implication of the refractive errors outside of this range cannot be discerned. Our findings imply that a simple comparison of the rate of change between different cohorts can be misleading, as numerous confounders might be involved.

Our study did not include healthy subjects because our goal was not focused on assessing the ability of the devices to detect progression, but rather to compare the rate of change in eyes that can be expected to show change over time. Furthermore, we did not standardize the treatment approach in the cohorts because we aimed to simulate the reality of typical progression analysis studies as they are performed in various sites. Both sites used the same inclusion and exclusion criteria, which are often used in such studies. The potential effect of different treatments is one of the confounders we wanted to highlight in this project. Another potential confounder is the high prevalence of myopia in Asian origin subjects. However, this study was limited to subjects within ± 6 diopters and the refractive error was similar between the cohorts.

In conclusion, Korean glaucoma eyes showed a significantly faster rate of change for mean RNFL thickness in comparison to a similar group in America. glaucoma suspect eyes had similar rates of change for structure and function parameters in both groups. Factors such as ethnicity, baseline severity, disease subtype, clinical diagnosis, and potentially other variables should be considered when comparing glaucoma progression studies.

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Figure 1. Individual rate of change in retinal nerve fiber layer thickness accounting for baseline measurements. Red markers – American participants. Blue – Korean participants.

Table 1Baseline characteristics of all subjects (mean $\pm$ SD)

	Total	American	Korean	P*
Eyes	313	126	187	
Gender (F/M)	186/127	87/39	99/88	0.005
Age (y)	58.7 $\pm$ 9.0	61.6 $\pm$ 8.9	57.0 $\pm$ 8.6	<0.001
Refraction (D)	-1.05 $\pm$ 2.33	-0.87 $\pm$ 2.51	-1.16 $\pm$ 2.21	0.297
Clinical Diagnosis (GS/G)	141/172	45/81	96/91	0.008
Glaucoma type (NTG/HTG)	167/146	5/121	162/25	<0.001
Follow-up duration (month)	37.6 $\pm$ 8.5	37.5 $\pm$ 10.8	37.7 $\pm$ 6.4	0.800
Baseline MD (dB)	-2.55 $\pm$ 5.08	-2.65 $\pm$ 5.82	-2.48 $\pm$ 4.46	0.800
Baseline mean RNFL thickness (μ m)	80.0 $\pm$ 13.4	78.3 $\pm$ 13.2	81.3 $\pm$ 13.3	0.040
Baseline average C/D ratio	0.67 $\pm$ 0.14	0.63 $\pm$ 0.15	0.72 $\pm$ 0.10	<0.001
Baseline vertical C/D ratio	0.66 $\pm$ 0.14	0.63 $\pm$ 0.15	0.69 $\pm$ 0.12	<0.001

F: female, M: male, D: diopters, GS: glaucoma suspect, G: glaucoma, NTG: normal-tension glaucoma, HTG: high-tension glaucoma.

* P value for the comparison between American and Korean cohorts.

Statistically significant values are marked with **bold** font.

Table 2

Rate of change for structural and functional parameters in **glaucoma subjects**. Parameters are reported as mean and 95% confidence intervals.

	American	Korean	<i>Difference (American – Korean)</i>
MD (dB/year)	–0.32 (–0.44; –0.20)	–0.27 (–0.38; –0.16)	–0.05 (–0.21; 0.11)
Mean RNFL (μm/year)	–0.24 (–0.48; 0.01)	–0.71 (–0.94; –0.48)	0.48 (0.14; 0.81)
Average C/D ratio (/year)	0.003 (0.002; 0.004)	0.003 (0.001; 0.004)	0.001 (–0.002; 0.002)
Vertical C/D ratio (/year)	0.003 (0.001; 0.005)	0.004 (0.002; 0.006)	0.001 (–0.003; 0.003)

MD: mean deviation, RNFL: retinal nerve fiber layer, C/D: cup-to-disc.

Statistically significant values are marked with **bold** font.

Table 3

Rate of change for structural and functional parameters in glaucoma suspects. Parameters are reported as mean and 95% confidence intervals.

	American	Korean	<i>Difference (American – Korean)</i>
MD (dB/year)	–0.17 (–0.33; –0.01)	0.01 (–0.10; 0.11)	–0.17 (–0.37; 0.03)
Mean RNFL (μm/year)	–0.36 (–0.71; –0.02)	–0.51 (–0.73; –0.28)	0.14 (–0.27; 0.55)
Average C/D ratio (/year)	0.001 (–0.001; 0.003)	0.001 (0.000; 0.002)	0.000 (–0.002; 0.003)
Vertical C/D ratio (/year)	0.001 (–0.002; 0.004)	0.002 (0.000; 0.004)	–0.001 (–0.004; 0.003)

MD: mean deviation, RNFL: retinal nerve fiber layer, C/D: cup-to-disc.

Statistically significant values are marked with **bold** font.

Factors affecting the rate of change for each parameter. P values for significant variables in the models and for interactions between variables are reported.

Table 4

	Ethnicity	Refraction	Baseline Age	Baseline Severity	Disease Subtype	Clinical Diagnosis	Interactions
MD (dB/year)	0.002	-	-	-	<0.001	<0.001	Diagnosis and Ethnicity (0.030) Ethnicity and Subtype (0.001) Diagnosis and Severity (<0.001)
Mean RNFL (µm/year)	<0.001	-	-	<0.001	-	-	Diagnosis and Ethnicity (<0.001)
Average C/D ratio (/year)	-	-	-	<0.001	-	<0.001	Diagnosis and Ethnicity (<0.001) Ethnicity and Refraction (0.045)
Vertical C/D ratio (/year)	-	-	-	-	<0.001	<0.001	Diagnosis and Ethnicity (0.018)

MD: mean deviation, RNFL: retinal nerve fiber layer, C/D: cup-to-disc.