

# Study of Retinal Nerve Fiber Layer Thickness Within Normal Hemivisual Field in Primary Open-Angle Glaucoma and Normal-Tension Glaucoma

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**Purpose:** To determine if nerve fiber layer thickness (NFLT) in glaucoma patients decreases before the development of visual field loss, and if there is a difference in the thinning of NFLT between primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG) eyes.

**Methods:** Thirty patients (33 eyes) with POAG and 31 patients (31 eyes) with NTG, who had visual field defects localized in either the upper or the lower hemifield verified by Humphrey Field Analyzer (HFA), were measured for NFLT by scanning laser polarimetry (Nerve Fiber Analyzer). Twenty-three normal subjects (23 eyes) matched in refraction and age with the glaucoma patients were recruited as the control group. The total deviation (TD) in each hemifield obtained by HFA and the 180° NFLT of each corresponding hemifield was calculated. Relationships between the TD of the normal or abnormal visual hemifield and the NFLT of the corresponding hemifield were compared among the POAG, NTG, and control groups.

**Results:** The NFLT of the corresponding normal hemifield was decreased both in the POAG group and in the NTG group when compared with the corresponding measurements in control subjects. In POAG eyes, thinning of the NFLT in the corresponding normal hemifield was more remarkable if the TD of the abnormal hemifield was greater, but this tendency was not observed in NTG eyes.

**Conclusion:** NFLT is already decreased when the visual field is still normal both in POAG eyes and in NTG eyes. However, the pattern of retinal nerve fiber layer damage in POAG may differ from that in NTG. **Jpn J Ophthalmol 2003;47:22–27** © 2003 Japanese Ophthalmological Society

**Key Words:** Hemifield defect, normal-tension glaucoma, primary open-angle glaucoma, retinal nerve fiber layer thickness, scanning laser polarimetry.

## Introduction

It is well-known that abnormalities of the retinal nerve fiber layer precede the visual field defect in primary open-angle glaucoma (POAG).<sup>1,2</sup> Approximately, 20–60% of the optic nerve axons have been lost when automated static perimetry detects irreversible visual field defect.<sup>3</sup> The introduction of scanning laser polarimetry (Nerve Fiber Analyzer; Laser Diagnostic Technologies, San Diego, CA,

USA) made it possible to obtain quantitative measurement of the retinal nerve fiber layer thickness (NFLT), and the accuracy and reproducibility of this new technology have been reported.<sup>1,4,5</sup> Previous studies have shown that NFLT measurements are useful to distinguish glaucoma patients from normal and ocular hypertension patients, and that NFLT decreases with the increasing severity of glaucoma.<sup>6–11</sup>

However, with the previous version of the nerve fiber analysis program, it was not possible to make an analysis of the NFLT divided into the upper and lower regions on the horizontal meridian. Thus, most of the reports on NFLT and visual field defects heretofore were obtained from the relationship between

Received: June 11, 2002

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the relative ratio of NFLT divided into four quadrants (superior, inferior, temporal, and nasal) and the mean deviation (MD), and not based on the relationship between the absolute value of the NFLT and the visual field defects. The assumption that a decrease in the NFLT develops earlier than visual field loss in glaucomatous eyes has stemmed from the correlation between total peripapillary NFLT and MD.

A few studies have been performed to determine whether the NFLT in the corresponding area of the normal field in glaucomatous eyes is decreased or not.<sup>9-12</sup> Reyes et al<sup>9</sup> studied patients with normal-tension glaucoma (NTG) in whose eyes glaucomatous damage was limited to either the upper or the lower hemifield, and indicated that the NFLT in the corresponding normal hemifield was decreased in the NTG eyes compared with healthy eyes. Kook et al<sup>12</sup> also studied glaucoma patients with hemifield-dominant visual field defect and reported that the mean NFLT in the unaffected quadrant of high-tension glaucoma (HTG) patients was significantly thinner than that in normal subjects.

However, their results were obtained from the relative ratio compensated by nasal NFLT. Recently, a scanning laser polarimeter (a new version of the Nerve Fiber Analyzer, GDx, also manufactured by Laser Diagnostic Technologies) has made it possible to evaluate NFLT at any angle; then, to evaluate the NFLT divided into two areas at 180° horizontally. Using this technique, we studied whether NFLT was decreased before the development of visual field loss, and whether the decrease ratio was different between POAG and NTG patients in whom visual field defects localized to either the upper or the lower hemifield.

## Materials and Methods

Thirty-three patients (33 eyes) with POAG and 31 patients (31 eyes) with NTG were recruited for this study. All patients had visual field defects localized either in the upper or the lower hemifield determined by static quantitative perimetry with the Humphrey Field Analyzer (HFA; Zeiss Humphrey systems, Dublin CA, USA) using program 30-2 standard, full threshold strategy. All subjects had the experience of static quantitative perimetry at least three times, corrected visual acuity of 0.7 or better, refraction within ± 5 diopters (D) and no history of intraocular surgery. Patients were diagnosed as having POAG if intraocular pressure (IOP) without medication was 22 mm Hg or higher as measured on at least three

consecutive occasions; both eyes had normal open angle; and glaucomatous optic nerve change and corresponding glaucomatous visual field loss had been identified. Patients were diagnosed as having NTG if untreated IOP was lower than 21 mm Hg in repeated readings, including diurnal variation; both eyes had normal open angle; glaucomatous optic nerve change and corresponding glaucomatous visual field loss had been identified; and there were no other ocular or neurosurgical pathologic conditions that could cause optic nerve damage. The abnormal hemifield was defined when at least three consecutive symbols of  $P < .05$  or at least two consecutive symbols of  $P < .02$  in Statpac II pattern deviation of HFA were recognized in only one hemifield (either upper or lower). The normal hemifield was the other side, which had no probability symbols not only in pattern deviation but also in total deviation (TD). All visual field test results adopted in this study had reliable performance (fixation loss, false positive and false negative of less than 20%).

In addition, 23 healthy subjects (23 eyes) without a family history of glaucoma, matched in refraction and age with the POAG and NTG patients, were recruited to serve as the control group. The control subjects had the experience of static quantitative perimetry at least three times. In the control group, fixation loss, false positive and false negative were less than 20% as measured with the HFA central 30-2 program, and probability symbols were not displayed on the probability map of total deviation and pattern deviation.

Age, refraction, sex, and the MD of the POAG, NTG, and control groups measured by HFA are shown in Table 1. There was no difference in refraction, age, or sex among the three groups. MD was significantly different between the control and the POAG groups (range, -14.0-1.87: mean,  $-3.6 \pm 3.8$ ) and between the control and the NTG groups (range, -9.6-3.47: mean,  $-3.1 \pm 3.2$ ). However, there was no difference between the POAG group and the NTG group (Student *t*-test).

**Table 1.** Background Data for Primary Open-Angle Glaucoma (POAG), Normal-tension Glaucoma (NTG) and Control

	Control	POAG	NTG
No. of eyes	23	33	31
Age (years)	55.3 ± 14.9	57.0 ± 11.4	56.9 ± 11.7
Refraction (D)	-0.89 ± 2.7	-0.91 ± 2.7	-0.88 ± 2.8
Sex (M/F)	14/9	21/12	19/12
Mean deviation (dB)	1.1 ± 1.8	-3.6 ± 3.8	-3.1 ± 3.2

NFLT was determined with the new version of the Nerve Fiber Analyzer (NFA, GDx Version 1.0.12: Laser Diagnostic Technology) in the groups of POAG, NTG, and controls. The analysis program version 2.0.05 was used to obtain peripapillary NFLT on the circumference of 1.75 disc diameters from the center of the disc by 180°; namely, the upper half hemifield and the lower half hemifield. Measurement was conducted three times consecutively, and the mean of the three values was made into the image. Cases with standard deviation (SD) over 8  $\mu\text{m}$ , and cases with peripapillary atrophy on the 1.75-diameter ring were excluded from the analysis.<sup>1</sup>

The TD of each hemifield obtained by HFA and by the 180° NFLT measurement was calculated. Relationships between the TD of the normal or abnormal hemifield and the corresponding NFLT were compared among the POAG, NTG, and control groups (unpaired *t*-test). In addition, to evaluate the effect of the severity of the abnormal hemifield on the NFLT of the normal hemifield, the relationship between the TD of the abnormal hemifield and the NFLT of the corresponding normal hemifield was analyzed (Pearson correlation coefficient). In the analysis, because it is shown that not only the visual field threshold but also the NFLT may differ between the upper and lower hemifield in normal human eyes,<sup>13,14</sup> we studied the relationship between TD and NFLT in the eyes with normal upper hemifield and in the eyes with normal lower hemifield, separately.

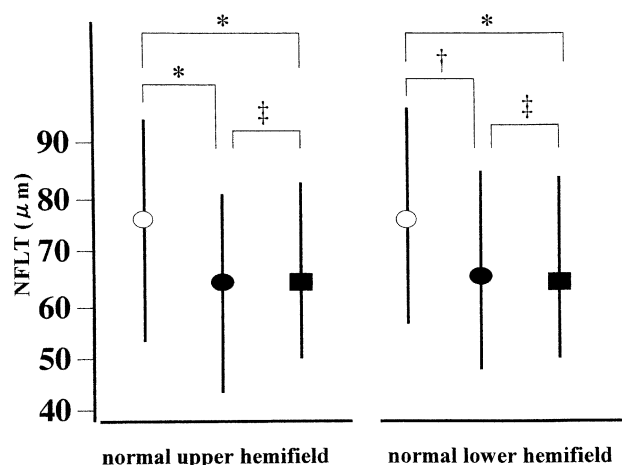
## Results

The upper hemifield was normal in 16 eyes of the POAG group and in 10 eyes of the NTG group. The NFLT in the corresponding normal upper hemifield was  $64.1 \pm 14.3 \mu\text{m}$  (mean  $\pm$  SD) and  $63.6 \pm 9.6 \mu\text{m}$  for the POAG group and the NTG group, respectively, compared to  $76.8 \pm 13.0 \mu\text{m}$  for the control group. There was a statistically significant difference in NFLT between the control group and the POAG group, as well as between the control group and the NTG group ( $P = .004$  and  $P = .009$ , respectively). However, there was no statistically significant difference in NFLT between the POAG group and the NTG group ( $P = .86$ ). The NFLT in the corresponding normal lower hemifield was  $65.5 \pm 14.3 \mu\text{m}$  for the POAG group (17 eyes),  $63.6 \pm 11.4 \mu\text{m}$  for the NTG group (21 eyes), and  $74.9 \pm 13.4 \mu\text{m}$  for the control group. Just as in the normal upper hemifield, there was a statistically significant difference in NFLT between the control group and the POAG

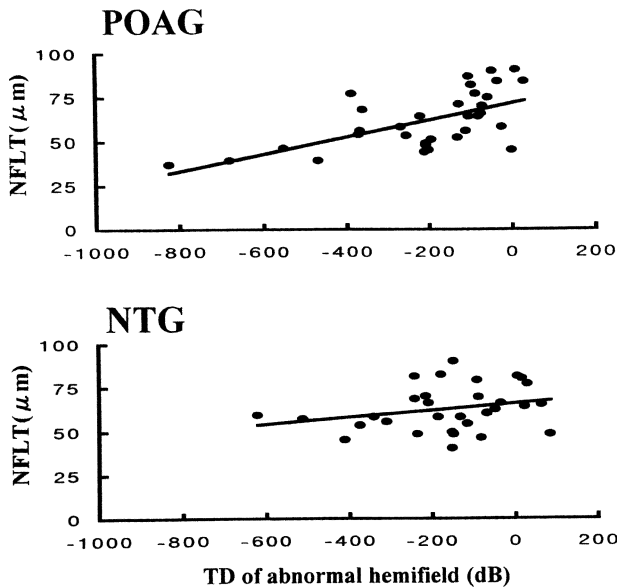
group as well as between the control group and the NTG group ( $P = .04$  and  $P = .006$ , respectively), but no difference between the POAG group and the NTG group ( $P = .66$ ; Figure 1).

In the POAG group, if the TD of the abnormal hemifield was greater, the corresponding NFLT was thinner (Pearson correlation coefficient,  $r = 0.61$ ,  $P < .0001$ ), while in the NTG group there was no significant relationship between TD and NFLT ( $r = 0.25$ ,  $P = .17$ ; Figure 2).

The analysis of the relationships between the severity of the abnormal hemifield and the corresponding NFLT normal hemifield showed that in POAG eyes with normal upper hemifield, the more severe the abnormal lower hemifield, the thinner the NFLT in the corresponding normal lower hemifield ( $r = 0.602$ ,  $P = .012$ ; Figure 3); whereas in the NTG eyes there was no significant relationship between these two parameters ( $r = 0.233$ ,  $P = .529$ ; Figure 4). The same tendency was found in eyes with normal lower hemifield: serious abnormalities in the upper hemifield were associated with decreased NFLT in the corresponding normal lower hemifield in the POAG group ( $r = 0.656$ ,  $P = .003$ ; Figure 3), but there was no significant relationship between these parameters in the NTG group ( $r = 0.290$ ,  $P = .205$ ; Figure 4). Furthermore, these relationships remained unchanged when eyes with abnormal upper hemifield and eyes with abnormal lower hemifield



**Figure 1.** (Left) Comparison of the nerve fiber layer thickness (NFLT) in the corresponding normal upper hemifield among three groups, control, primary open-angle glaucoma (POAG) and normal-tension glaucoma (NTG). (Right) Comparison of the NFLT in the corresponding normal lower hemifield among the three groups (control, POAG, and NTG). ○ control, ● POAG, ■ NTG. \* $P < .01$ , † $P < .05$ , ‡ $P > .10$ .



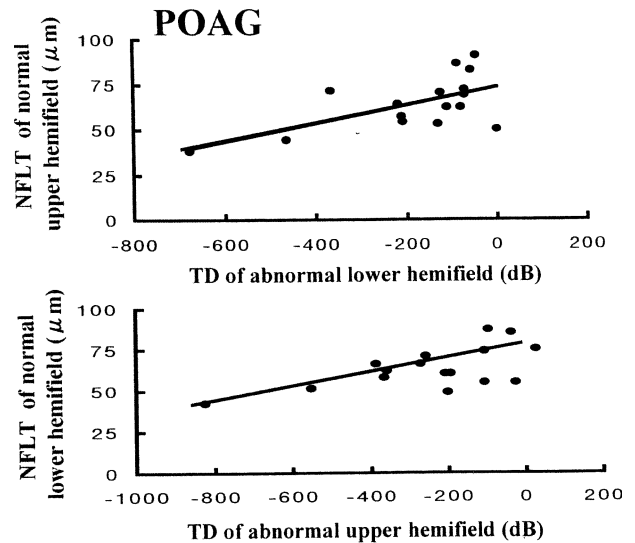
**Figure 2.** (Top) The relation between the nerve fiber layer thickness (NFLT) and total deviation (TD) of the corresponding abnormal hemifield in primary open-angle glaucoma (POAG) (Pearson correlation coefficient,  $r = 0.61$ ,  $P < .0001$ ). (Bottom) The relation between the NFLT and TD of the corresponding abnormal hemifield in normal-tension glaucoma (NTG) (Pearson correlation coefficient,  $r = 0.25$ ,  $P = .17$ ).

were combined. In the POAG group, if abnormalities in the abnormal hemifield were more serious, the NFLT in the corresponding normal hemifield was decreased ( $r = 0.613$ ,  $P < .0001$ ), while in the NTG group there was no significant relationship between these two parameters ( $r = 0.203$ ,  $P = .277$ ).

### Discussion

Many studies have been conducted on the relationships between the NFLT and glaucomatous visual field loss, and it has been reported that more serious visual field loss is associated with thinner NFLT.<sup>6,7</sup> Also, eyes with ocular hypertension are known to have thinner NFLT compared with healthy eyes.<sup>10,11</sup> Therefore, glaucomatous eyes may already have decreased NFLT before the development of visual field loss.

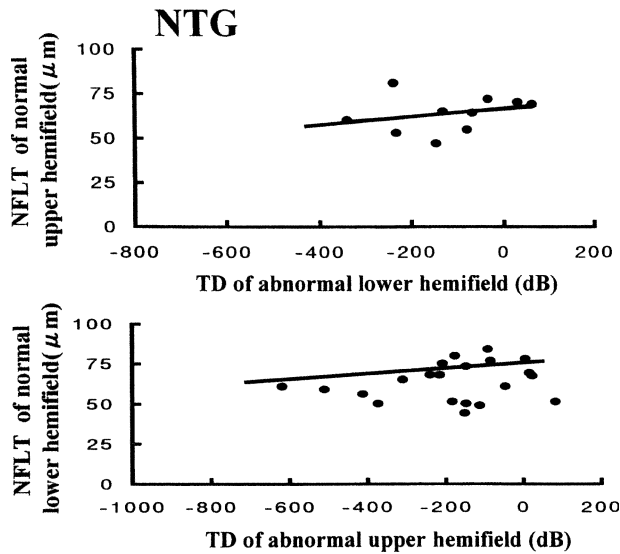
However, to determine whether NFLT is actually decreased before the development of visual field loss in glaucomatous eyes, it is necessary to follow-up the NFLT of those patients without visual field abnormalities, even though they have glaucomatous optic nerve findings. Intervals of 5–10 years between the onset of optic neuropathy and the onset of visual field loss<sup>2,15–18</sup> make such study difficult to conduct.



**Figure 3.** (Top) The relation between the normal upper hemifield nerve fiber layer thickness (NFLT) and total deviation (TD) of abnormal hemifield in the primary open-angle glaucoma (POAG) group (Pearson correlation coefficient,  $r = 0.602$ ,  $P = .012$ ). (Bottom) The relation between the normal lower hemifield NFLT and TD of abnormal hemifield in the POAG group (Pearson correlation coefficient,  $r = 0.656$ ,  $P = .003$ ).

In addition, intersubject variation of NFLT, overlapping of NFLT between normal eyes and glaucomatous eyes,<sup>1</sup> and decrease in NFLT with aging<sup>5,19,20</sup> may make the study even more difficult. Therefore, in this study we selected patients with abnormalities localized either to the upper or to the lower hemifield, and compared NFLT measurements in the corresponding normal hemifield to evaluate the changes in NFLT before the development of visual field loss in glaucomatous eyes.

It should be noted, however, that several reports recently admonished that because polarization effects of the cornea would affect the results of NFLT measurements, the comparison of interindividual results should be interpreted with caution.<sup>21</sup> There is, however, no way to adjust or avoid the corneal polarization. In this study, we matched age and refraction, parameters that were likely to affect the NFLT, between patients with POAG or NTG and controls. Cases with SD over 8  $\mu\text{m}$  in NFLT measurements<sup>1</sup> and cases with peripapillary atrophy on the 1.75-diameter ring were excluded from the analysis.<sup>1</sup> Because it is also known that the degree of visual field loss affects NFLT, only patients from POAG and NTG groups who were equal in MD were included in the analysis.



**Figure 4.** (Top) The relation between the normal upper hemifield nerve fiber layer thickness (NFLT) and total deviation (TD) of abnormal hemifield in the normal-tension glaucoma (NTG) group (Pearson correlation coefficient,  $r = 0.233$ ,  $P = .529$ ). (Bottom) The relation between the normal lower hemifield NFLT and TD of abnormal hemifield in the NTG group (Pearson correlation coefficient,  $r = 0.290$ ,  $P = .205$ ).

In the present study, we found that the NFLT of the normal hemifield was decreased not only in the POAG group but also in the NTG group compared with normal subjects. Kook et al<sup>12</sup> reported that the NFLT of the normal visual field in HTG was significantly thinner than that in normal subjects, based on 40 eyes with HTG having the hemifield-dominant visual field defect. Reyes et al<sup>9</sup> showed the NFLT in the corresponding normal hemifield was decreased in NTG eyes compared with normal eyes. This was based on 17 eyes with NTG having visual field defects localized in either the upper or lower hemifield. However, these results were obtained from the relative NFLT ratio with compensation for nasal NFLT, and from the combined data of the cases with normal upper hemifield and the cases with normal lower hemifield, even though it is known that NFLT differs between the upper and the lower hemifield even in normal subjects.<sup>11</sup>

In the present study we analyzed eyes with normal upper hemifield and eyes with normal lower hemifield separately, and confirmed that the decrease in NFLT in the corresponding normal hemifield occurred both in the POAG eyes and in the NTG eyes. Our findings support those of Reyes et al<sup>9</sup> and Kook et al.<sup>12</sup> In addition, we showed that in comparing NFLT between POAG and NTG eyes, the severity of the abnormal

hemifield (TD) was associated with the decrease in the NFLT in the corresponding normal hemifield only in POAG eyes. In NTG eyes, no significant relation was observed between the TD of the abnormal hemifield and the NFLT in the corresponding normal hemifield. These findings indicate that although NFLT decreases, the pattern of retinal nerve fiber layer damage in POAG may differ from that in NTG.

Caprioli and Spaeth<sup>22</sup> compared the disk rim between NTG and POAG patients having a similar extent of visual field loss, and showed that especially the inferior rim and the inferior temporal rim were thinner in NTG patients compared to POAG patients, indicating that there is a difference in the type of optic neuropathy between POAG and NTG. Also in visual field studies, it has been reported that the location and depth of scotoma are different between POAG and NTG patients, which may also reflect the difference in the type of optic neuropathy.<sup>23–25</sup> Drance et al<sup>26</sup> compared the sensitivity of the normal hemifield between POAG and NTG patients in whom visual field defects were localized either in the upper or the lower hemifield, and suggested the presence of diffuse optic neuropathy in POAG because they found the sensitivity of the normal hemifield lower in POAG than in NTG patients.

In our patients, POAG eyes and NTG eyes did not differ in TD, not only for the abnormal hemifield but also for the normal hemifield. However, in POAG eyes thinning of the NFLT in the corresponding normal hemifield was more remarkable if the TD of the abnormal hemifield was greater, but this tendency was not observed in NTG eyes. This may suggest that in POAG eyes the retinal nerve fiber damage extended to the normal hemifield diffusely along with the progression of the disease. In contrast, in NTG eyes there was no significant relationship between TD and NFLT, not only for the abnormal hemifield but also for the normal hemifield, suggesting that optic neuropathy is localized in NTG eyes.

Our study showed that NFLT was already decreased when visual field was still normal, based on HFA analysis, in POAG eyes and NTG eyes. Because the degree of thinning can be correlated with the degree of damage of the abnormal hemifield in POAG eyes, we suggest that measurement of NFLT is a useful method to determine the extent of the retinal nerve fiber damage in POAG eyes.

## References

1. Weinreb RN, Shakiba S, Zangwill L. Scanning laser polarimetry to measure the nerve fiber layer of normal and glaucomatous eyes. *Am J Ophthalmol* 1995;119:627–636.

2. Sommer A, Miller NR, Pollack I, Maumenee AE, George T. The nerve fiber layer in the diagnosis of glaucoma. *Arch Ophthalmol* 1977;95:2149–2158.
3. Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol* 1989;107:453–464.
4. Hoh ST, Ishikawa H, Greenfield DS, Liebmann JM, Chew SJ, Ritch R. Peripapillary nerve fiber layer thickness measurement reproducibility using scanning laser polarimetry. *J Glaucoma* 1998;7:12–15.
5. Chi Q-M, Tomita G, Inazumi K, Hayakawa T, Ido T, Kitazawa Y. Evaluation of the effect of aging on the retinal nerve fiber layer thickness using scanning laser polarimetry. *J Glaucoma* 1995;4:406–413.
6. Shirakashi M, Abe H, Sawaguchi S. Relationship between retinal nerve fiber layer thickness and visual field loss in glaucoma. *Atarashii Ganka (J Eye)* 1996;13:597–599.
7. Shirakashi M, Abe H, Sawaguchi S. Visual field loss and thickness of retinal nerve fiber layer in glaucoma eyes. *Rinsho Ganka (Jpn J Clin Ophthalmol)* 1996;50:269–272.
8. Weinreb RN, Shakiba S, Sample PA, et al. Association between quantitative nerve fiber layer measurement and visual field loss in glaucoma. *Am J Ophthalmol* 1995;120:732–738.
9. Reyes RDC, Tomita G, Kitazawa Y. Retinal nerve fiber layer thickness within the area of apparently normal visual field in normal-tension glaucoma with hemifield defect. *J Glaucoma* 1998;7:329–335.
10. Tjon-Fo-Sang MJ, deVries J, Lemij HG. Measurement by nerve fiber analyzer of retinal nerve fiber layer thickness in normal subjects and patients with ocular hypertension. *Am J Ophthalmol* 1996;122:220–227.
11. Choplin NT, Lundy DC, Dreher AW. Differentiating patients with glaucoma from glaucoma suspects and normal subjects by nerve fiber layer assessment with scanning laser polarimetry. *Ophthalmology* 1998;105:2068–2076.
12. Kook MS, Sung KR, Kim S, Park R, Kang W. Study of retinal nerve fibre layer thickness in eyes with high tension glaucoma and hemifield defect. *Br J Ophthalmol* 2001;85:1167–1170.
13. Heijl A, Lindgren G, Lindgren A, et al. Extended empirical statistical package for evaluation of single and multiple fields in glaucoma: Statpac 2. *Perimetry Update* 1990/91:303–315.
14. Åsman P, Heijl A. Evaluation of methods for automated hemifield analysis in perimetry. *Arch Ophthalmol* 1992;110:820–826.
15. Iwata K. Ophthalmoscopy in the detection of optic disc and retinal nerve fiber layer changes in early glaucoma. *Surv Ophthalmol* 1989;33:447–448.
16. Tuulonen A, Airaksinen PJ. Initial glaucomatous optic disk and retinal nerve fiber layer abnormalities and their progression. *Am J Ophthalmol* 1991;111:485–490.
17. Sommer A, Katz J, Quigley HA, et al. Clinically detectable nerve fiber atrophy precedes the onset of glaucomatous field loss. *Arch Ophthalmol* 1991;109:77–83.
18. Zeyen TG, Caprioli J. Progression of disc and field damage in early glaucoma. *Arch Ophthalmol* 1993;111:62–65.
19. Funaki M, Shirakashi M, Abe H. Relationship between age and thickness of the retinal nerve fiber layer in normal subjects. *Nippon Ganka Gakkai Zasshi (J Jpn Ophthalmol Soc)* 1998;102:383–388.
20. Poinooswamy D, Fontana L, Wu JX, Fitzke FW, Hitchings RA. Variation of nerve fibre layer thickness measurements with age and ethnicity by scanning laser polarimetry. *Br J Ophthalmol* 1997;81:350–354.
21. Greenfield DS, Knighton RW, Huang XR. Effect of corneal polarization axis on assessment of retinal nerve fiber layer thickness by scanning laser polarimetry. *Am J Ophthalmol* 2000;129:715–722.
22. Caprioli J, Spaeth GL. Comparison of the optic nerve head in high- and low-tension glaucoma. *Arch Ophthalmol* 1985;103:1145–1149.
23. Hitchings RA, Anderson SA. A comparative study of visual field defects seen in patients with low-tension glaucoma and chronic simple glaucoma. *Br J Ophthalmol* 1983;67:818–821.
24. Caprioli J, Spaeth GL. Comparison of visual fields in the low-tension glaucomas with those in the high-tension glaucomas. *Am J Ophthalmol* 1984;97:730–737.
25. Chauhan BC, Drance SM, Douglas GR, Johnson CA. Visual field damage in normal-tension and high-tension glaucoma. *Am J Ophthalmol* 1989;108:636–642.
26. Drance SM, Douglas GR, Airaksinen PJ, Schulzer M, Hitchings RA. Diffuse visual field loss in chronic open-angle and low-tension glaucoma. *Am J Ophthalmol* 1987;104:577–580.