

Detection and Prognostic Significance of Optic Disc Hemorrhages during the Ocular Hypertension Treatment Study

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Purpose: To compare the rates of detection of optic disc hemorrhages by clinical examination and by review of optic disc photographs at the Optic Disc Reading Center (ODRC), to assess the incidence of and the predictive factors for disc hemorrhages in the annual disc photographs of the Ocular Hypertension Treatment Study (OHTS), and to determine whether optic disc hemorrhages predict the development of primary open-angle glaucoma (POAG) in the OHTS.

Design: Cohort study.

Participants: Three thousand two hundred thirty-six eyes of 1618 participants.

Methods: Both eyes of participants were examined for optic disc hemorrhages every 6 months by clinical examination, with dilated fundus examinations every 12 months, and by annual review of stereoscopic disc photographs at the ODRC.

Main Outcome Measures: Incidence of optic disc hemorrhages and POAG end points.

Results: Median follow-up was 96.3 months. Stereophotography-confirmed glaucomatous optic disc hemorrhages were detected in 128 eyes of 123 participants before the POAG end point. Twenty-one cases (16%) were detected by both clinical examination and review of photographs, and 107 cases (84%) were detected only by review of photographs ($P < 0.0001$). Baseline factors associated with disc hemorrhages were older age, thinner corneas, larger vertical cup-to-disc ratio, larger pattern standard deviation index on perimetry, family history of glaucoma, and smoking status. The occurrence of a disc hemorrhage increased the risk of developing POAG 6-fold in a univariate analysis ($P < 0.001$; 95% confidence interval, 3.6–10.1) and 3.7-fold in a multivariate analysis that included baseline factors predictive of POAG ($P < 0.001$; 95% confidence interval, 2.1–6.6). The 96-month cumulative incidence of POAG in the eyes without optic disc hemorrhage was 5.2%, compared with 13.6% in the eyes with optic disc hemorrhage. In eyes with a disc hemorrhage in which a POAG end point developed, the median time between the 2 events was 13 months.

Conclusions: Review of stereophotographs was more sensitive at detecting optic disc hemorrhage than clinical examination. The occurrence of an optic disc hemorrhage was associated with an increased risk of developing a POAG end point in participants in the OHTS. However, most eyes (86.7%) in which a disc hemorrhage developed have not experienced a POAG end point to date. *Ophthalmology* 2006;113:2137–2143
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The Ocular Hypertension Treatment Study (OHTS) was designed to determine whether lowering intraocular pressure in participants with ocular hypertension (OHT) delays or prevents the development of primary open-angle glaucoma (POAG). Results to date have shown an approximate 50% reduction in conversion from OHT to

POAG with a 20% reduction in intraocular pressure (IOP).¹ Baseline predictive factors for conversion include higher IOP, larger cup-to-disc ratio, thinner cornea, higher pattern standard deviation index on visual field testing, and older age.²

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The presence of an optic disc hemorrhage at baseline examination excluded participation in the study, whereas a hemorrhage that developed subsequently was not by itself considered a POAG end point.³ The presence or absence of optic disc hemorrhages was determined by investigators using clinical examination every 6 months and by review of stereophotographs at the Optic Disc Reading Center (ODRC) annually. The purposes of this study were to compare the detection of glaucomatous optic disc hemorrhages by clinical examination and by review of disc photographs, to assess the incidence of disc hemorrhages in the annual disc photographs of the OHTS participants before and after the development of a POAG end point, to identify baseline factors associated with optic disc hemorrhage during follow-up, and to determine whether optic disc hemorrhages predict the development of POAG end points in participants of the OHTS.

Patients and Methods

The design of the OHTS has been described previously.³ The OHTS data files used in this report include data from February 1994 through November 2003, with 168 eyes that progressed to a POAG end point. More than 60% of participants had completed their 96-month visit by the time of this review, with the longest follow-up being 108 months. The median follow-up of all participants was 96.3 months.

During the course of the study, investigators evaluated the optic nerve by means of direct or slit-lamp biomicroscopy, noting whether a disc hemorrhage was present in either or both eyes at each examination. The presence of a hemorrhage at the disc margin or within the disc tissue was recorded without making a distinction between splinter hemorrhages typical of glaucoma and hemorrhages resulting from other concurrent diseases. Clinical examinations were scheduled approximately every 6 months. Annual examinations of the fundus were performed after pupil dilation, whereas those conducted at 6-month interval visits were performed without dilation. At the annual visit, stereoscopic optic disc photographs were obtained and were reviewed by the ODRC. A minimum of 2 primary readers reviewed each pair of stereophotographs. In addition to other features, readers determined whether a disc hemorrhage was present. If a difference of opinion existed between readers, a third, senior reader (DLB, DRA, or

RKP) determined whether a disc hemorrhage was present. A POAG end point was defined as a reproducible optic disc deterioration or a reproducible visual field abnormality attributed to POAG by a masked end point committee.³

Definition of Glaucomatous Disc Hemorrhage

At the ODRC, the presence of a glaucomatous optic disc hemorrhage was recorded if it was of a type considered typical of glaucoma, specifically a flame- or splinter-shaped hemorrhage, often with feathered ends, that was radially oriented and perpendicular to the disc margin. These hemorrhages characteristically extend from within the optic nerve head to the adjacent retina, crossing any peripapillary zone of absent or disrupted retinal pigment epithelium, but need not occupy the entire length of this typical position. An example of a disc hemorrhage considered typical of glaucoma in an OHTS participant is shown in Figure 1. A splinter- or flame-shaped hemorrhage on the disc was not considered related to glaucoma if the disc was swollen or otherwise obviously abnormal from anterior ischemic optic neuropathy, papillitis, or another nonglaucomatous optic neuropathy. Similarly, a hemorrhage within the optic disc was not considered related to glaucoma if multiple nearby retinal hemorrhages suggested diabetic retinopathy, vein occlusion, or another retinal vascular abnormality. In contrast, clinical investigators were asked simply to note the presence or absence of a hemorrhage anatomically located at the disc margin or within the disc tissue without regard to presumed cause. To avoid potential misclassification of disc hemorrhages, only eyes that satisfied the disc hemorrhage criteria above detected by the ODRC or detected by the clinician and confirmed by disc photographs were included in this report.

Statistical Methods

A McNemar chi-square test was performed to determine differences in detection of optic disc hemorrhages by the ODRC and by clinical examination. Only the 128 eyes with optic disc hemorrhages detected or confirmed by the ODRC were included in the analysis of predictive factors. The incidence of disc hemorrhage before development of POAG was assessed with Kaplan-Meier methods. A Cox univariate proportional hazards regression, with the robust sandwich variance estimate option to account for the correlation between the 2 eyes of participants, was performed to determine which baseline characteristics were predictive of disc hemorrhage during follow-up before the onset of a POAG end

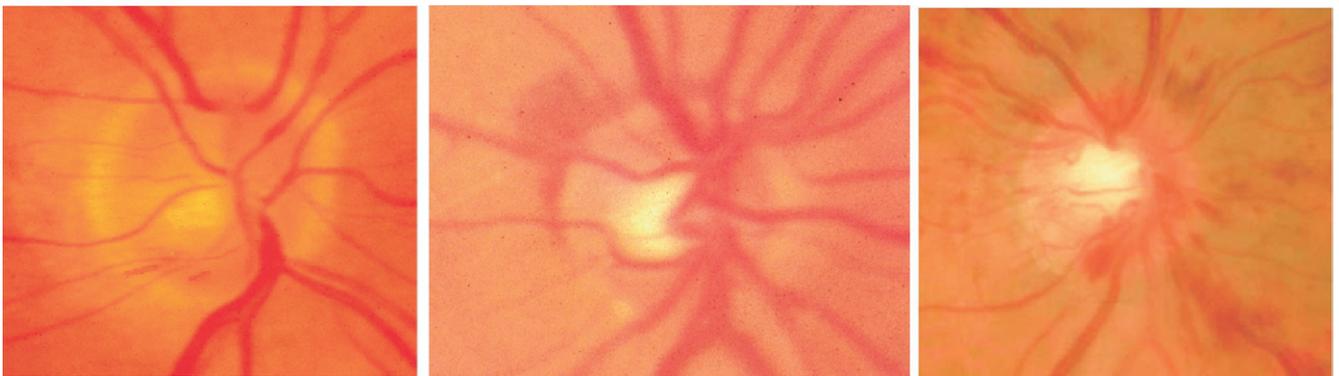


Figure 1. Images of participants in the Ocular Hypertension Treatment Study. **Left,** Splinter hemorrhage typical of glaucoma. Nonglaucomatous peripapillary hemorrhage between the neural retina and the retinal pigment epithelium and therefore sharply delimited at the disc margin. **Middle,** Hemorrhage is not in the nerve fiber layer. **Right,** Multiple disc and retinal hemorrhages typical of central retinal vein occlusion.

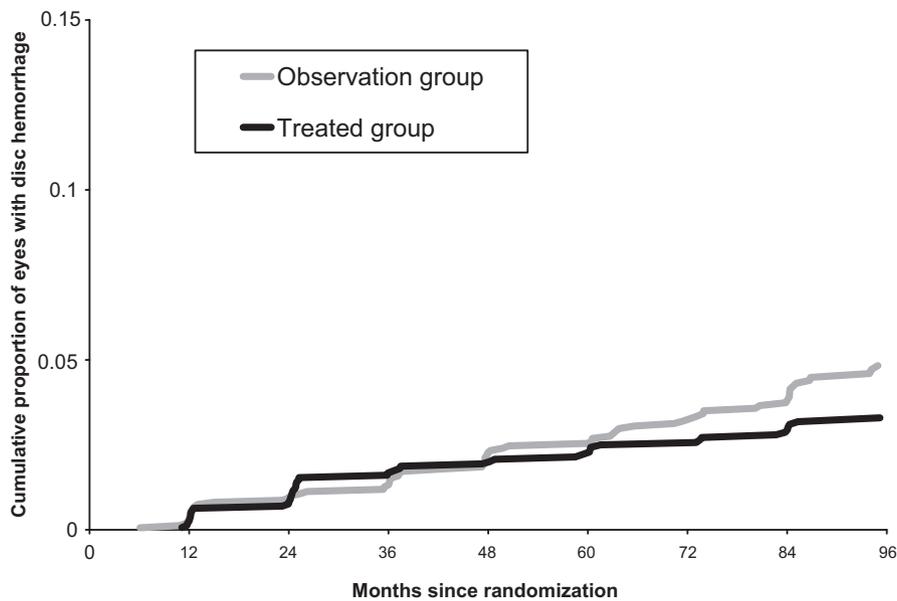


Figure 2. Graph showing cumulative incidence of optic disc hemorrhages in annual photographs of treated and observation groups.

point. The incidence of disc hemorrhage after a POAG end point was estimated with a second Kaplan-Meier analysis. Thirteen eyes of 13 participants were found to have disc hemorrhage at the same visit as an end point was reached and were not included in either the pre-POAG or post-POAG end point incidence calculations.

After adjusting for treatment assignment, a Cox multivariate proportional hazards regression model, with the robust sandwich variance estimate option to account for the correlation between the 2 eyes of participants, was performed to examine whether having a disc hemorrhage, included as a time-dependent covariate during follow-up, was an independent predictive factor for the development of POAG. Other baseline variables in this model included age, vertical cup-to-disc ratio, pattern standard deviation index on visual field testing, IOP, and central corneal thickness. Another time-dependent Cox survival regression analysis assessed whether the occurrence of a POAG end point increased the risk of a subsequent disc hemorrhage.

Results

Detection of optic disc hemorrhages during clinical examination was compared with detection by review of stereoscopic disc photos at the ODRC in eyes that had not yet reached POAG end point through November 2003. One hundred forty-three eyes were found to have disc hemorrhages by a clinical examination, review of disc photos, or both. Of these, 107 (74.8%) were reported from photographic evaluation at the ODRC alone, 15 (10.5%) were found during clinical examination alone, and 21 (14.7%) were identified by both ($P < 0.001$, McNemar test). Of disc hemorrhages detected by clinical examination, 21 of 24 (12.5%) were found at annual examinations, possibly because of dilation of pupils at these annual examinations. Disc photos of the 15 eyes with hemorrhages reported only by clinical examination were reevaluated by 2 masked independent senior readers at the ODRC (DLB and DRA). In 12 cases, the photographs showed a hemorrhage that was not classified as a type considered typical of glaucoma by the criteria used by the ODRC outlined above, but included hemorrhages associated with multiple retinal hemorrhages and dilated veins typical of

retinal vein occlusion (Fig 1), peripapillary subretinal hemorrhage (Fig 1), or structures that mimicked hemorrhages such as a tortuosity of a vein, beading of choroidal vessels, large retinal vessels crossing the disc, or clumping of the retinal pigment epithelium. In the other 3 cases, disc hemorrhages were noted only at a semiannual clinical examination, but no disc photographs were available for comparison, so there was no way to classify these disc hemorrhages definitively as glaucomatous or nonglaucomatous. Both misclassified and unclassified hemorrhages were excluded from the remainder of the analyses that followed. Therefore, 128 eyes were defined as having glaucomatous disc hemorrhages before a POAG end point.

Through November 2003, a POAG end point developed in 168 eyes of 159 participants, 94 (56%) by optic disc criteria alone, 59 (35%) by visual field criteria alone, and 15 (9%) by both. The cumulative incidence of eyes with at least 1 disc hemorrhage before POAG by follow-up years 1 through 8 was 0.3% ($n = 9$), 0.9% ($n = 27$), 1.5% ($n = 46$), 2.1% ($n = 65$), 2.3% ($n = 71$), 2.8% ($n = 86$), 3.3% ($n = 98$), and 4.1% ($n = 115$), or approximately 0.5% per year. Figure 2 shows the cumulative incidence of optic disc hemorrhages in the treated and observation groups over 8 years of follow-up. Disc hemorrhages occurred slightly more often in the observation group, but this difference was not statistically significant ($P = 0.13$, Cox proportional hazard regression analysis). Table 1 displays a frequency distribution of the numbers of pre-end point disc hemorrhages detected in 128 eyes of 123

Table 1. Number of Disc Hemorrhages per Eye and Percent of Eyes Reaching Primary Open-Angle Glaucoma End Point

No. of Disc Hemorrhages per Eye	No. of Eyes	No. (%) of Eyes Reaching Primary Open-Angle Glaucoma End Point (N = 168)
0	3108	151 (4.9%)
1	112	15 (13.4)
2	12	2 (16.7%)
3	2	0
4	2	0

Table 2. Baseline Factors and Disc Hemorrhage in the Ocular Hypertension Treatment Study

Baseline Variable	Group Sizes (for Categorical Variables)	Risk Ratio	P Value	95% Confidence Limit on Risk Ratio	
				Lower	Upper
Pressure-lowering therapy					
Yes	1612	0.76	0.13	0.53	1.09
No*	1624				
Age (per decade increase; yrs)		1.58	<0.001	1.32	1.88
Corneal thickness (per 40- μ m decrease)		1.23	0.024	1.03	1.47
Vertical cup-to-disc ratio (per 0.1 DD increase)		1.14	0.005	1.04	1.25
Pattern standard deviation (1 unit increase)		2.51	0.005	1.32	4.78
IOP (per 10-mmHg increase)		1.57	0.12	0.89	2.77
Myopia					
Spherical equivalent $\leq -3, > -6$ D	523	1.22	0.41	0.76	1.98
Spherical equivalent ≤ -6 D	105	0.59	0.40	0.18	1.98
Spherical equivalent > -3 D*	2608				
Smoked at least 100 cigarettes					
Yes	1252	1.53	0.027	1.05	2.24
No*	1532				
Lens status					
Aphakic or pseudophakic [†]	25	2.61	0.19	0.63	10.8
Phakic*	3211				
Gender					
Female	1842	0.72	0.062	0.51	1.02
Male*	1394				
Ethnicity					
Black	798	0.67	0.094	0.42	1.07
Hispanic	112	1.46	0.37	0.64	3.35
White, non-Hispanic*	2264				
Family history of glaucoma					
Yes	1106	1.59	0.023	1.07	2.38
No*	2130				
History of asthma					
Yes	224	0.33	0.057	0.11	1.03
No*	3006				
History of cancer					
Yes	188	1.58	0.15	0.85	2.93
No*	3048				
History of diabetes mellitus					
Yes	382	1.17	0.57	0.69	1.97
No*	2848				
History of high blood pressure					
Yes	1222	0.98	0.91	0.68	1.40
No*	2004				
History of low blood pressure					
Yes	142	0.87	0.76	0.36	2.11
No*	3088				
History of heart disease					
Yes	202	1.91	0.028	1.07	3.38
No*	3030				
History of lung disease					
Yes	78	1.06	0.92	0.34	3.34
No*	3152				
History of stroke					
Yes	38	0.89	0.91	0.13	6.34
No*	3198				
History of other systemic condition					
Yes	910	0.95	0.81	0.65	1.40
No*	2322				
Migraine Headaches					
Yes	356	0.85	0.60	0.47	1.54
No*	2844				

D = diopters; DD = disc diameter; IOP = intraocular pressure.

*Reference group.

[†]None of the 16 eyes of the 8 aphakic patients experienced a disc hemorrhage.

Table 3. Frequency of Disc Hemorrhages per Eye after Primary Open-Angle Glaucoma End Point

Frequency of Disc Hemorrhages per Eye	No. (%) of Eyes (N = 168)
0	153 (91)
1	11 (7)
2	2 (1)
3	1 (1)
4	0
5	1 (1)

participants. Of these, 111 (86.7%) did not experience a POAG end point during a median follow-up of 30.7 months after disc hemorrhage occurred. Seventeen eyes (13%) were observed with a disc hemorrhage before development of a POAG end point, 8 (47%) by optic disc criteria, 8 (47%) by visual field criteria, and 1 (6%) by both. In eyes with a disc hemorrhage that later developed into a POAG end point, the median time from optic disc hemorrhage to a POAG end point was 13 months.

The association of baseline factors on the incidence of optic disc hemorrhages, determined with univariate Cox proportional hazard regression analysis, is presented in Table 2. Older age, thinner central corneal thickness measurement, greater vertical cup-to-disc ratio, and greater pattern standard deviation index on perimetry were statistically significantly associated with disc hemorrhage. Baseline IOP and assignment to pressure-lowering medications were not associated with the development of a disc hemorrhage, although there was a trend in both cases ($P = 0.12$ and 0.13 , respectively). Family history of glaucoma ($P = 0.023$) and a lifetime history of smoking at least 100 cigarettes ($P = 0.027$) also were associated with disc hemorrhages.

To assess whether the risk of POAG increased after disc hemorrhage, disc hemorrhage was included as a time-dependent covariate in a Cox survival regression model of time to end point. The risk of developing POAG after occurrence of a disc hemorrhage was 6.0 times higher than without a disc hemorrhage (hazard ratio, 6.0; 95% confidence interval, 3.6–10.1; $P < 0.001$). After adjusting for baseline factors previously identified as being predictive of POAG in the OHTS,² as well as treatment assignment, the independent contribution of a disc hemorrhage to risk was less (hazard ratio, 3.7; 95% confidence interval, 2.1–6.6; $P < 0.001$). All of the baseline risk factors previously found to be significant prognostic factors for the development of POAG (assignment to observation, older age, higher IOP, thinner cornea, larger cup-to-disc ratio, higher pattern standard deviation, no diabetes) remained statistically significant after the inclusion of optic disc hemorrhage in the multivariate model.

Of the 168 eyes in which POAG developed, 15 eyes of 15 participants had documented disc hemorrhages after the development of POAG. Of these 15 eyes, 13 (87%) had no documented disc hemorrhages before a POAG end point; 1 of the two remaining eyes had a single pre-POAG disc hemorrhage, and 1 had 2 pre-POAG disc hemorrhages. The cumulative incidence of 1 or more disc hemorrhages after the date of the development of POAG from 1 to 4 years, respectively, was 3.1% ($n = 5$), 5.1% ($n = 8$), 6.5% ($n = 10$), and 9.9% ($n = 13$), or approximately 2.5% per year. The occurrence of a POAG end point significantly increased the incidence of a first disc hemorrhage ($P < 0.001$). The maximum number of POAG disc hemorrhages after reaching the end point was 5 in a single eye. Table 3 displays the frequency distribution of disc hemorrhages in 168 eyes of 159 participants after a POAG end point had been reached. No difference was found in the incidence of disc hemorrhages after an end point between patients

that had reached an end point by disc criteria versus field criteria ($P = 0.83$, log-rank test).

Discussion

The current analysis of the OHTS data provides evidence that careful review of optic disc photographs detects optic disc hemorrhages more frequently than does clinical examination, at least in the context of this clinical trial. This was true despite the fact that photographs were obtained, in general, once annually and that clinical examinations occurred twice annually. If optic disc photographs had been obtained as often as clinical examinations were performed, the difference most likely would have been even greater. There are several possible explanations for this finding. First, detecting an optic disc hemorrhage from a photograph performed on a dilated eye may be easier than detecting it with the direct ophthalmoscope or condensing lens and slit lamp in an eye that is not stationary and not always dilated. Second, 2 readers working from photographs may devote more time reviewing photographs compared with the time used by a single clinician during a clinical examination. Third, perhaps investigators in the study were relying more on the ODRC to detect disc hemorrhages.

The OHTS participants in whom optic disc hemorrhages developed share baseline characteristics with OHTS participants in whom POAG developed, including older age, thinner corneas, and larger baseline cup-to-disc ratio. Some of these predictive factors, such as age, contribute to an increased susceptibility to damage. Some predictive factors, such as an enlarged cup or a disc hemorrhage, may represent the beginning of the actual damage process itself.⁴ Any of these predictive factors make it more likely the person will experience glaucoma, and the clinician should realize that patients with one or more of these risk factors are at increased risk. Of note, in the multivariate analysis, when these other factors that correlate with POAG development are taken into account, the occurrence of a disc hemorrhage independently adds additional risk.

Assignment to the treatment arm of the study reduced the incidence of POAG, but was not found to reduce the incidence of splinter hemorrhages on the disc at a statistically significant level, perhaps because of the small number of disc hemorrhages to date. The disassociation that IOP-lowering reduces the incidence of POAG but not of hemorrhages may signify that those who experience hemorrhages are more susceptible to higher IOP, such that the IOP lowering achieved in the OHTS was not adequate to prevent either the hemorrhages or conversion to fully manifest glaucoma. Another possible explanation may be that those with splinter hemorrhages are “bleeders” as a result of a different pathogenic factor that causes hemorrhage and axon damage. However, the number of cases in this series is too small to support any particular potential explanation.

In this study, although a participant with an optic disc hemorrhage during follow-up was 6.0 times more likely to experience a POAG end point, 86.7% of the participants with an optic disc hemorrhage did not experience a POAG end point to date, a mean follow-up period of

approximately 31 months. Thus, the occurrence of an optic disc hemorrhage is not synonymous with development of glaucoma, nor is it a sign that POAG will soon become manifest with certainty. The results of the study also do not suggest that all OHT patients be subjected to photographs annually solely to detect optic disc hemorrhages. They may well be evident on careful clinical examination in which attention is directed toward their detection, knowing that outside the context of a clinical trial, photographs may not be examined as thoroughly.

An additional, interesting finding in the current study is that the cumulative incidence of optic disc hemorrhages was 0.5% per year before the development of POAG and 2.5% per year in eyes after the development of POAG. This is consistent with findings in several cross-sectional studies that found that patients with POAG have an increased prevalence of optic disc hemorrhages compared with patients with OHT.^{5,6} To our knowledge, this is the first report to show a higher incidence of optic disc hemorrhages after the development of POAG in a longitudinal study. It is important to recognize, however, that these incidence rates are underestimates because disc hemorrhages are transient and photographs were taken annually. It is likely that disc hemorrhages occurring between annual photographs are missed.

Of note, when considering the implications of the present study, one must realize that an optic disc hemorrhage at time of recruitment was an exclusion criterion because of an uncertain relationship between OHT, disc hemorrhages, and POAG. Thus, we are most likely studying a group of participants who are less likely to have optic disc hemorrhages throughout follow-up than an all-inclusive cohort of eyes with OHT.

The present longitudinal data and multivariate analysis add to the literature that suggests that optic disc hemorrhages are a negative predictive factor in OHT, as distinct from its already well-established predictive value in fully manifest glaucoma. Longitudinal studies have shown this predictive association for both primary open-angle⁷⁻⁹ and normal-tension glaucoma.¹⁰⁻¹³ However, the evidence for an association between optic disc hemorrhage and development of POAG in patients with OHT is less abundant. In a univariate longitudinal analysis, Drance et al⁷ studied 29 ocular hypertensive individuals with optic disc hemorrhages compared with 29 ocular hypertensive individuals without optic disc hemorrhages and found that 10 progressed in the optic disc hemorrhage group, whereas only 1 progressed in the group without optic disc hemorrhages over the same follow-up period. The follow-up period was not mentioned in this report. Airaksinen et al¹⁴ retrospectively studied 25 ocular hypertensive patients with optic disc hemorrhage, 8 of whom had experienced glaucomatous visual field or optic disc changes 1 to 2 years after the development of a disc hemorrhage with an average follow-up time of 6 years. No control group was included in this study. In a prospective cohort study, Diehl et al⁹ found that glaucoma suspects with optic disc hemorrhages (n = 7) were 14 times more likely to experiencing worsening nerve fiber layer status than those with suspected glaucoma without optic disc hemorrhages (n = 56) after 1 year of follow-up. Siegner and

Netland¹⁵ performed a retrospective study of 17 patients followed up for OHT and found that optic disc hemorrhages were associated with glaucomatous changes in the optic disc or visual field compared with OHT control eyes without optic disc hemorrhages, with changes occurring a similar time after optic disc hemorrhage as in the current study (1–2 years). The OHTS is the largest prospective longitudinal study to show that optic disc hemorrhages are a predictive factor for the development of POAG in patients with OHT.

It is important to note that splinter-shaped optic disc hemorrhages must be evaluated in the context of other clinical findings. Here they are found to be predictive for the development of POAG in the presence of elevated IOP, but hemorrhages of similar location and morphologic features may be the result of other ocular and systemic causes. Disc hemorrhages may occur with posterior vitreous detachment,^{16,17} nonglaucomatous optic neuropathies,¹⁸ optic disc drusen,¹⁸ and vascular occlusive diseases of the retina,¹⁸ all of which are readily apparent on dilated fundus examination. Systemic disorders associated with optic disc hemorrhage include diabetes mellitus, systemic hypertension, systemic lupus erythematosus, and leukemia.¹⁸ If any of these other ocular or systemic conditions are present, it cannot be concluded from the present data that a patient with OHT is necessarily at a higher risk for future development of POAG or normal-tension glaucoma.

Results of the current study do not suggest that all OHT patients with an optic disc hemorrhage should be treated, because most patients with optic disc hemorrhage did not develop manifest POAG during the study period. However, there is evidence from other studies that lowering IOP in patients with POAG reduces the incidence of future optic disc hemorrhages.¹⁹ The present study suggests that optic disc hemorrhage in the setting of OHT places patients at a higher risk of developing POAG, as does older age, thinner corneas, higher pattern standard deviation on automated perimetry, and larger vertical cup-to-disc ratio. Thus, an optic disc hemorrhage should be included in the decision matrix about initiating treatment in a patient with OHT. Because optic disc hemorrhages are such a strong predictive factor for the development of POAG in OHT, we recommend frequent monitoring for optic disc hemorrhages by careful examination of the optic disc through a dilated or undilated pupil or optic disc photography, or both.

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