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Longitudinal Changes in Peripapillary Atrophy in the Ocular Hypertension Treatment Study

A Case–Control Assessment

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Purpose: To explore the association between peripapillary atrophy (PPA) area and conversion from ocular hypertension (OHT) to glaucoma.

Design: Prospective, longitudinal cohort study of cases and controls.

Participants: We included 279 age-matched and follow-up time–matched eyes with OHT that converted to glaucoma and 279 eyes with OHT that did not convert to glaucoma.

Methods: Initial and last acceptable optic disc photos were analyzed. Disc, α-zone, and β-zone PPA were traced independently by 2 trained readers and their areas were measured with Photoshop. The α-zone and β-zone areas were expressed as a percentage of optic disc area.

Main Outcome Measures: α-Zone and β-zone PPA size over time.

Results: Intraclass correlation coefficients (ICCs) demonstrated that readers had good agreement on disc area (ICC = 0.97) and β-zone (ICC = 0.82), but not α-zone (ICC = 0.48). The ß-zone, as a percentage of disc area, increased in size ($P < 0.001$) in both eyes with incident primary open-angle glaucoma (mean, 10.6%; standard deviation, 22.6%) and matched controls (mean, 10.1%; standard deviation, 33.7) over follow-up (mean, 12.3 years). The increase in size did not differ between cases and controls ($P = 0.82$). Enlargement of the β-zone was not correlated with follow-up time ($P = 0.39$).

Conclusions: The results did not show a difference in size of the β-zone at baseline between eyes that proceed to develop glaucoma and those that do not. Moreover, the β-zone enlarges equally in case and control eyes during follow-up. *Ophthalmology 2015;122:79-86 © 2015 by the American Academy of Ophthalmology.*

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Peripapillary atrophy (PPA) is among the parameters that are often taken into consideration in diagnosing open-angle glaucoma (OAG).[1,2] The association between PPA and OAG has been extensively investigated. Although there are a few studies to the contrary,[3–5] most cross-sectional[6–13] and prospective studies[14,15] have found that PPA is more frequent and larger in patients with OAG than those without OAG. Other longitudinal studies have demonstrated that PPA enlarges in some eyes as glaucoma progresses,[7,15–19] as well in some eyes with age.[15] It has also been reported that there is a significant association between the location of PPA and that of the most marked visual field loss[20–22] and that the extent of PPA significantly correlates with the degree of optic disc damage and visual field defects.[20,23,24]

There have been only a few reports on the prevalence of PPA in patients with ocular hypertension (OHT),[25,26] and the issue of whether the presence and/or progression of PPA is a risk factor for conversion from OHT to OAG remains uncertain.[5,27–31] However, many of these past investigations included relatively small numbers of patients, had poorly defined inclusion and exclusion criteria, and were cross-sectional rather than longitudinal. These limitations have also made it difficult to make comparisons across studies and highlight the need for more data to clarify the association between PPA progression in OHT and conversion to glaucoma. Because not all eyes with OHT develop OAG,[32–35] it is important to identify other factors, such as structural changes to the optic disc, that may help to determine the risk of conversion from OHT to glaucoma. Evaluation of a large set of prospectively collected data on PPA in OHT patients carries the potential to improve our understanding of the association of PPA and changes in PPA in OHT with conversion to glaucoma. The Ocular Hypertension Treatment Study (OHTS), which has provided

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the largest data set of prospectively collected information on patients with OHT, is well suited to studying the association of PPA progression in this group of subjects with the onset of glaucoma. The OHTS data files contain detailed demographic and clinical information, including evaluations of serial stereoscopic optic disc photographs taken annually and results of visual field testing performed every 6 months. The present study was designed to assess digitized photographs to explore whether PPA enlarges over time during the course of OHT and whether enlargement of PPA is associated with conversion to glaucoma.

Methods

Study Population

The patients enrolled in this study participated in the OHTS, whose protocol has been presented elsewhere.[35] The institutional review boards at all clinical sites approved their respective informed consent statements and procedures. The design of the OHTS followed the tenets of the Declaration of Helsinki.[36] The OHTS data set files include information of 3200 eyes from 1600 subjects studied from February 1994 to December 2009, with >300 eyes that converted from OHT to glaucoma through 2008 (Mae Gordon, personal communication, OHTS, January 2009). Determination of conversion to primary OAG (POAG) in the OHTS was defined as the development of a reproducible visual field abnormality and/or a reproducible optic disc change consistent with glaucoma in 1 or both eyes that was attributed to POAG by an end point committee masked to randomized treatment assignment. Definitions for visual field abnormality and optic disc deterioration are detailed elsewhere.[32]

This is a nested case−control study. Cases included 279 eyes of 279 participants with OHT that converted to POAG and controls were 279 eyes of 222 participants with OHT that did not meet conversion criteria in either eye. Case follow-up photographs were those collected at the last follow-up study visit. Control follow-up photographs were selected from eyes of participants who did not convert to glaucoma and matched with respect to eye laterality, participant age within 5 years, and study follow-up visit within 6 months. Controls and cases were matched by the same follow-up visit in all but 2 matches (1%) and by the same age (88% of matches), within 1 year of age (9% of matches), or within 2 to 5 years of age (3% of matches).

Optic Disc Slide Scanning and Digitization

Optic disc photographs in the OHTS were acquired at annual visits for both eyes after pupil dilation. All images were captured using 35-mm film-based technology. The images were then mounted in 2×2-inch slide format, labeled with individual anonymous codes to protect confidentiality, and stored at the Optic Disc Reading Center of the OHTS at the Bascom Palmer Eye Institute, University of Miami School of Medicine. Standard 35-mm Fujifilm 100 ASA (Fuji, Tokyo, Japan) was used for film capture because of its good image quality. Funding from the National Eye Institute supported the creation of a digital archive of all stereoscopic disc photographs collected during the OHTS. All original photographic transparencies of all subjects' visits were then digitized in RGB format using a Nikon Super CoolScan 5000ED scanner with SilverFast Ai software (LaserSoft Imaging Inc., Sarasota, FL) and saved in tagged image file format (.tiff). If the disc photos were taken with a sequential fundus camera, left and right images were scanned individually, cropped with Adobe Photoshop 3.0 (Adobe Systems, Inc., Mountain View, CA), placed side by side, and then saved as a single image of the stereoscopic pair. Disc photos taken with a simultaneous fundus camera were scanned and saved with no image manipulation. All images were labeled after the scanning process and moved to server storage.

Scanned Optic Disc Image Evaluation and PPA Margin Delineation

Baseline and study follow-up visit digital stereoscopic optic disc photographs of eyes with glaucoma and matched controls were retrieved from the server and presented on an interactive battery-free pen and liquid crystal display unit (Cintiq 12WX; Wacom, Vancouver, WA) for evaluation. Stereoscopic disc photographs with poor image quality (e.g., owing to cataract or technical reasons) that prevented reliably outlining the disc margin or the boundaries of the peripapillary zones α and β[37] were excluded and replaced by the one taken immediately after (if a baseline photograph) or immediately before (if a follow-up photograph). Each stereoscopic photograph was evaluated independently by 2 readers (E.S., R.V.) from the Optic Disc Reading Center of the OHTS using a handheld stereoscope (Screen-VU, Portland, OR) to view the images stereoscopically on the liquid crystal display. The Optic Disc Reading Center readers underwent extensive training in identification of optic disc structures and tracing by a senior investigator (D.R.A.).

The drawing tool (pen) was calibrated before each tracing session and standardized in terms of tip size (in pixels) and hardness. The structures to be quantified (optic disc, peripapillary zones α and β areas) were outlined on the inside edge so that the thickness of the trace would be incorporated in the total delineated area. Images were evaluated in a masked fashion without knowledge of the clinical diagnosis or other clinical information.

The border of the optic disc was defined as the inner margin of the peripapillary scleral ring of Elschnig, recognized as a white band seen in part of or all around the circumference of the optic disc, or by the boundary between disc tissue and retinal pigment epithelium when it obscured the scleral ring. The PPA was differentiated into the α-zone and β-zone as described by Jonas et al.[37] The α-zone was defined as an irregular area of hypopigmentation and hyperpigmentation adjacent to the scleral ring or located on the outer side of the β-zone if present. The β-zone, when present, extended from the scleral ring and was characterized by the absent retinal pigment epithelium, making visible the sclera or the choroid with its large vessels. The peripapillary scleral ring was included in the measurements of the β-zone (Fig 1). Because the width of the scleral ring was usually very thin, any error introduced by adding the scleral ring area to the β-zone was considered to be inconsequential. For each stereoscopic image, readers outlined successively 3 concentric regions: The edge of the optic disc, the area occupied by the optic disc and the PPA β-zone, and the region including optic disc and PPA β-zone and α-zone on the right side of the stereo pair, unless the left side provided a better quality image.

Planimetric Analysis

Measuring tools in Adobe Photoshop were used to generate the areas automatically, in pixels, on an outlined image. For each disc image, the software calculated the areas corresponding to disc area, along the inner edge of the scleral ring, if visible, a second area that included the optic disc with any visible scleral rim and the β-zone (if present), and a third area that included the previous plus the α-zone (if present).

The α-zone and β-zone areas (obtained by subtracting the 3 traced outlines) were normalized to the optic disc area by expressing it as a percentage of the disc area to minimize the effects

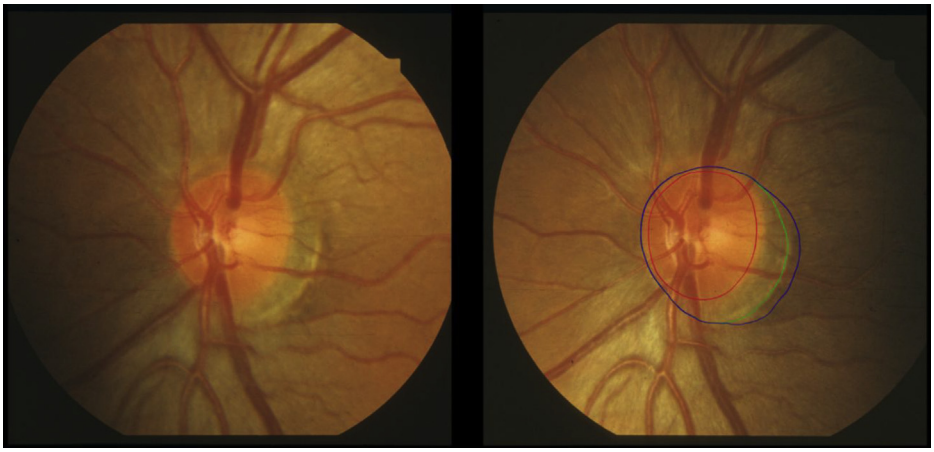

Figure 1. Left eye optic disc photographs of one of the study participants without (left) and with delineation of the disc in red, peripapillary atrophy (PPA) α-zone in green, and PPA β-zone combined with scleral ring in blue (right). In this case, the PPA α- and β-zone margins coincide nasally.

of the difference in camera magnification and/or refraction-related errors.

Statistical Analysis

Paired *t* tests were used to compare the spherical equivalent, optic disc area in pixels, and PPA areas in pixels and in percentage of optic disc. Participant age was compared with the *t* test and gender was compared with chi square test. The intraclass correlation coefficient (ICC) was used to assess between reader agreement for disc, β-zone, and α-zone areas in pixels and the β-zone and α-zone as a percentage of optic disc area. In an ancillary analysis, generalized estimating equations with exchangeable covariance structure and robust estimates were used to account for use of the contralateral eye as a control in >1 matched pair in the comparison of follow-up minus baseline zone areas as a percentage of disc areas. $P \leq 0.05$ was considered significant.

Results

Characteristics of the case and control groups at the baseline visit are summarized in Table 1. Mean age was identical owing to study design. Mean spherical equivalent was also comparable between the 2 groups (paired *t* test). None of the eyes in the 2 groups had a spherical equivalent refractive error more myopic than −9 diopters. Sixteen (5.7%) converted by both optic disc and visual field; 153 (54.8%) converted by optic disc criteria first, and 16 (39.4%) of the 279 cases converted by visual field criteria first.

Table 1. Participant Demographic and Ocular Characteristics at Baseline Visit

Characteristics	Progressive OHT (n = 279)	Nonprogressive OHT (n = 222)	*P*
Mean age (±SD), yrs	58 (9)	58 (9)	0.99
Male sex, no. (%)	157 (56)	117 (53)	0.48
Mean spherical equivalent (±SD), D	−0.56 (2.5)	−0.37 (2.4)	0.36

D = diopter; OHT = ocular hypertension; SD = standard deviation.

Reproducibility of Measurements

An ICC was used to assess between reader agreement for disc, β-zone, and α-zone areas in pixels and β-zone and α-zone as a percentage of optic disc area. Table 2 presents the between-reader reproducibility of baseline and follow-up optic disc, PPA β-zone, and PPA α-zone area measurements for cases and controls based on all images measured. Agreement was assessed before conversion from pixels to percentage of disc area to assess reproducibility of disc measurements and to ensure that the conversion had not adversely impacted the reproducibility of overall measurements. The scale of agreement strength as proposed by Fleiss is as follows: Values >0.75 represent excellent agreement beyond chance, values between 0.40 and 0.75 represent fair to moderate agreement, and values <0.40 represent poor agreement.[38] Between-reader ICCs were excellent for both baseline and follow-up PPA β-zone measurements and moderate for PPA α-zone measurements. In this study, the ICC of between-reader PPA change over time as a percentage of disc area were 0.72 (95% confidence interval [CI]. 0.67−0.75) for the β-zone, considered good reproducibility; and 0.51 (95% CI, 0.45−0.57) for the α-zone, considered fair to moderate. Examination of Bland-Altman plots revealed no systematic differences between readers with respect to size of PPA changes (Fig 2).

Baseline PPA Measurements as a Percentage of Disc Area

Baseline β-zone areas averaged 49.9% (standard deviation, 24.3%; range, 20.1%−143.6%) in cases and 47.4% (standard

Table 2. Between-Reader Reproducibility of Optic Disc and Peripapillary Atrophy Areas before and after Conversion to Percentage of Disc Area

Variables	Preconversion ICC (95% CI), in Pixels	Postconversion ICC (95% CI), in % of Disc Area
Optic disc	0.967 (0.86−0.99)	N/A
β-Zone	0.831 (0.67−0.90)	0.823 (0.77−0.86)
α-Zone	0.582 (0.53−0.63)	0.483 (0.40−0.55)

ICC = intraclass correlation coefficient.

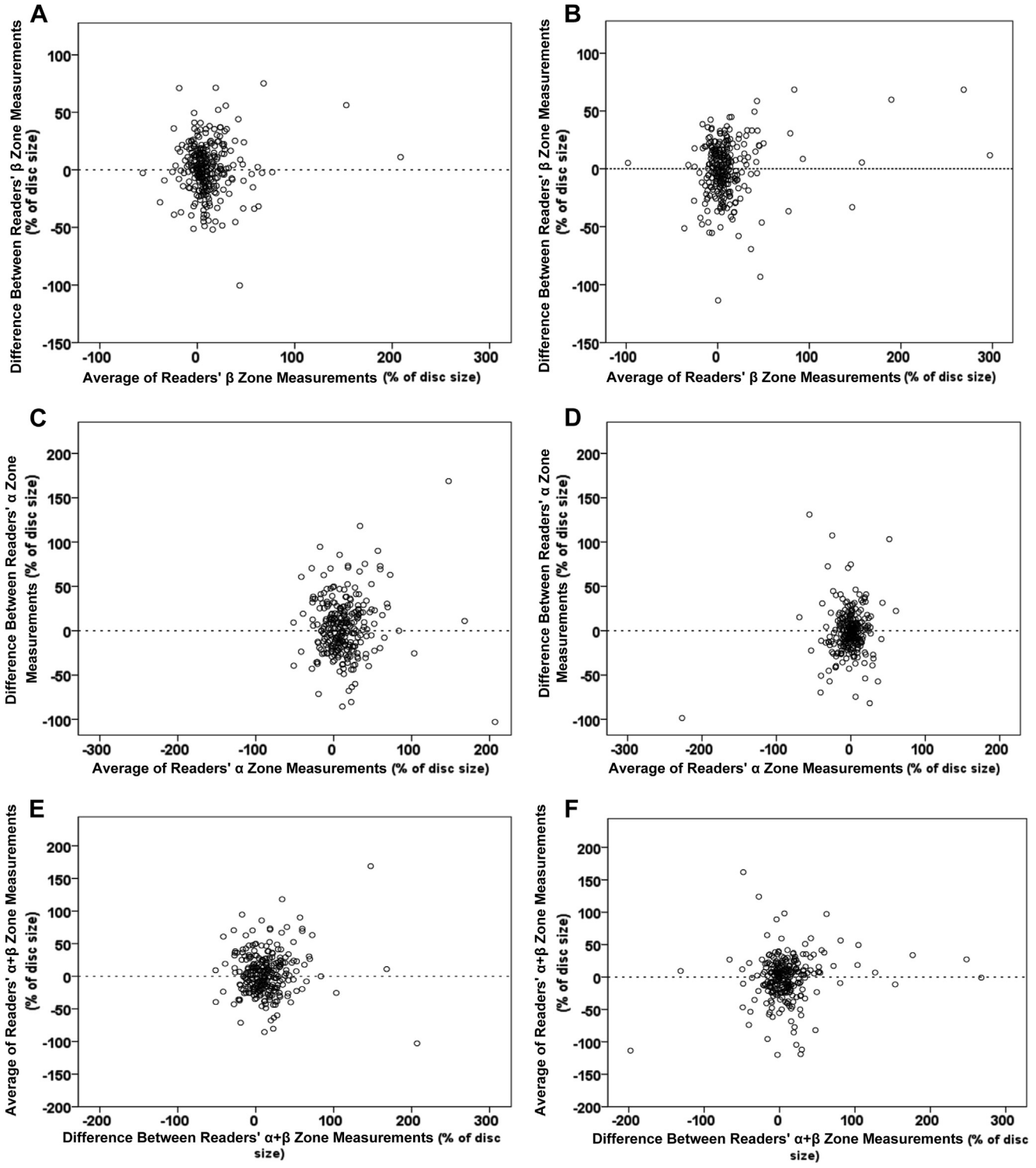

Figure 2. Bland-Altman plots of the difference (percentage of disc size) between the 2 readers against their averages. The plots show the interreader agreement on measurements of change in β-zone (**A** and **B**), α-zone (**C** and **D**), and α-zone and β-zone (**E** and **F**). Plots on the left are for eyes with nonprogressive ocular hypertension and plots on right are for eyes that converted to primary open-angle glaucoma.

Table 3. Mean β-Zone and α-Zone Areas (as a Percentage of Disc Area) at Baseline and Follow-up and Their Difference (Follow-up Minus Baseline) in the Glaucoma Conversion and Control Groups

Groups	Mean β-Zone Area (±SD)	Mean α-Zone Area (±SD)
Percentage of disc area at baseline		
Control	49.9 (24.3)	19.1 (21.0)
Glaucoma	47.4 (20.3)	20.4 (15.8)
*P**	0.18	0.41
Percentage of disc area at follow-up		
Control	59.8 (48.3)	17.5 (13.4)
Glaucoma	57.7 (29.6)	22.4 (17.8)
*P**	0.51	<0.001
Follow-up minus baseline area as a percentage of disc area		
Control	10.1 (33.7)	−1.70 (21.0)
Glaucoma	10.5 (22.6)	2.20 (17.3)
*P**	0.82	0.021

SD = standard deviation.
*Paired *t* test.

deviation, 20.3%; range, 19.2%−246.6%) in controls ($P = 0.18$; paired *t* test). Baseline α-zone areas averaged 19.1% (standard deviation, 21.0%; range, 0%−101.1%) in cases and 20.4% (standard deviation, 15.8%; range, 0%−275.3%) in controls ($P = 0.41$; paired *t* test). At baseline, 24 cases (9%) and 22 controls (8%) had no measurable α-zone, which did not differ significantly between the groups ($P = 0.88$, McNemar test, data not shown). The β-zone was present in all cases and controls, except in 1 control eye, because Elschnig's scleral ring was incorporated to β-zone measurements. Thus, the β-zone measurements, when small, represent measurements of the scleral rim area only without any true β-zone in which retinal pigment epithelium did not completely cover peripapillary choroid. We did not attempt to distinguish these 2 anatomic structures because the scleral rim is small and does not disrupt calculations of any β-zone increase with time.

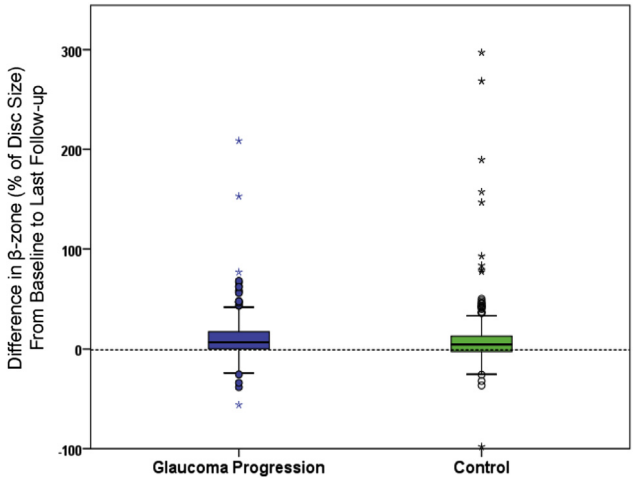

Figure 3. Differences between follow-up and baseline β-zone areas (percentage of disc size) in case and control eyes.

PPA Change over Time as a Percentage of Disc Area

The study follow-up visit at which disc photos used in this analysis were collected ranged from 12 to 168 months (median, 156 months). The 10th and 90th percentiles were 120 and 162 months, respectively, so most follow-up times were within a 3.5-year range of each other (range, 10−13.5 years). Over this time, the β-zone increased by 10% in both cases that converted to OAG ($P < 0.001$, paired *t* test) and unconverted controls ($P < 0.001$, paired *t* test; Table 3). Change in β-zone area (follow-up minus baseline) in cases and controls were not different ($P = 0.82$, paired *t* test; Fig 3). The *P* value was similar when generalized estimating equations were used in an ancillary analysis ($P = 0.87$). There was a highly significant difference ($P < 0.001$) in mean α-zone areas expressed as a percentage of disc area between the 2 groups (Table 3). There was similarly a significant difference between the mean change of α-zone from baseline to follow-up (3.9% difference; $P = 0.021$, paired *t* test). An ancillary analysis using generalized estimating equations produced a similar result ($P = 0.018$). However, this difference included a small increase in cases and an apparent small reduction of α-zone area in the nonconverting controls. The range of the differences was from −60.0% to +242.0% (standard deviation of 27.9% around the mean change of 3.9%); with such an overlap, the small mean change cannot be considered of much importance. Analysis of the combined α-zone and β-zone change over follow-up also failed to show differences between converters to OAG and nonconverter controls ($P = 0.1$, paired *t* test).

Cases that converted by disc criteria (with or without visual field conversion) averaged an 11.5%±23.6% β-zone enlargement as a percentage of the disc area as opposed to 7.1%±18.5% β-zone enlargement in controls; the difference was not significant ($P = 0.17$, *t* test; $P = 0.18$, analysis of covariance accounting for months of follow-up). Whether conversion was by disc or visual field criteria also did not influence the difference in β-zone enlargement rate in cases versus controls ($P = 0.19$, repeated measures analysis of variance test of case/control status with evaluation for potential interaction between β-zone enlargement and study protocol determination of conversion by disc or field criteria). In cases, β-zone enlargement from baseline to last follow-up did not correlate with the time interval (range, 0−156 months) from determination of the end point to the date at which the follow-up disc photograph was obtained (Pearson $r = -0.04$; $P = 0.57$).

Discussion

Because of the uncertainty of the relationship between PPA and the development of glaucoma, the opportunity for a longitudinal study with large number of subjects was the impetus for designing this study. Although PPA has been associated with glaucoma in cross-sectional studies, it is unknown whether PPA or its worsening precedes the development of POAG coincides with it, or is unrelated in time. In addition, the issue of whether PPA is larger in OHT eyes that subsequently convert to glaucoma compared to PPA in nonconverting eyes has been suggested[25] but not definitively explored. Determining whether PPA size at baseline is associated with a greater risk of later conversion of OHT to OAG is of clinical importance because it may allow closer monitoring or earlier treatment of OHT patients who are deemed to be at risk. Alternatively, PPA may enlarge in concert with development and progression of glaucomatous cupping, which is of interest in understanding the pathogenesis of each. The OHTS data set is well suited

for the study of these questions because of a large overall sample size, long-term prospective follow-up, and rigorous criteria for POAG end points.

We found that both at baseline and follow-up, the ICCs were excellent for PPA β-zone and moderate for α-zone measurements in these eyes matched and paired with each other. There was no difference between cases and controls in baseline or follow-up of either the PPA β-zone or α-zone. The magnitude of change in β-zone area over time was similar in cases and controls. In contrast, the change in α-zone area was significantly different between the 2 groups, but small and highly variable. To see whether there was evidence that β-zone enlargement occurred after conversion to glaucoma, we also assessed the strength of correlation between β-zone enlargement and months between conversion and last follow-up in the cases. No correlation was found. Abnormal intraocular pressure and a large β-zone each possibly represent a risk factor, but in combination with other causative risk factors in a quantified manner not yet known, and none of which are necessary if other factors dominate.

Determination of optic disc borders is somewhat subjective and potentially brings a certain degree of variability into the measurements. However, we found excellent between-reader agreements for both PPA zones, which implies that measurement variability did not impact our results. Tuulonen et al[39] evaluated the variability of baseline PPA measurements (in square millimeters) obtained by manual planimetry in 23 eyes of 23 OAG patients and age-matched controls and reported between-observer Pearson correlation values of 0.97 for optic disc area, 0.91 for β-zone area, and 0.63 for α-zone area. The reported agreement is comparable with that in this study.

Unlike some previous studies, we chose to estimate α-zone and β-zone measurements as a percentage of optic disc area rather than absolute areas because optic disc photographs were taken with different cameras having different magnifications and because the clinical parameters needed to calculate the absolute areas were not available. Nevertheless, assuming disc area to be constant over time, a change in the PPA (α-zone or β-zone) area-to-disc ratio should be related to the change in PPA area. The α-zone changes are more difficult to delineate than β-zone changes (especially with media changes over time) and changes are consequently quite variable within each of the study groups. The ICC is only moderate, and the smaller, although significant, reduction in the nonconverter controls (Table 3) is difficult to interpret.

Enlargement of PPA, in particular the β-zone, has been correlated with progressive glaucomatous damage in several studies with various methodologies. Rockwood and Anderson,[15] in a retrospective optic disc stereophotograph review, found a qualitatively noticeable increase in PPA size as a whole in 21% of eyes with progressive glaucoma versus 4% of eyes with nonprogressive glaucoma and eyes with OHT that did not become glaucomatous over a 12-month follow-up period. Interestingly, they also noted that the changes in PPA observed in eyes with progressive glaucoma were both too small and too rare to explain the high prevalence and large size of PPA in eyes with glaucoma. They speculated that eyes with an inherited large β-zone may be more susceptible to the development of glaucoma, a view later shared by Healey et al[40] after their investigation on the inheritance of PPA. Tezel et al[31] analyzed serial optic disc photographs of 350 OHT eyes with 10-year follow-up and observed PPA enlargement in 9.9% of nonprogressive eyes and in 49% of eyes that eventually developed OAG. In another retrospective study[19] performed in 75 glaucomatous eyes with PPA at baseline and a minimum follow-up of 4 years, 93% of the 28 eyes in which progression of PPA was observed showed progressive optic disc damage or visual field loss. Budde and Jonas[16] in a longitudinal large series of OAG, OHT, and normal eyes described a progressive enlargement of PPA β-zone in 2.7% of glaucomatous eyes and in 0.3% of OHT eyes. In eyes with OAG, PPA β-zone enlargement was more frequently observed in eyes with progressive rather than stable glaucoma. On the contrary, after comparing both baseline and progression rates of PPA area and neuroretinal rim area measured with scanning confocal laser tomography every 6 months for 8.6 years in 94 patients with OAG and 7.1 years in 54 normal control subjects, See et al[4] reported similar baseline and follow-up PPA areas in the 2 groups. In addition, they found no correlation between rates of global PPA area and neuroretinal rim area progression in both groups. In agreement with our findings, Quigley et al[5] found no difference in the prevalence of PPA between OHT patients who progressed and those who did not progress to overt glaucoma after a 5-year follow-up. Because the clinical value of PPA with regard to the diagnosis of OAG remains controversial, Ehrlich and Radcliffe[41] used generalized linear models to determine whether clinical PPA assessment improves the prediction of Glaucoma Hemifield Test beyond that of standard assessment of variables such as age, central corneal thickness, intraocular pressure, and cup-to-disc ratio. The results indicated that adding PPA parameters to a model already containing these commonly assessed variables does not improve the ability to discriminate between OAG and no glaucoma status.

The similar rates of PPA β-zone enlargement in converters and in nonconverters found in our series of OHT subjects suggest a lack of relationship between increase in PPA β-zone area and development of glaucomatous damage. This discrepancy compared with the earlier studies described in the previous paragraph may be due to differences in study design (i.e., cross-sectional or longitudinal), follow-up duration, sample size, border delineation methods (i.e., manual or automated), PPA size assessment (i.e., qualitative or quantitative), and definition of glaucoma progression. Our findings are based on manual planimetry performed by 2 independent, masked, and consistent readers on digitized optic disc stereoscopic photographs analyzed with a computerized measuring tool. In some eyes, the PPA β-zone was large and easily detected, but in many others it was small with poorly definable borders, increasing the chance of being overlooked without the detailed evaluation and standardized delineation performed in this study. Surprisingly, none of the earlier studies clearly acknowledged the difficulty associated with delineating PPA boundaries in some eyes, which has led to the erroneous belief that outlining PPA boundaries is always relatively easy. With

our thorough disc assessment and tracing technique, we observed a mean 10% PPA β-zone area enlargement on follow-up photographs in both cases and controls. Of the 28 eyes with quantitative PPA progression described by Uchida et al,[19] 7 (25%) were not detected by qualitative assessment by observers. The average increase in PPA area not detected by qualitative analysis was 8.2% versus a quantitatively detectable increase of 18.3%. We also found diversity between groups in PPA α-zone measurements during follow-up, which we believe generated a difference in α-zone enlargement between cases and controls and an apparent small reduction in α-zone area in nonconverters. Interpretation of this finding is limited because PPA α-zone measurements had a less than optimal reproducibility, as in other studies.

As far as we know, we have studied the largest and longest prospectively collected series of optic disc photographs in OHT patients. Some variability in measurements is introduced by manual delineation of optic disc and α-zone and β-zone margins on stereoscopic disc photographs, but it seems relatively small. New technologies such as computerized optic nerve head analyzers may provide more objective and even more consistent delineation of optic disc and PPA margins and perhaps the ability to detect even smaller changes in the area of PPA more reliably. For example, spectral domain optical coherence tomography (SD OCT) reconstructs "in vivo" 3-dimensional optic disc and peripapillary structures by detecting termination of the various retinal layers.[42–45] Lee et al[42] used SD OCT to evaluate the cross-sectional configuration of α and β-zones in 120 normal eyes, all of which showed an α-zone and 75% presented a β-zone on optic disc photographs. Specific optical coherence tomography findings corresponding to α-zone and β-zone, respectively, were the gradual thinning of retinal layers immediately related to Bruch's membrane (inner segment−outer segment junction of the photoreceptors and the external limiting membrane), found in 87% of the eyes, and absence of the retinal pigment epithelial layer, observed in 100% of the 90 eyes in which β-zone was visible. Kim et al[43] analyzed the continuity of Bruch's membrane in 161 OAG eyes presenting with a β-zone and observed intact Bruch's membrane in 76 eyes (47%). This group was significantly older compared with groups presenting discontinuous or absent Bruch's membrane, suggesting that PPA presenting an intact Bruch's membrane could be an age-related atrophic change and that the pathogenesis of PPA may be diverse. We found an increase in PPA size over time in converters to OAG and controls, indicating that PPA enlargement may be due to other factors, such as age. This observation corroborates the findings of histologic[46] and SD OCT studies.[47]

In conclusion, based on results of previous studies and the findings of our series, it seems that the value of measuring PPA size over time in subjects with OHT for the diagnosis of conversion to glaucoma remains uncertain. Although PPA is seen in patients with glaucoma, clinical decisions should not be based on the presence of and/or change in PPA alone. In OHT subjects, PPA enlargement may occur independently of glaucoma conversion, and systematically with time, suggesting that a substantial part of this phenomenon may be age related.

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*Group members listed online at the Ocular Hypertension Treatment Study can be found in the Appendix (available at www.aaojournal.org).

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Abbreviations and Acronyms:
D = diopters; **ICC** = intraclass correlation coefficient; **OAG** = open-angle glaucoma; **OHT** = ocular hypertension; **OHTS** = Ocular Hypertension Treatment Study; **POAG** = primary open-angle glaucoma; **PPA** = peripapillary atrophy; **SD** = spectral domain; **SD OCT** = spectral domain optical coherence tomography.

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