Effect of Diabetic Retinopathy and Panretinal Photocoagulation on Retinal Nerve Fiber Layer and Optic Nerve Appearance

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Objective: To determine if panretinal photocoagulation (PRP) alters retinal nerve fiber layer (RNFL) thickness and optic nerve appearance.

Methods: Patients with diabetes who did and did not undergo PRP and nondiabetic control subjects were enrolled in a prospective study. Participants underwent optical coherence tomography of the peripapillary retina and optic nerve. Stereoscopic optic nerve photographs were graded in a masked fashion.

Results: Ninety-four eyes of 48 healthy individuals, 89 eyes of 55 diabetic patients who did not undergo PRP, and 37 eyes of 24 subjects with diabetes who underwent PRP were included in this study. Eyes that had been treated with PRP had thinner peripapillary RNFL compared with the other groups; this was statistically significantly different in the inferior ($P = .004$) and nasal ($P = .003$) regions. Optic nerve cupping did not increase with severity of disease classification, but the proportion of optic nerves graded as suspicious for glaucoma or as having nonglaucomatous optic neuropathy did ($P = .008$). These grading categories were associated with thinner RNFL measurements.

Conclusions: Diabetic eyes that have been treated with PRP have thinner RNFL than nondiabetic eyes. Optic nerves in eyes treated with PRP are more likely to be graded as abnormal, but their appearance is not necessarily glaucomatous and may be related to thinning of the RNFL.

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The optic nerve in eyes that have received laser photocoagulation treatment for diabetic retinopathy can appear to have glaucomatous damage. However, many clinicians suspect that the nerve appears damaged because panretinal photocoagulation (PRP) destroys retinal ganglion cells, whose axons form the optic nerve of the eye, not because the patient actually has glaucoma, a disease in which retinal ganglion cells may die from damage originating at the optic nerve.

Visual field testing in this patient population is not helpful, as PRP can cause loss of visual sensitivity in a pattern similar to that of glaucomatous damage. Other disease entities, such as anterior ischemic optic neuropathy, central retinal artery occlusion, age-related macular degeneration, and compressive lesions of the anterior visual system, can likewise lead to a glaucomatous-appearing optic nerve. Trobe et al commented that 20% of eyes with optic atrophy not associated with glaucoma can exhibit disc cupping.

Results from prior studies are inconclusive as to the effects of PRP on the optic nerve. In a masked retrospective study, Johns et al evaluated the stereoscopic disc photographs of 100 patients with proliferative diabetic retinopathy before and 1 year after PRP and saw no significant change. In contrast, Hsu and Chung demonstrated retinal nerve fiber layer (RNFL) thinning in a cohort of 27 eyes with diabetic retinopathy after PRP using scanning laser polarimetry. They did not assess whether there was a relationship between RNFL thinning and optic nerve appearance. This study will investigate changes in RNFL thickness and optic nerve head morphology in diabetic patients with and without PRP to improve our understanding of whether PRP might alter optic nerve appearance and the mechanism by which this occurs.

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Methods: This was a prospective cross-sectional observational case series. The protocol was approved by the institutional review board of the University of California–Davis Office of Human Research Protection and by the ethics committee of the Federal University of São Paulo. All participants signed informed consent forms. We prospectively enrolled 82 patients from the Department of Oph-
Thalamology & Vision Science, University of California–Davis, and 52 subjects from the Department of Ophthalmology, Federal University of São Paulo, during a 2-year period.

Diabetic patients with and without diabetic retinopathy and those who had received PRP for proliferative diabetic retinopathy more than 3 months before the beginning of the study were invited to participate. Nondiabetic control subjects were also enrolled in this cross-sectional study from comprehensive/ophthalmic clinics as well as from a pool of staff volunteers and spouses or friends of patients from both departments of ophthalmology. Subjects were excluded if they had significant ocular disease other than diabetic retinopathy, a history of intraocular pressures greater than 22 mm Hg, a history of treatment for glaucoma, or a family history of glaucoma. Subjects with diabetes were not excluded based on optic nerve appearance alone nor the presence of macular edema. Participants received an ophthalmic evaluation, which included visual acuity assessment, slitlamp examination, intraocular pressure measurement, dilation, grading of diabetic retinopathy according to an international classification system developed by Wilkin-son et al., and grading of the extent of PRP, with mild defined as less than 50% of the peripheral retina treated; moderate, 50% to 75% treated; and heavy, more than 75% treated. The principles of optical coherence tomography have been described elsewhere. Peripapillary RNFL measurements were obtained using optical coherence tomography (Stratus OCT 3, Carl Zeiss Meditech, Dublin, California). Through a dilated pupil, a 3.4 mm–diameter ring was centered around the optic nerve head and 768 A-scans were acquired using the fast RNFL thickness protocol. The following regions were assessed: temporal (316°–3.45°), superior (46°–135°), nasal (136°–225°), and inferior (226°–315°). In clock-hour positions, 3 o’clock was considered temporal; 6 o’clock, inferior; 9 o’clock, nasal; and 12 o’clock, superior. The average thickness (360°) was also measured.

Optic nerve measurements were obtained using the Stratus OCT 3 fast optic disc protocol, which acquires the image with a series of 6 equally spaced radial line scans with a diameter of 4 mm. The following optic nerve parameters were assessed: disc, cup and rim area, cup-disc area ratio, and cup-disc ratio (vertical and horizontal).

At least 3 replicate optical coherence tomography scans were performed for each program. Scans with signal strength of less than 6 as well as those with error messages indicating low analysis confidence, missing data, or poor centration were excluded from analysis. Each scan was carefully reviewed and those with segmentation lines that appeared to deviate from the RNFL were excluded.

Digital stereoscopic photographs of the optic nerves were obtained with the Nidek 3DX camera (Nidek Co Ltd, Fremont, California) from subjects at 1 of the centers (Department of Ophthalmology & Vision Science, University of California–Davis). Two glaucoma specialists (M.C.L. and J.D.B.) who were masked to diagnosis graded each nerve as normal, suspicious for glaucoma (notching, pallor, or cup excavation), or having nonglaucomatous optic neuropathy (diffuse or sectoral pallor without enlargement of the cup-disc ratio). The two observers discussed discrepancies in grading and agreed on a grade.

Statistical analysis was performed using Stata, version 10.1 (Stata Corp, College Station, Texas), and Statistica, version 7.0 (StatSoft Inc, Tulsa, Oklahoma). The Pearson χ² test was used to compare sex between diagnostic groups and the Fisher exact test was used to compare race between the groups. Analysis of variance was performed to compare age between the diagnostic groups. To analyze intraocular pressure, RNFL thickness, and optic nerve head measurements, the generalized estimating equation with exchangeable correlation and robust variance estimator was used to adjust for correlation between measurements from both eyes of the same individual. To compare the proportions of optic nerve head grading categories across the diagnostic groups, a modified version of the Pearson χ² statistic was used to adjust for intrasubject correlation. In light of the multiple comparisons performed, the significance level was set at P = .01 (rather than P = .05) and 99% confidence intervals were reported.

RESULTS

A total of 94 eyes of 48 healthy individuals, 89 eyes of 55 diabetic patients who did not undergo PRP, and 37 eyes of 24 subjects with diabetes and PRP were included in this study. Patient demographic data revealed no statistically significant difference in sex, race proportion, or age among groups (Table 1). Intraocular pressure was statistically significantly different among groups and was slightly higher in diabetic eyes without PRP. Eleven eyes, from all diagnostic classifications, had focal macular laser treatment performed more than 3 months before inclusion in this study: 1 with mild diabetic retinopathy, 6 with moderate diabetic retinopathy, and 4 with PRP.

RNFL THICKNESS

A statistically significant difference in RNFL thickness was detected in the inferior (6- and 7-o’clock meridians) and nasal (average, 10-o’clock meridian) peripapillary regions among the 3 groups when adjusted for study center, age, and race (Figure 1 and Table 2). Compared with normal eyes, those that had PRP treatment had statistically significantly thinner RNFL measurements in the inferior 6-o’clock (P = .001) and 7-o’clock (P = .002) meridians, nasal average (P = .002), and 10-o’clock meridian (P = .001). In comparison with diabetic eyes without PRP, those that had undergone PRP had thinner RNFL measurements in these regions that approached or reached statistical significance (Table 2). For the superior, inferior, and nasal regions, a trend existed in which RNFL measurements in eyes with PRP were thinnest followed by diabetic eyes without PRP and then normal eyes. The RNFL measurements in the temporal peripapillary region were similar among diagnostic groups. The RNFL measurements among diabetic patients without PRP were compared, and when adjusted for study center, age, and race, no statistically significant difference existed in any region (P ≥ .03). Eyes with PRP had thinner average RNFL measurements in the inferior region (111.9 µm) compared with those with moderate (123.3 µm), severe (135.7 µm), or proliferative (131.1 µm) diabetic retinopathy.

OPTIC NERVE HEAD ANALYSIS

No significant differences existed among groups for any of the optic nerve head parameters assessed (disc area, P = .19; cup area, P = .27; rim area, P = .80; cup-disc area ratio, P = .31; vertical, P = .26, and horizontal, P = .57, cup-disc ratio). A nonsignificant trend did exist for larger cup area and cup-disc ratio and smaller rim area for the PRP group vs the other 2.

OPTIC NERVE HEAD GRADING

As severity of disease classification increased, the proportion of optic nerves graded as suspicious for glau-
coma or as having nonglaucomatous optic neuropathy increased while the proportion of nerves graded as normal decreased (Figure 2 and Table 3). The differences among the 3 classification groups were statistically significant ($P = .008$).

The relationship between optic nerve grading and RNFL measurements was assessed and a statistically significant difference in RNFL measurements among optic nerve grade categories was noted (Figure 3 and Table 3). Nerves graded as nonglaucomatous optic neuropathy were associated with thinner RNFL compared with the other 2 classification groups for average, superior, and inferior measurements. Optic nerves graded as suspicious for glaucomatous optic neuropathy were associated with thicker RNFL than those graded as nonglaucomatous optic neuropathy but thinner than those graded as normal.

| Table 1. Patient Demographics |
|-----------------------------|------------------|------------------|------------------|------------------|
| Characteristic               | Patients With Normal Eyes | Patients With Diabetic Retinopathy |                             |                             |
|                             | (n=48)             | Without PRP (n=55) | With PRP (n=24) | $P$ Value         |
| No. of eyes                  | 94                | 89                | 37              | NA               |
| Sex, No.                     |                   |                   |                 |                  |
| M                            | 17                | 28                | 12              | .09              |
| F                            | 31                | 27                | 12              |                  |
| Race, No.                    |                   |                   |                 |                  |
| White                        | 40                | 43                | 19              |                  |
| Black                        | 5                 | 6                 | 3               |                  |
| Hispanic                     | 0                 | 4                 | 1               | .09              |
| Asian                        | 3                 | 2                 | 1               |                  |
| Age, mean (SD), y            | 57.3 (11.0)       | 60.1 (10.8)       | 58.5 (9.9)      | .41              |
| Time since diabetes diagnosis, median (range), y | NA | 16 (1-60) | 17 (3-44) | NA |
| Visual acuity, median (range), logMAR | 0.0 (0.0-0.2) | 0.2 (0.0-1.4) | 0.2 (0.0-1.5) | NA |
| Intraocular pressure, mean (SD), mm Hg | 14.7 (2.6) | 16.3 (3.3) | 15.3 (3.1) | .02 |
| Time since last PRP session, median (range), mo | NA | NA | 15 (3-276) | NA |
| PRP grade, No.               |                   |                   |                 |                  |
| Mild                         | NA                | NA                | 8               |                  |
| Moderate                     |                   |                   | 19              | NA               |
| Heavy                        |                   |                   | 10              |                  |

Abbreviations: NA, not applicable; PRP, panretinal photocoagulation.
This study showed a statistically significant difference in RNFL thickness in the inferior and nasal peripapillary regions among controls, diabetic patients without PRP, and diabetic patients with PRP. For these regions, a trend existed in which RNFL measurements in eyes with PRP were thinnest, followed by diabetic eyes without PRP and then normal eyes.

Diabetic subjects with and without PRP were more likely to have nerves graded as abnormal compared with control subjects. Nerves graded as suspicious for glaucoma or as having nonglaucomatous optic neuropathy were associated with thinner RNFL in specific regions.

Changes in the RNFL in diabetic eyes after PRP have been investigated by Hsu and Chung,11 but the effect of diabetes alone, without PRP, was not taken into account in their study. The presence of diabetes itself can cause neurodegenerative changes in the retina. Studies using diabetic rats show a loss of retinal ganglion cells and thinning of the retinal inner and outer plexiform nuclear layers18 and a loss of retinal axons.19,20 Atrophy of the retinal neural cells in human cadaver eyes of diabetic patients have been documented,21,22 and in vivo photographic studies show loss of the nerve fiber layer, which correlates with severity of diabetic retinopathy.23 Clinically available devices such as scanning laser polarimetry and optical coherence tomography have also been used to show that diabetic patients without background diabetic retinopathy and those with nonproliferative diabetic retinopathy have thinner RNFL compared with control subjects.15,24-26 A study by Takahashi et al27 suggests that RNFL thinning in diabetes increases with worsening disease severity. We did not find a statistically significant difference in RNFL measurements among diabetic eyes without PRP with varying severity of retinopathy. However, our study differs from that by Takahashi et al in our inclusion of eyes with macular edema, which could be a possible confounding factor.

In studying the effect of PRP on RNFL thickness, we included a cohort of eyes with diabetes; our intent was to differentiate the effect of laser treatment from the effect of the disease process itself. In several regions around the optic nerve, RNFL in the PRP group was thinner than in the diabetic group without PRP; these results approached statistical significance (Figure 1 and Table 2). In addition, eyes with PRP had thinner RNFL than those with moderate to proliferative diabetic retinopathy in the inferior peripapillary region. Our data suggest that PRP may thin the RNFL beyond the effects of diabetes alone, but the possibility that this observation may be due to worsening retinal ischemia in eyes with proliferative diabetic retinopathy after PRP also needs to be entertained.

Most previously published literature regarding RNFL and diabetes focuses on the effect of diabetes on the reti-
nal layers and do not correlate this with optic nerve appearance nor comment on how this might be confused with glaucoma.13,15,26 Our study assessed the morphological appearance of the optic nerve as assessed by optical coherence tomography and stereophotography and correlated this with RNFL measurements. Optical coherence tomography assessment of optic nerve structure did not show significantly greater cupping in the optic nerves of diabetic eyes, though this trend did exist in our study. These findings are consistent with population studies in which optic nerves do not have a consistently greater cup-disc ratio in the diabetic eye. The Wisconsin Epidemiologic Study of Diabetic Retinopathy28 showed that severity of diabetic disease and the presence of PRP did not relate to larger cup-disc ratio. Likewise, in a photographic study of optic nerve appearance, Königsreuther and Jonas29 did not find a significant difference in cup-disc ratio between diabetic eyes with varying degrees of disease severity and normal eyes.

In our study, eyes that had been treated with PRP were more likely to be graded as abnormal owing to nonglaucomatous optic neuropathy. This grading category would describe a nerve that is not cupped like a glaucomatous nerve, but one that shows diffuse or sectoral pallor. In specific regions, the RNFL was thinnest in eyes graded in this category. These findings suggest that eyes with PRP treatment that have abnormal-appearing nerves are more likely to have thinner RNFL. Previous studies have also noted optic nerve head pallor in diabetic eyes with PRP treatment1 and in eyes with diabetes alone.29 The presence of abnormal-appearing optic nerves in diabetes may be due to direct damage from glycation end products of diabetes24,30; however, it may also be due to dysfunction or loss of RNFL, which may be explained by several mechanisms, including impairment of ganglion cell retrograde axonal transport,19,31 apoptosis of ganglion cells,18,32 and thermal damage from photocoagulation.1

This study and others28,29,33 demonstrate that optic nerve cupping is not a feature of diabetes as it is in glaucomatous eyes despite both disease entities exhibiting RNFL wedge defects.23 An explanation for the lack of optic nerve cupping in diabetic eyes may be found by examining the way in which cells at the optic nerve head respond to nonglaucomatous damage. For example, after transection of the optic nerve at the orbital apex in primate eyes, astrocytes filled in areas of damage at the optic nerve head, precluding cupping.34 The absence of optic nerve cupping in diabetes reinforces the idea that glaucoma is not a disease that originates with retinal ganglion cell damage, rather that it is the sequela of some event in the optic nerve that causes retinal ganglion cell damage, such as a disturbance in the lamina cribrosa.2,35,36

The prevalence of diabetes in a recent survey of the US population in 2000 was estimated at 7.3%.37 As noted by Takahashi et al.,27 when patients with diabetes are being evaluated for glaucoma, one must keep in mind that the RNFL may be thin from diabetes itself. The use of RNFL imaging for glaucoma diagnosis in this patient population must therefore be made with caution.

Table 3. Optic Nerve Head Grading by Diagnostic Group and Comparison With Retinal Nerve Fiber Layer Thickness

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal Eyes (n = 106)</th>
<th>Eyes Suspicious for Glaucomatous Optic Neuropathy (n = 15)</th>
<th>Eyes With Nonglaucomatous Optic Neuropathy (n = 14)</th>
<th>P Value</th>
<th>Adjusted P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic group, No. (%)</td>
<td>60 (92)</td>
<td>3 (5)</td>
<td>2 (3)</td>
<td>.008</td>
<td>P Value</td>
</tr>
<tr>
<td>Diabetic retinopathy without PRPb</td>
<td>34 (71)</td>
<td>8 (17)</td>
<td>6 (12)</td>
<td>.08</td>
<td>Adjusted P Valuea</td>
</tr>
<tr>
<td>Diabetic retinopathy with PRPb</td>
<td>12 (55)</td>
<td>4 (18)</td>
<td>6 (27)</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>Retinal nerve fiber layer thickness, mean (SD), µm</td>
<td>97.9 (12.1)</td>
<td>95.9 (13.0)</td>
<td>85.7 (14.3)</td>
<td>.04</td>
<td>.006</td>
</tr>
<tr>
<td>Superior</td>
<td>119.8 (18.7)</td>
<td>115.8 (17.9)</td>
<td>95.0 (22.9)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Inferior</td>
<td>71.8 (14.9)</td>
<td>79.1 (29.2)</td>
<td>68.5 (22.0)</td>
<td>.34</td>
<td>.16</td>
</tr>
<tr>
<td>Nasal</td>
<td>125.1 (18.5)</td>
<td>113.8 (15.7)</td>
<td>110.4 (21.7)</td>
<td>.02</td>
<td>.008</td>
</tr>
<tr>
<td>Average</td>
<td>74.8 (17.9)</td>
<td>73.8 (17.1)</td>
<td>68.6 (15.6)</td>
<td>.54</td>
<td>.32</td>
</tr>
</tbody>
</table>

Abbreviation: PRP, panretinal photocoagulation.

a Adjusted for age and race.
b Relative frequency within each row.

Figure 3. Optic nerve grade and retinal nerve fiber layer (RNFL) measurements.
ies of RNFL in diabetic patients, in which only the superior region showed significant thinning.\textsuperscript{15,25,26} More microaneurysms and acellular capillaries\textsuperscript{26} in the superior portion of the retina and possible differences in retinal blood flow in this region have been offered as an explanation for this regional finding.\textsuperscript{26} We do not have an explanation for why we found significant thinning in the inferior region.

We also included 11 eyes that had undergone focal macular laser treatment more than 3 months before the study. The inclusion of these eyes may have influenced RNFL measurements, though no significant difference among groups was found in this study in the temporal peripapillary region, an area that would have been affected by a macular laser. Past reports have suggested that myopia and longer axial length may be related to thinner RNFL measurements\textsuperscript{39,40}; however, refractive error was not prospectively collected in this study.

In conclusion, diabetic eyes with PRP have thinner RNFL than healthy nondiabetic eyes. Our study shows that optic nerves in eyes treated with PRP are more likely to be graded as abnormal but that the appearance of these nerves is not necessarily glaucomatous. The mechanism of abnormal optic nerve appearance in this setting may be related to thinning of the RNFL.

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REFERENCES