Peripheral Lesions Identified on Ultrawide Field Imaging Predict Increased Risk of Diabetic Retinopathy Progression over 4 Years

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Objective: To determine whether peripheral diabetic retinopathy (DR) lesions identified on ultrawide field (UWF) imaging are associated with increased DR progression.

Design: Prospective, longitudinal cohort.

Participants: Two hundred eyes of 100 participants previously enrolled in a comparative instrument validation study.

Methods: Baseline mydriatic 7-standard field Early Treatment Diabetic Retinopathy Study (ETDRS) photographs and UWF images were obtained. On UWF images, DR lesions with a greater extent outside versus inside standard ETDRS fields were defined as predominantly peripheral lesions (PPLs). Follow-up ETDRS photographs were obtained 4.2±0.3 years after baseline. Baseline and follow-up DR severity were graded from ETDRS photographs.

Main Outcome Measures: Rates of 2-step or more progression and progression to proliferative DR (PDR) in eyes with PPLs compared with eyes without PPLs identified on UWF imaging at baseline.

Results: In eyes without PDR (n = 109) at baseline, 56 (51%) had at least 1 field with PPLs and 43 (39%) had DR progression. Compared with eyes without PPLs, eyes with PPLs had a 3.2-fold increased risk of 2-step or more DR progression (6 [11%] vs. 19 [34%]; P = 0.005) and a 4.7-fold increased risk for progression to PDR (3 [6%] vs. 14 [25%]; P = 0.005). These findings remained statistically significant after adjusting for gender, diabetes type, diabetes duration, hemoglobin A1c (HbA1c) levels, and baseline DR severity. Increasing extent of fields with PPLs increased the risk for 2-step or more DR progression (P = 0.004) and progression to PDR (P = 0.009).

Conclusions: Presence and increasing extent of PPLs were associated with increased risk of DR progression over 4 years, independent of baseline DR severity and HbA1c levels. Increasing extent of PPLs substantially increased the risk of DR progression and progression to PDR, especially with less severe DR at baseline. These findings demonstrate that detailed peripheral retinal evaluation provides important information that is necessary to assess completely the risk of DR progression. Ophthalmology 2015;122:949-956 © 2015 by the American Academy of Ophthalmology.

See Editorial on page 869.

The established gold standard for determining severity of diabetic retinopathy (DR) is the extended modified Airlie House classification used in the Early Treatment Diabetic Retinopathy Study (ETDRS).1 This rigorously standardized classification scheme provides a grading scale characterized by evaluation of the location and extent of specific retinal lesions in the posterior pole that are highly predictive of the risk of DR progression over time.1 Detailed ETDRS severity grading is derived from rigorous evaluation of 30° retinal images, 14 images per eye, from 7 standard defined retinal fields that encompass in total approximately 30% of the entire retinal surface. The ETDRS grading scale describes 13 distinct levels, ranging from absence of DR to the most severe manifestations of the disease with good reproducibility, and has been used to define both overall DR severity and changes in severity over time.2 The detailed ETDRS classification of DR is used widely in research settings, including multicenter clinical trials that have set the standard of care for DR and diabetic macular edema.1,3,4,5 This accepted DR scale serves as the basis for clinical evaluation of severity, providing an estimated risk of progression and informing follow-up timing recommendations by eye care professionals worldwide.6

Clinical observations and previous retinal imaging studies have demonstrated that substantial pathologic features can develop or be present in the retinal periphery in areas not evaluated by 7-standard field ETDRS.
photography. 5–8 When the original ETDRS criteria were developed, systematic imaging of the retinal periphery was not technically feasible, and, consequently, ETDRS grading did not include evaluations of these peripheral lesions.

With the advent of commercially available high-resolution ultrawide field (UWF) scanning laser ophthalmoscopes, approximately 82% of the retinal surface can now be captured readily in a single image, which permits evaluation of peripheral retinal lesions both within and outside the area typically encompassed by the 7 standard ETDRS fields. Independent groups have demonstrated substantial agreement between UWF images and ETDRS imaging for grading of DR severity. 9,10 In addition, UWF imaging has demonstrated that diabetic retinal lesions occur in the retinal periphery outside of the ETDRS fields in up to 40% of eyes and that these lesions may result in a more severe level of ETDRS DR severity grading in 10% of eyes. 7,11,12

Given that UWF images identify peripheral DR lesions that are not visualized using 7-standard field ETDRS photography, a key clinical question is whether the evaluation of these peripheral retinal lesions provides additional prognostic value with regard to risks of DR onset, progression, or outcomes. Thus, using UWF retinal imaging, we sought to determine whether the predominance of peripheral retinal lesions in any field peripheral to the area visualized by 7-standard field ETDRS photography may be predictive of an increased risk of DR progression or onset of proliferative DR (PDR).

Methods

This prospective, longitudinal cohort study involved 200 eyes of 100 patients who had been enrolled in a previously published prospective, comparative instrument validation study. 9,12 The study designs of both the initial validation study and longitudinal follow-up study were consistent with the tenets of the Declaration of Helsinki and were approved by the Committee on Human Studies of the Joslin Diabetes Center. Patients invited to participate in the longitudinal study were asked to return and provided informed consent again before participation and follow-up retinal imaging. The conduct of the study complied with the Health Insurance Portability and Accountability Act.

The participants in the initial validation study were recruited at the Beetham Eye Institute of the Joslin Diabetes Center as they arrived for regularly scheduled eye appointments. Patients were eligible for the initial validation study if they met all the following inclusion criteria: age 18 years or older, diagnosis of type 1 or type 2 diabetes mellitus as defined by the American Diabetes Association, 7,12,13 willingness to comply with the study imaging procedures, and willingness to sign the institutionally approved informed consent form for this study. Patients were excluded from the initial validation study if they had no history of diabetes, had a history of a condition in either eye that might preclude pupil dilation, or were using eye drops (mydriatic or miotic) that would alter pupil size or reactivity. Patient enrollment was stratified to ensure the inclusion of a wide distribution of various levels of DR, ranging from no DR (ETDRS level 10) to high-risk PDR (ETDRS level 75).

The study methodology for retinal imaging and evaluation has been described in detail in prior publications. 9,12 Briefly, certified photographers obtained both mydriatic nonsimultaneous, stereoscopic 7-standard field ETDRS photographs using 35-mm color slide film with a Zeiss (FF4) 30° fundus camera (Carl Zeiss Meditec, Inc, Dublin, CA) and mydriatic nonsimultaneous stereoscopic 200° UWF images using the Optos P200MA (Optos plc, Dunfermline, Scotland, UK). The imaging was completed in all 200 eyes of 100 patients. Stereoscopic 7-field ETDRS 35-mm color film slides were evaluated on a standard slide light box through Donaldson viewers according to ETDRS protocol by a masked grader (P.S.S.) experienced in grading DR. Retinal findings were recorded directly onto a standardized electronic template modified from the Wisconsin Reading Center ETDRS retinal evaluation form using unique patient study identification numbers. Grading was performed using the ETDRS protocol to determine the presence and severity of the following lesions: hemorrhages, microaneurysms, or both (H/Ma); intraretinal microvascular abnormalities (IRMA); venous beading (VB); cotton wool spots; hard exudates; retinal thickening; new vessels on the disc; new vessels elsewhere (NVE) on the retina; preretinal hemorrhage; vitreous hemorrhage; and traction retinal detachment.

Baseline mydriatic UWF images were evaluated specifically for the distribution of H/Ma, VB, IRMA, and NVE. The UWF images were compared visually with a standard ETDRS 7-field montage template 12 (Fig 1), and distribution of each lesion (H/Ma, VB, IRMA, and NVE) was characterized in fields 3 through 7 of every image as follows: (1) lesion predominantly or only present within ETDRS fields, (2) lesion predominantly or only present outside ETDRS fields (Fig 1), (3) lesion distributed approximately equally in areas imaged and not imaged by ETDRS fields, (4) ETDRS field notgradable, and (5) peripheral field notgradable.

For a specific field, a lesion was considered predominantly peripheral if more than 50% of the lesion being graded was in the retinal peripheral field compared with the modified ETDRS field (e.g., peripheral field 4 compared with ETDRS field 4). 12 Severity grading took into account both number and extent of the lesion being graded within the field. A lesion was considered uniformly distributed in a specific field if the severity of the lesion was equivalent (±10% by reader decision) both within and outside the ETDRS field.
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Statistical Analysis

Nonparametric analyses (Wilcoxon rank-sum tests) were used to compare distributions of continuous variables between groups of eyes with versus without PPLs. The Fisher exact test or chi-square test was used to compare frequencies of categorical variables as appropriate. In addition to these unadjusted analyses, logistic regression models were created with either 2-step or more DR progression or PDR onset as the dependent variable, with the presence and extent of PPLs as the major covariate of interest. These multivariate models also adjusted for potential confounders such as gender, diabetes type, diabetes duration, and glycemic control over the 2 years before baseline imaging. All analyses were performed using SAS software version 9.3 (SAS Inc, Cary, NC).

Results

Characteristics of the Follow-up Cohort

All patients in the original cohort (n = 100) were invited to participate via telephone and certified mail. A total of 91 participants (91%) were alive at follow-up. Patients were imaged during their regularly scheduled appointment or at a specifically designated study visit. Follow-up ETDRS photography was obtained in 74 living participants (81%) and 146 eligible eyes (80%).

The baseline characteristics of the follow-up cohort are presented in Table 1. There was no significant difference in baseline age, race, diabetes type, diabetes duration, visual acuity, DR severity, or 2-year prior hemoglobin A1c (HbA1c) levels between patients who participated versus those who did not participate. There was no difference in the baseline proportion of female participants compared with the subgroup lost to follow-up. A greater proportion of female participants completed follow-up and were re-imaged (57% vs. 33%; P < 0.01). The mean time from baseline to follow-up imaging was 4.2±0.3 years.

Presence of Predominantly Peripheral Lesions

Baseline UWF images were evaluated for the presence or absence of PPLs. There were no significant differences in baseline demographics among eyes with PPLs compared with eyes without PPLs. Baseline and 4-year follow-up DR severity in eyes are presented in Table 2. Baseline characteristics by presence, extent, and severity of PPLs in eyes with no PDR are presented in Table 3. The PREP study characterized the follow-up cohort are presented in Table 1. There was no significant difference in baseline age, race, diabetes type, diabetes duration, visual acuity, DR severity, or 2-year prior hemoglobin A1c (HbA1c) levels between patients with versus without PPLs. The Fisher exact test or chi-square test was used to compare frequencies of categorical variables as appropriate. In addition to these unadjusted analyses, logistic regression models were created with either 2-step or more DR progression or PDR onset as the dependent variable, with the presence and extent of PPLs as the major covariate of interest. These multivariate models also adjusted for potential confounders such as gender, diabetes type, diabetes duration, and glycemic control over the 2 years before baseline imaging. All analyses were performed using SAS software version 9.3 (SAS Inc, Cary, NC).

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Table 1. Demographic Features of the Study Population at Baseline (n = 74 patients)

<table>
<thead>
<tr>
<th>Baseline Features</th>
<th>Mean ± Standard Deviation (Range) or No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.1±14.2 (18–78)</td>
</tr>
<tr>
<td>Female/male</td>
<td>42 (56.8)/32 (43.2%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62 (83.8%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (8.1%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2 (2.7%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Other/ unspecified</td>
<td>3 (4.0%)</td>
</tr>
<tr>
<td>Diabetes type 1/type 2</td>
<td>36 (49%)/38 (51%)</td>
</tr>
<tr>
<td>Diabetes duration (yrs)</td>
<td>22.9±11.9 (&lt;1–49)</td>
</tr>
<tr>
<td>2-year average HbA1c, % (n = 55)</td>
<td>8.0±1.5 (5.2–15.2)</td>
</tr>
<tr>
<td>Number of measurements</td>
<td>5.2±3.0 (1–16)</td>
</tr>
<tr>
<td>ETDRS electronic visual acuity*</td>
<td></td>
</tr>
<tr>
<td>Median letter score (Snellen equivalent)</td>
<td>85 (20/20)</td>
</tr>
<tr>
<td>Range letter score (Snellen equivalent)</td>
<td>55–98 (20/80–20/10)</td>
</tr>
<tr>
<td>≥20/20</td>
<td>104 (71.2%)</td>
</tr>
<tr>
<td>&lt;20/20–≥20/40</td>
<td>35 (24.8%)</td>
</tr>
<tr>
<td>&lt;20/40–20/100</td>
<td>7 (4.8%)</td>
</tr>
<tr>
<td>Duration from baseline imaging (yrs)</td>
<td>4.2±0.3 (3.1–4.9)</td>
</tr>
</tbody>
</table>

ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = hemoglobin A1c.
*Data from 146 eyes of 74 patients and presented as no. (%) or mean ± standard deviation (range).

The ETDRS field. Any DR lesion type that was present predominantly in any peripheral field was defined as a predominantly peripheral lesion (PPL).

Approximately 4 years after initial imaging, follow-up standard digital ETDRS imaging was performed and evaluated in a similar manner by the centralized reading center. Digital ETDRS images were viewed stereoscopically using a handheld Screen-Vu stereoscope viewer (PS Manufacturing, Portland, OR) and displayed on 27-inch, color-calibrated, high-definition liquid crystal display monitors (model VG278H; Asus, Taipei, Taiwan) with Quadro 600 video cards (Nvidia, Santa Clara, CA). All eyes identified at follow-up with any change (progression or regression) in DR severity level from baseline were adjudicated independently by a second grader (J.D.C.) masked to all prior gradings. Severity of DR was defined in relation to the ETDRS severity scale as follows: no DR (ETDRS level 10), questionable or minimal (ETDRS level 14, 15, or 20), mild nonproliferative DR (NPDR; ETDRS level 35), moderate NPDR (ETDRS level 43 or 47), severe NPDR (ETDRS level 53a–d), very severe NPDR (ETDRS level 53e), PDR (ETDRS level 60, 61, or 65); and PDR high risk (ETDRS level 71, 81, or 85). These DR severity levels have been validated in multiple prior retinal imaging studies.9,12,14–16

Table 2. Retinopathy Progression on Early Treatment Diabetic Retinopathy Study Photographs after 4 Years in Eyes with Nonproliferative Diabetic Retinopathy at Baseline (n = 109)

<table>
<thead>
<tr>
<th>Baseline Nonproliferative DR Severity</th>
<th>None</th>
<th>Questionable</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very Severe</th>
<th>Proliferative DR</th>
<th>HRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>9</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Questionable</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>3</td>
<td>0</td>
<td>18</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>29</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Very severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

DR = diabetic retinopathy; HRC = proliferative diabetic retinopathy with high-risk characteristics.

*Retinopathy progression at year 4 was observed in 42 eyes (39%).
Table 3. Subject Characteristics by Extent and Severity of Predominantly Peripheral Lesions in Eyes with No Proliferative Diabetic Retinopathy at Baseline (n = 109 eyes)

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>Eyes with Predominantly Peripheral Lesions (n = 56)</th>
<th>Eyes with Predominantly Peripheral Lesions (n = 53)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>52.4 (14.8)</td>
<td>55.4 (15.7)</td>
<td>0.3489</td>
</tr>
<tr>
<td>Gender (female/male)</td>
<td>27 (51)/26 (49)</td>
<td>31 (55)/25 (45)</td>
<td>0.5056</td>
</tr>
<tr>
<td>White race</td>
<td>44 (85)</td>
<td>49 (88)</td>
<td>0.2606</td>
</tr>
<tr>
<td>Diabetes type 1/type 2</td>
<td>22 (42)/31 (58)</td>
<td>27 (48)/29 (52)</td>
<td>0.4818</td>
</tr>
<tr>
<td>HbA1c (hemoglobin A1c)</td>
<td>9.8 (2.2)</td>
<td>10.1 (2.4)</td>
<td>0.8021</td>
</tr>
<tr>
<td>DR severity</td>
<td>No DR: 12 (23)</td>
<td>6 (11)</td>
<td>0.0071</td>
</tr>
<tr>
<td></td>
<td>Mild NPDR: 15 (28)</td>
<td>18 (33)</td>
<td>0.4975</td>
</tr>
<tr>
<td></td>
<td>Moderate NPDR: 19 (36)</td>
<td>26 (48)</td>
<td>0.0821</td>
</tr>
<tr>
<td></td>
<td>Severe NPDR: 6 (11)</td>
<td>5 (9)</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>Very severe NPDR: 1 (2)</td>
<td>1 (2)</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Figure 2. Distribution of predominantly peripheral diabetic retinopathy lesions by lesion type in eyes without proliferative diabetic retinopathy on Early Treatment Diabetic Retinopathy Study photographs at baseline (n = 56 eyes). H/Ma = hemorrhages, microaneurysms, or both; IRMA = intraretinal microvascular abnormalities; NVE = new vessels elsewhere; VB = venous beading.

had DR progression. In this group, 56 (51%) had at least 1 field with PPLs, and the most common PPL identified on UWF images was H/Ma. Predominantly peripheral H/Ma were present in 95% of eyes with PPLs (Fig 2). Predominantly peripheral IRMA, VB, and NVE were observed in 50%, 16%, and 4% of eyes, respectively. This peripheral distribution of lesion types was similar to the distribution of lesion types observed in the posterior retina, which had 82% H/Ma, 52% IRMA, and 27% VB.

The complete distribution of combinations for PPL types in eyes with no baseline PDR on ETDRS photographs is shown in Figure 2: H/Ma were present in 45% and H/Ma plus IRMA were present in 38% of eyes with PPL. Other PPL combinations were much less frequent. In eyes with baseline PDR (n = 37), 19 (51%) had at least 1 field with PPLs, and H/Ma again were the most common PPL, being present in 16 eyes (43%). In these eyes with baseline PDR, predominantly peripheral VB, IRMA, and NVE were present in 7 (19%), 11 (30%), and 8 (22%) eyes, respectively.

Impact of Peripheral Lesions on Diabetic Retinopathy Progression

Among eyes with no PDR at baseline, those with any peripheral field containing PPLs had a 3.2-fold increased risk of 2-step or more DR progression (6 [11%] vs. 19 [34%]; P = 0.005) compared with eyes without PPLs. In addition, these eyes with PPLs had a 4.7-fold increased risk for progression to PDR (3 [6%] vs. 14 [25%]; P = 0.005) compared with eyes without PPLs. These findings remained statistically significant for DR progression (P = 0.042; odds ratio [OR], 0.219; 95% confidence interval [CI], 0.051–0.946) but were not significant for PDR onset (P = 0.082; OR, 0.113; 95% CI, 0.010–1.333) after adjusting for baseline DR severity, 2-year prior HbA1c levels, DM duration, and DM type (Table 4).

The 4-year rates of DR progression for each baseline DR severity level of eyes with no PDR at baseline (n = 109) and either presence or absence of PPLs are presented in Figure 3. The diagonal line represents no change in DR severity over the 4-year period. Circles centered above the diagonal represent DR progression, those centered below represent DR regression, and the size of the circle represents the number of patients at that point. In eyes without PPLs (left panel), only eyes with severe or very
severe NPDR at baseline progressed to PDR. However, in eyes with PPLs (right panel), there were many more eyes with DR progression compared with those without PPLs at baseline. This was especially evident for eyes with more advanced DR at baseline. Furthermore, many more eyes progressed to PDR, and they did so from less severe levels of baseline DR than eyes with predominantly posterior lesions.

**Effect of Predominantly Peripheral Lesions on Diabetic Retinopathy Progression in Eyes with No Diabetic Retinopathy Evident on Early Treatment Diabetic Retinopathy Study Photographs at Baseline**

There were 18 eyes with no DR at baseline based on ETDRS photography. In 12 (67%) of these eyes, no additional peripheral DR lesions were identified on UWF images. In 6 eyes (33%), additional DR lesions were identified, and thus the eyes could have been graded as mild NPDR based on UWF image findings. All lesions showed H/Ma located outside the fields covered by ETDRS photographs, and none of the eyes had involvement of more than 1 peripheral field. At 4 years of follow-up, the proportion of eyes in which DR developed was 2.5-fold greater in the eyes with PPLs identified on UWF (83% vs. 33%; \( P = 0.004 \) for 2-step or more DR progression; \( P = 0.009 \) for PDR onset). These relationships remained significant even after correcting for baseline diabetes type, diabetes duration, and 2-year HbA1c levels (\( P = 0.039 \), 2-step or more DR progression; \( P = 0.042 \), PDR onset). The ORs for 2-step or more progression given baseline PPLs were 6.864 (95% CI, 0.597–78.914), 6.697 (95% CI, 1.929–23.251), and 1.910 (95% CI, 0.453–8.058) for mild, moderate, and severe or very severe NPDR, respectively. The ORs for onset of PDR were 6.864 (95% CI, 0.597–78.914), 8.064 (95% CI, 2.023–32.150), and 1.479 (95% CI, 0.384–5.690) for mild, moderate, and severe or very severe NPDR, respectively.

**Table 4. Effect of Baseline Predominantly Peripheral Lesions on Retinopathy Progression after 4 Years in Eyes with No Proliferative Diabetic Retinopathy at Baseline (n = 109)**

<table>
<thead>
<tr>
<th>Extent of Diabetic Retinopathy Worsening*</th>
<th>Eyes without Predominantly Peripheral Lesions (n = 53), no. (%)</th>
<th>Eyes with Predominantly Peripheral Lesions (n = 56), no. (%)</th>
<th>P Value†</th>
<th>Corrected P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 step or more</td>
<td>13 (24)</td>
<td>29 (51)</td>
<td>0.0035</td>
<td>0.0419</td>
</tr>
<tr>
<td>2 steps or more</td>
<td>6 (11)</td>
<td>19 (34)</td>
<td>0.0050</td>
<td>0.0474</td>
</tr>
<tr>
<td>Proliferative Diabetic Retinopathy Onset</td>
<td>3 (6)</td>
<td>14 (25)</td>
<td>0.0054</td>
<td>0.0834</td>
</tr>
</tbody>
</table>

* Determined using Early Treatment Diabetic Retinopathy Study photography.
† Chi-square test.
‡ Corrected for diabetes duration, baseline diabetic retinopathy severity, and 2-year prior hemoglobin A1c levels.

**Effect of Predominantly Peripheral Lesion Extent on Diabetic Retinopathy Progression and Development of Proliferative Diabetic Retinopathy in Eyes with Nonproliferative Diabetic Retinopathy on Early Treatment Diabetic Retinopathy Study Photographs at Baseline**

The effect of an increasing number of retinal fields containing PPLs at baseline on 2-step or more DR progression and onset of PDR after 4 years is shown in Figure 4. The proportion of eyes with 2-step or more progression or in which PDR developed increased with increasing extent of PPLs at baseline (\( P = 0.004 \) for 2-step or more DR progression; \( P = 0.009 \) for PDR onset). These relationships remained significant even after correcting for baseline diabetes type, diabetes duration, and 2-year HbA1c levels (\( P = 0.039 \), 2-step or more DR progression; \( P = 0.042 \), PDR onset). The ORs for 2-step or more progression given baseline PPLs were 6.864 (95% CI, 0.597–78.914), 6.697 (95% CI, 1.929–23.251), and 1.910 (95% CI, 0.453–8.058) for mild, moderate, and severe or very severe NPDR, respectively. The ORs for onset of PDR were 6.864 (95% CI, 0.597–78.914), 8.064 (95% CI, 2.023–32.150), and 1.479 (95% CI, 0.384–5.690) for mild, moderate, and severe or very severe NPDR, respectively.

**Figure 3.** Retinopathy progression after 4 years in eyes with no proliferative diabetic retinopathy (PDR) at baseline (n = 109), comparing eyes without predominantly peripheral lesions (PPL; left panel) versus with PPL (right panel) at baseline. Each bubble represents a specific retinopathy outcome. The position on the x-axis represents the baseline severity of the eyes represented by the bubble. The position of the y-axis represents the diabetic retinopathy (DR) severity at 4 years of follow-up. The size of each bubble represents the proportion of the eyes that is represented by the bubble for each group. HRC = PDR with high-risk characteristics; NPDR = nonproliferative diabetic retinopathy; No = no DR; Mild = mild NPDR; Mod = moderate NPDR; Ques = questionable DR; Severe = severe NPDR; V. Sev = very severe NPDR.
Association of Predominantly Peripheral Lesions with Diabetic Macular Edema Development and with Progression and Visual Acuity

Comparing eyes with PPLs and without PPLs at baseline, there were no statistically significant differences in the rates of development of macular edema ($P = 0.509$), progression of macular edema ($P = 0.728$), or progression or development of clinically significant macular edema ($P = 0.669$) based on ETDRS photography at 4 years of follow-up. The median baseline and 4-year visual acuity for the follow-up cohort was 20/20 ($P = 0.222$).

There was no statistically significant difference in baseline ($P = 0.126$) or final ($P = 0.104$) visual acuity comparing eyes with PPLs and without PPLs at baseline.

Discussion

In this cohort of eyes with a wide range of baseline DR severity, approximately 50% had at least 1 field with DR lesions located predominantly peripheral to the retinal area visualized by ETDRS photography. Furthermore, the presence of PPLs increased the risk of DR progression and onset of PDR over 4 years by 3.2-fold and 4.7-fold, respectively. In eyes that had PPLs at baseline, a greater extent of PPLs was associated highly with a greater risk of DR progression ($P < 0.004$) and onset of PDR ($P < 0.009$), and the relationships remained significant even after correcting for baseline diabetes type, diabetes duration, and 2-year HbA1c levels. These data suggest that the presence and extent of PPLs identified using UWF imaging may serve as robust markers of substantially increased DR progression risk that would not be detectable using standard ETDRS 7-field photography alone.

A previous analysis of this cohort reported that PPLs may suggest a more severe level of DR in 10% of eyes. This initial observation was confirmed in an analysis of UWF images from 1516 eyes obtained in an established DR telemedicine program in which a more severe DR level was suggested in 9% of eyes based on peripheral lesions identified on UWF imaging. Ultrawide-field fluorescein angiography studies in a limited number of eyes similarly have suggested that pathologic features not evident within the ETDRS photographic area exist in 10% of eyes. In the current study, increased risk of DR progression was associated with greater involvement of the peripheral retina. Although currently unproven, the appearance of these peripheral lesions may reflect underlying vascular pathologic features related to peripheral retinal ischemia, nonperfusion, or both, which seem to be highly prevalent in UWF angiographic studies of diabetic eyes.

Recent cross-sectional UWF fluorescein angiography studies suggested a relationship between peripheral nonperfusion and vascular leakage, but the presence of peripheral nonperfusion has not been associated definitively with changes in visual acuity or retinal thickening. Similarly, our longitudinal cohort of 200 eyes over 4 years did not find an association between the presence of peripheral lesions with either macular edema or visual acuity. Elucidation of the underlying mechanisms by which the presence of peripheral lesions is associated with increased retinopathy progression, and the relative contributions of retinal perfusion abnormalities, will require additional investigation but eventually may offer new insights into pathophysiologic mechanisms of diabetic retinal disease.

Because the presence of PPLs may identify a population at substantially increased risk of DR progression that cannot be ascertained using standard posterior retinal photography alone, assessment of the retinal periphery takes on additional importance. The presence and severity of PPLs are not assessed in current standard ETDRS severity grading algorithms. Given that evaluation of these peripheral lesions may
alter substantially the risks of DR progression and onset of PDR, revision of the current ETDRS standard grading system may become necessary. However, the current study was not designed to ascertain the optimal method of UWF grading in terms of PPL and DR progression. Also, this study did not address the actual impact on visual impairment should PPLs be overlooked clinically, although the significantly increased risk of developing PDR in such patients indicates the potential for preventable visual loss resulting from subsequent complications such as vitreous hemorrhage. Finally, although substantial agreement (weighted \(\kappa, 0.69\)) between dilated retinal examination and mydriatic UWF imaging in identifying ETDRS DR severity has been reported previously,\(^\text{12}\) the ability of clinicians specifically to identify peripheral DR lesions was not evaluated in his cohort, nor in prior reports. Thus, additional studies of PPLs are necessary before refining the ETDRS grading protocol so as to optimize its predictive potential in research and clinical use.

The results of this current study may be particularly pertinent in clinical trial settings requiring more precise prediction of DR progression rates or more accurate evaluation of treatment effect, and in teleophthalmology programs to improve the identification, risk assessment, and appropriate triage of eyes with DR being assessed primarily by retinal imaging. If the predictive value of PPLs is confirmed, it may have particular impact in situations in which the peripheral retina generally is not assessed, such as teleophthalmology programs. In teleophthalmology programs for DR, UWF images have been demonstrated to be comparable for DR and diabetic macular edema assessment with those obtained by standard ETDRS protocol,\(^\text{9,10,19}\) with added efficiency benefits including reduction in the number of images acquired, reduction in total imaging time, reduction in image evaluation time, reduced requirements for imager training, and reduced rates of ungradable images.\(^\text{11}\) In such programs, determining the risk associated with an individual’s retinal findings is of paramount importance because it is fundamental to determining referral and timing of re-imaging or follow-up.

In summary, UWF imaging allowed the evaluation of retinal lesions peripheral to those visualized with 7-standard field ETDRS photography. The presence of DR lesions located predominantly in this peripheral area seemed to identify a subset of eyes at greatly increased risk of DR progression and onset of PDR. Furthermore, a greater extent of PPLs was highly associated with a greater risk of these outcomes worsening. If these results are confirmed and refined in a broader diabetes population, the rigorous evaluation of the peripheral retina may become an essential and routine component of accurately characterizing DR severity, and thus may prompt a revision of the ETDRS grading algorithms to best optimize the association of DR severity grade and clinical outcome.

References


Footnotes and Financial Disclosures
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Abbreviations and Acronyms:
CI = confidence interval; DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Study; HbA1c = hemoglobin A1c; H/Ma = hemorrhages and/or microaneurysms; IRMA = intraretinal microvascular abnormalities; NPDR = nonproliferative diabetic retinopathy; NVE = new vessels elsewhere; OR = odds ratio; PDR = proliferative diabetic retinopathy; PPL = predominantly peripheral lesion; UWF = ultrawide field; VB = venous beading.

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