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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;■:1–8 © 2015 by the American Academy of Ophthalmology.*

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.[2] 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] 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.[5]

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

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photography.[6–8] 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).

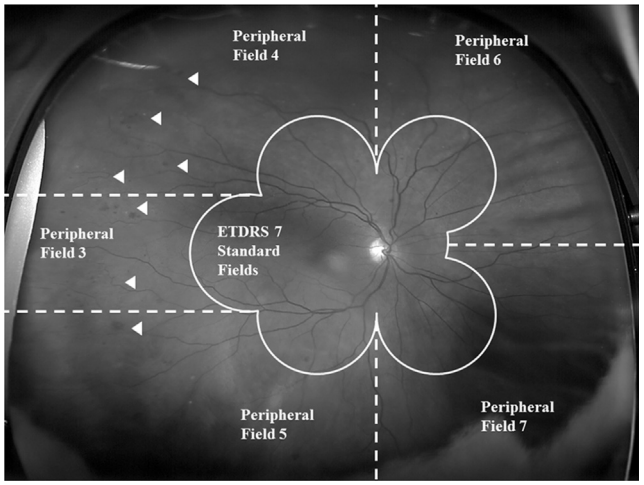

Figure 1. Ultrawide-field image showing diabetic retinopathy lesions predominantly peripheral to the Early Treatment Diabetic Retinopathy Study (ETDRS) fields. Solid white outline shows a standardized template for the combined ETDRS 7 standard fields. The white arrowheads show the diabetic retinopathy lesions occurring predominantly in the area peripheral to the ETDRS standard field template. The dotted lines represent the 5 peripheral fields outside the ETDRS fields defined in this study.

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,[9,12,13] 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 not gradable, and (5) peripheral field not gradable.

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