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Hemorrhage and/or Microaneurysm Severity and Count in Ultrawide Field Images and Early Treatment Diabetic Retinopathy Study Photography

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Objective: To evaluate detection of hemorrhage and/or microaneurysm (H/Ma) using ultrawide field (UWF) retinal imaging as compared with standard Early Treatment Diabetic Retinopathy Study (ETDRS) 7-field photographs (ETDRS photos).

Design: Single-site comparative study of UWF images and ETDRS photos.

Participants: One hundred twenty-six eyes of 69 patients with no diabetic retinopathy (DR) or mild or moderate nonproliferative DR (NPDR).

Methods: Stereoscopic 200° UWF images and stereoscopic 35mm 30° 7-field color photographs were acquired on the same visit. Images were graded for severity and distribution of H/Ma. H/Mas were counted in ETDRS fields 2 to 7 in both ETDRS photos and UWF images. H/Mas in the UWF peripheral fields were also counted.

Main Outcome Measures: Kappa (κ) and weighted κ statistics for agreement. Number of H/Ma within and outside ETDRS fields identified in UWF images and ETDRS photos.

Results: Distribution of DR severity by ETDRS photos was 24 (19.0%) no DR, 48 (38.1%) mild NPDR, and 54 (42.9%) moderate NPDR. A total of 748 of 756 fields (98.9%) were gradable for H/Mas on ETDRS photos and UWF images. Simple κ/weighted κ statistics for severity of H/Ma: all fields 0.61/0.69, field 2 0.70/0.77, field 3 0.62/0.73, field 4 0.50/0.62, field 5 0.54/0.65, field 6 0.64/0.70, and field 7 0.58/0.63 with overall exact agreement in 81.3% and within 1 step in 97.9% of fields. A greater proportion of fields was graded a more severe H/Ma level in UWF images than in the corresponding ETDRS photos (UWF: 12.7% vs. ETDRS: 6.5%). Evaluating comparable areas in UWF images and ETDRS photos (fields 2−7), a mean of 42.8 H/Mas were identified using ETDRS photos and 48.8 in UWF images ($P = 0.10$). An additional mean of 21.3 H/Mas (49.8% increase, $P < 0.0001$) were identified in the peripheral fields of the UWF images.

Conclusions: There is good to excellent agreement between UWF images and ETDRS photos in determining H/Ma severity, with excellent correlation of H/Ma counts within ETDRS photo fields. UWF peripheral fields identified 49.8% more H/Ma, suggesting a more severe H/Ma in 12.7% of eyes. Given the additional lesions detected in peripheral fields and the known risks associated with H/Ma and peripheral lesions, quantification of H/Ma using UWF images may provide a more accurate representation of DR disease activity and potential greater accuracy in predicting DR progression. *Ophthalmology 2017;■:1−7 © 2017 by the American Academy of Ophthalmology*

Retinal hemorrhage and/or microaneurysm (H/Ma) is among the earliest clinically evident signs of early diabetic retinopathy (DR).[1] The presence and severity of retinal H/Ma have been reliably used to assess the presence, severity, and risk for progression of DR.[2] Based on standard 7-field Early Treatment Diabetic Retinopathy Study (ETDRS) fundus photographs, microaneurysms are critical features that need to be present to make the diagnosis of DR, and the number of H/Mas has been used to classify early stages of DR in both clinical and research settings.[2] Furthermore, data suggest that retinal microaneurysm counts and turnover rates may be an important early measure of an increased risk for progression to proliferative DR and clinically significant macular edema.[3−6]

Using ultrawide field (UWF) retinal imaging, up to a fourfold greater area of the retinal surface is imaged. This increased visualized area allows the identification of additional peripheral diabetic retinal lesions that would otherwise not have been identified using ETDRS fundus photography alone.[7] Multiple independent groups have shown that when compared with ETDRS standard

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photography, peripheral diabetic lesions identified on UWF images suggest a more severe level of DR in approximately 10% to 15% of eyes[7–12] and provide greater prognostic information with regard to DR progression over 4 years.[7,13] A review of more than 1500 UWF retinal images obtained from patients with varying levels of DR demonstrated that in more than 86% of eyes the primary lesions located predominantly outside the ETDRS photograph area are H/Ma.[8] The presence of these predominantly peripheral lesions predicts eyes at an increased risk for DR progression and development of proliferative DR.[13] Thus, quantification of H/Ma in the entire retina may provide a more accurate representation of DR disease activity and provide greater accuracy in predicting DR progression and diabetic macular edema (DME) development than have prior approaches.

Methods to identify those at risk of DR progression at earlier stages of disease are critical. Changes in microaneurysm counts and turnover have been associated with DR progression risk.[3–6] These associations are not as strong as would be desirable to use as a predictive biomarker upon which to base individual patient counseling, treatment decisions, or clinical trial surrogate endpoints. However, to date, these analyses have only evaluated H/Ma in the ETDRS fields. This posterior area only encompasses about 30% of the retinal surface. The use of UWF imaging allows the evaluation of more than 80% of the retinal surface in a single image. Thus, evaluation of H/Ma using UWF imaging may reflect a more global assessment of DR risk.

Methods

Retinal images were reviewed from a previously completed single-site, prospective, clinic-based, comparative-instrument validation study[7,14] that was specifically conducted to evaluate the agreement in assessing severity of DR at the retinal lesion level between stereoscopic mydriatic 200° UWF images and mydriatic ETDRS 7-field 35mm slide film photography (ETDRS photos). Both UWF imaging (stereoscopic 200° pairs of each eye, acquired using an Optos P200Tx, Optos plc, Dunfermline, Scotland, UK) and ETDRS photos (stereoscopic 35mm color 7-field 30° photography acquired using Zeiss FF4, Carl Zeiss Meditec Inc, Dublin, CA) were acquired using a standardized protocol after pupillary dilation at the same visit. Based on prior published data, a higher DR severity level was suggested using UWF images in 10% of all eyes.[7] However, in the current analysis we assessed eyes with no DR, mild NPDR, and moderate NPDR by ETDRS photos, as these eyes had the greatest suggested change in DR severity using UWF images. The graded level of DR was assessed as more severe with UWF images in 18% of no DR, mild NPDR, or moderate NPDR (n = 126) compared with only 1.5% of eyes with severe or very severe NPDR or proliferative DR (n = 70).[7] This observation has been reported and replicated by multiple independent groups.[9–11]

For this study, only eyes with no DR to moderate NPDR on ETDRS photos (n = 126) were evaluated. All digital image evaluation was performed with calibrated display monitors as part of the centralized reading center of the Joslin Vision Network. Routine internal quality control and assurance testing is performed on a quarterly basis through review of metrics including intergrader and intragrader variability. Agreement for the overall severity level of diabetic retinopathy across graders is excellent with weighted kappa (κ) values between 0.88 and 0.93 for UWF images and between 0.83 and 0.84 for ETDRS 7-standard fields. The study design was consistent with the tenets of the Declaration of Helsinki and approved by the Committee on Human Studies of the Joslin Diabetes Center.

Grading of Hemorrhage and/or Microaneurysm Severity

The process by which ETDRS and UWF images were graded has been validated and published previously.[7,14] Fields 2 to 7 were evaluated on both modalities based on the ETDRS severity scale for H/Ma (absent; mild: definite H/Ma less than standard 1 [approximately <20 microaneurysms and 1 small hemorrhage]; moderate: definite H/Ma greater than standard 1, but less than ETDRS standard 2A; severe: definite H/Ma greater than ETDRS standard 2A, but less than ETDRS standard 2B; very severe: definite H/Ma greater than ETDRS standard 2B). The evaluation of stereoscopic 7-field ETDRS 35mm color film slides was performed on a standardized slide light box through Donaldson viewers and the stereoscopic UWF image pairs were viewed using mirrored stereoscopes (Screen-Vu, PS Mfg, Portland, OR) and displayed using Optos Vantage (version 2.9.4.2, Optos, plc, Dunfermline, Scotland, UK) on high-definition display monitors calibrated to a color temperature of 6500K and a gamma setting of 2.2 (Spyder4PRO, Datacolor, Lawrenceville, NJ). Both imaging modalities were evaluated in a masked manner and according to field-by-field, lesion-level ETDRS protocol by a retina specialist (P.S.S.) experienced in grading DR at different time points to prevent recall. The grading protocol for UWF image review has been previously published.[14] Briefly, this followed an initial automated software rendering and adjustment of color composite images and subsequent manual adjustment of the green separation (red-free, green wavelength) image. Color-composite green- and red-separation images were viewed individually with varying digital zoom and magnification of at least 100% and image rendering as appropriate. The overall DR severity agreement rates in ETDRS photos and UWF images have been previously published[14] and subgroups analysis of H/Ma agreement specifically evaluating eyes with no DR to moderate NPDR is presented in this study.

Determining Hemorrhage and/or Microaneurysm Counts

Stereographic pairs of ETDRS photographs and UWF images were reviewed to identify the image in the pair with better quality. The better-quality image of the stereoscopic pair was used in the measurement of the H/Ma count. To determine H/Ma counts from ETDRS photos, each ETDRS field was viewed using standardized light boxes and evaluated stereoscopically using Donaldson viewers. In ETDRS fields 1 to 7, H/Mas were counted and recorded into standardized electronic templates. To determine H/Ma counts from UWF images, each UWF 200° image pair was evaluated and the best image was selected for analysis. All H/Mas in the selected UWF image were digitally annotated using a software tool provided by the manufacturer (Optomapper tool, Optos plc, Dunfermline, Scotland, UK). To localize the annotated H/Ma into individual ETDRS fields, a standardized ETDRS field template was digitally overlaid on the image based on disc and foveal location (Fig 1). Individual field counts and locations of annotated H/Mas in the UWF images were based on this standardized overlay.