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ORIGINAL RESEARCH

Quantitative Biomarkers of Diabetic Retinopathy Using Ultra-Widefield Fluorescein Angiography

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Introduction: Diabetic retinopathy (DR) is a leading cause of blindness. Retinal imaging is an important tool to monitor the progression of DR. While seven-standard retinal fields are the traditional method for evaluating DR, ultra-widefield (UWF) imaging allows for improved visualization of peripheral areas of nonperfusion (NP) and neovascularization (NV), which could be used as biomarkers to monitor and predict progression of DR.

Methods: A retrospective, cross-sectional study was conducted on 651 eyes from 363 patients diagnosed with type 1 or type 2 diabetes who received UWF-FA over 10 years. Fluorescein Angiography (FA) images were segmented, and surface areas of NP and NV were analyzed using multivariate regression to determine if biomarkers of DR and DR severity are associated with increasing areas of NP and NV.

Results: Each additional year with a diagnosis of DR was associated with a 10.75 mm^2 increase in the total NP (95% CI, 1.94—19.56; P = 0.02) and 7.87 mm^2 increase in NP far-periphery (95% CI, 1.62—14.13; P = 0.01). A one-unit change in severity as defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification was associated with a 25.75 mm^2 increase in total NP (95% CI, 11.16—40.33; P = 0.001), a 13.15 mm^2 increase in mid-periphery NP (95% CI, 6.93—19.38; P < 0.0001), and a 12.29 mm^2 increase in far-periphery NP (95% CI, 3.62—20.97; P = 0.01).

Discussion: Biomarkers identified through UWF imaging such as total and regional areas of NP can be used to monitor and predict the progression of DR. This may provide a quantitative method for prognostication in patients with DR.

keywords: diabetic retinopathy, ultra-widefield fluorescein angiography, nonperfusion, neovascularization

Introduction

Diabetic retinopathy (DR) is a leading cause of blindness among working age adults. Prevalence rates are predicted to increase significantly over the next twenty years, affecting an estimated 16 million Americans by the year 2050.[1,2] The Early Treatment Diabetic Retinopathy Study (ETDRS) seven standard retinal fields (7-SF), which focuses primarily on the posterior pole, is the traditional method for evaluating DR.[3,4] Ultra-widefield (UWF) imaging covers 200 degrees or 82% of the retinal surface and encompasses retinal features anterior to the vortex vein ampullae in all 4 quadrants.[5,6] This is in contrast to the 90 degrees created via a montage of seven 30-degree images produced with 7-SF imaging.[7,8] The greater peripheral visualization by UWF may enable better grading and monitoring of disease, as demonstrated by prior studies showing its capability to detect larger areas of retinal lesions compared to ETDRS 7-SF images.[9–16]

Clinical and biochemical biomarkers are frequently used to objectively evaluate disease severity and progression.[17] Biomarkers such as HbA1c have been used to predict the severity of hyperglycemia, nephropathy, and retinopathy.[18] More targeted circulating biomarkers such as TNF-alpha have been shown to positively correlate with the occurrence of DR.[19] Local biomarkers such as vitreous or aqueous humor sampling have the advantage of providing a more direct characterization of pathology, although the invasive nature of these tests limits utility for screening and monitoring.[18] The presence or absence of microaneurysms, intraretinal hemorrhage, and areas of nonperfusion (NP) and neovascularization (NV), identifiable on retinal imaging, have the advantage of being highly specific yet less invasive.[17] Previous studies show that the number and surface area of intraretinal hemorrhages and microaneurysms identified are predictive of an increased risk of DR progression (DRP).[20]

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Additionally, there has been recent attention on quantifying lesions to better classify DR severity.[21–23] Previous studies have demonstrated the ability to quantify areas of NP and NV.[24,25] There are several advantages to quantification. This allows for a more objective classification of disease pathology, with defined threshold areas that determine the risk of disease progression.[24,26] Moreover, the ability to quantify adds to the standardization of disease classification and provides a method for tracking disease change over time.

In addition to biomarker quantification, recent studies have investigated lesion location and the ability to predict disease progression. Peripheral lesions on UWF have been shown to be associated with DRP over a four-year time, with peripheral lesions providing the most significant predictive value.[27] AI algorithms analyzing color fundus photographs collected during a single visit have predicted DRP over a two-year period by primarily relying on findings in the peripheral retinal fields and areas far from the fovea and optic nerve.[28] Thus, lesion location is a strong predictor of DRP, with peripheral lesions indicating a poorer prognosis compared to centrally located lesions.[29–32] Lesion location combined with analysis of quantifiable areas of retinal disease may provide more precise methods for monitoring DRP.

While advances have been made to quantitatively assess the severity of DR using UWF-FA, assessment of biomarkers associated with disease progression is limited using UWF-FA. The objective of this study is to assess whether measured areas of NP and NV on UWF FA images in a cohort of patients with type 1 or 2 diabetes were associated with DR progression over time. Identification of quantitative biomarkers that are predictive of disease progression and disease time course can assist clinicians in better long-term follow-up and prognostication of patients.

Materials and Methods

Patients diagnosed with type 1 or type 2 diabetes who received UWF FA imaging at the University of Michigan W. K. Kellogg Eye Center between January 2009 (when the camera was first acquired at our institution) and May 2018 were enrolled in a retrospective cross-sectional study. University of Michigan Institutional Review Board approval was obtained for this study (HUM00120509), and consent was obtained through a Health Insurance Portability and Accountability Act waiver provided by the Institutional Review Board. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Inclusion criteria for the study were as follows: patient age greater than or equal to 18 years, a diagnosis of type 1 or type 2 diabetes, and an evaluation with a dilated fundus exam and UWF-FA performed at the University of Michigan Kellogg Eye Center. Exclusion criteria were as follows: poor image quality leading to undifferentiable areas of NP or NV, image opacities or poor view to the retina, evidence of prior treatment with laser photocoagulation, or technical issues in secondary image processing such as improper image formatting or failed image projections. Patients with previous laser photocoagulation were excluded from the study due to the concern that the laser scars would interfere with the nonperfusion measurements. Patients who had received previous anti-vascular endothelial growth factor (anti-VEGF) therapy were not excluded.

Age, sex, race, and type of diabetes (1 or 2) were determined for each patient. Severity of DR by ETDRS grading, presence of diabetic macular edema on clinical exam, and ophthalmic treatments including laser photocoagulation were determined for all clinic visits. Duration of follow-up was calculated from the date of initial UWF FA imaging through the last clinical encounter in the study period. Patients without any subsequent encounters after the initial UWF FA were designated as lost to follow-up for analysis (Figure 1).

UWF FA and Image Segmentation

FA images captured using Optos 200Tx or California (Optos PLC, Dunfermline, Scotland, UK) were used to create a stereographic projection of the retina using proprietary Optos software, as described previously.[33,34] A single retina specialist selected the best macula-centered image for segmentation from a series of FA images within the arteriovenous, venous, and late phases obtained from each eligible eye. Using open-source ITK-SNAP software, four masked and trained graders segmented surface areas of FAZ (characterized by hypofluorescence on FA in the central macula), NP (characterized by regions of hypofluorescence on FA following a vascular pattern without a fundus finding leading to

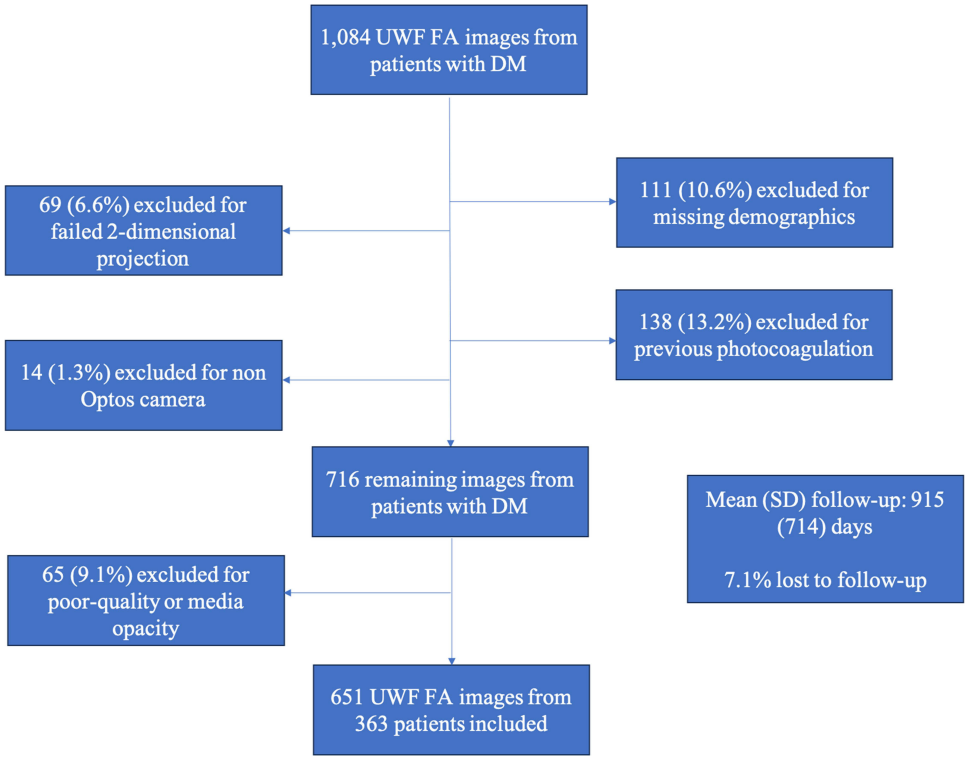

Figure 1 Patient flow diagram indicating the number of initial patients and the number that were excluded due to exclusion criteria leading to analysis of 651 UWF FAs from 363 patients.

blockage), and NV (characterized by progressive hyperfluorescence on FA) in square millimeters (mm^2). Each segment was quantified by one single grader with confirmation by the retina specialist for areas of uncertainty. Surface areas for NP and NV were then grouped by region based on distance from FAZ as follows: regions within and including 3.00 mm from identified FAZ were designated as the "posterior pole", those between 3.00 mm and including 10.00 mm were categorized as the "mid-periphery", and those between 10.00 mm and including 15.00 mm were considered the "far-periphery". Our previous manuscript outlines the above procedures in greater detail, and also includes representative graded and ungraded images with complete directions for quantification.[24]

Statistical Analysis

All statistical analysis for this study was conducted using the R programming language (R Core Team, 2019).[35] Both parametric and nonparametric analyses were used to compare between groups. Mean, standard deviation, and confidence intervals (CI) were calculated for continuous variables, and frequencies were calculated for categorical variables such as age and race. Generalized estimating equation models were used to identify associations between biomarkers, demographic factors, and DR progression over time (Table 1). The geepack R package was used to determine P values. P less than 0.05 was suggestive for further exploration.[36] Linear regression models were used to identify correlations between left-eye and right-eye measurements for single patients. For regression analysis, each race/ethnicity was compared with white race/ethnicity.

Multivariate regression was used to explore the relationship between segmented biomarker areas, demographics, and changes in DR severity (Table 1). DR severity was determined using the ETDRS classification system where 0, 1, 2, 3, or 4 were defined as no DR, mild NPDR (non-proliferative DR), moderate NPDR, severe NPDR, or PDR (proliferative DR), respectively. Progression was defined as a one-step increase in DR severity. Patients with PDR at baseline were excluded from the progression analysis.

Table 1 Association of Demographic Factors and Change in Severity with Areas of NP and NV Calculated After Adjusting for the Previous Area

Demographic	Biomarker	Percent Change (95% CI)	P value
Right vs Left	NP Total	−6.11 (−18.7 to 6.49)	0.34
	NP Posterior	0.12 (−1.11 to 1.34)	0.85
	NP Mid	**−7.61 (−13.76 to −1.45)**	**0.02**
	NP Far	1.04 (−7.83 to 9.90)	0.82
	NV Total	0.24 (−0.25 to 0.73)	0.33
	NV Posterior	−0.03 (−0.06 to 0)	0.08
	NV Mid	0.31 (−0.10 to 0.72)	0.13
	NV Far	−0.08 (−0.32 to 0.17)	0.55
Male vs Female	NP Total	10.71 (−11.96 to 33.39)	0.35
	NP Posterior	−0.79 (−1.71 to 0.13)	0.09
	NP Mid	0.25 (−7.09 to 7.58)	0.95
	NP Far	12.63 (−2.31 to 27.57)	0.10
	NV Total	−0.12 (−0.63 to 0.39)	0.65
	NV Posterior	**−0.12 (−0.2 to −0.04)**	**0.004**
	NV Mid	−0.17 (−0.57 to 0.23)	0.41
	NV Far	0.02 (−0.12 to 0.15)	0.81
Black vs White	**NP Total**	**23.88 (8.31 to 39.44)**	**0.003**
	NP Posterior	−0.15 (−0.96 to 0.66)	0.71
	NP Mid	4.04 (−3.00 to 11.08)	0.26
	NP Far	**21.73 (8.60 to 34.87)**	**0.001**
	NV Total	**0.73 (0.10 to 1.37)**	**0.02**
	NV Posterior	0.02 (−0.09 to 0.12)	0.73
	NV Mid	0.39 (−0.02 to 0.79)	0.06
	NV Far	0.36 (−0.11 to 0.82)	0.13
Asian vs White	NP Total	11.58 (−5.01 to 28.17)	0.17
	NP Posterior	−0.699 (−1.44 to 0.06)	0.07
	NP Mid	−6.6 (−13.77 to 0.57)	0.07
	NP Far	**18.10 (4.65 to 31.55)**	**0.01**
	NV Total	0.20 (−0.13 to 0.7)	0.44
	NV Posterior	**−0.18 (−0.28 to −0.07)**	**0.001**
	NV Mid	0.09 (−0.33 to 0.51)	0.67
	NV Far	0.08 (−0.04 to 0.21)	0.20

(*Continued*)

Table 1 (Continued).

Demographic	Biomarker	Percent Change (95% CI)	P value
White vs Other	NP Total	6.93 (−11.81 to 25.66)	0.47
	NP Posterior	−0.42 (−1.11 to 0.27)	0.23
	NP Mid	−1.41 (−9.67 to 6.84)	0.74
	NP Far	6.05 (−6.51 to 18.61)	0.35
	NV Total	0.23 (−0.20 to 0.66)	0.29
	NV Posterior	−0.1 (−0.23 to 0.02)	0.11
	NV Mid	0.19 (−0.17 to 0.55)	0.31
	NV Far	−0.08 (−0.48 to 0.33)	0.71
Additional year of age	NP Total	−0.71 (−1.51 to 0.09)	0.08
	NP Posterior	−0.02 (−0.08 to 0.05)	0.58
	NP Mid	**−0.51 (−0.88 to −0.14)**	**0.01**
	NP Far	−0.27 (−0.84 to 0.3)	0.35
	NV Total	**−0.04 (−0.06 to −0.01)**	**0.01**
	NV Posterior	0 (0 to 0)	0.82
	NV Mid	−0.02 (−0.05 to 0)	0.03
	NV Far	**−0.01 (−0.02 to 0)**	**0.01**
Diabetes Type 2 vs Type 1	NP Total	−24.7 (−69.05 to 19.65)	0.28
	NP Posterior	−1.00 (−2.58 to 0.58)	0.22
	NP Mid	1.5 (−12.33 to 15.34)	0.83
	NP Far	−24.84 (−54.94 to 5.26)	0.11
	NV Total	−0.32 (−1.03 to 0.40)	0.38
	NV Posterior	**0.12 (0.01 to 0.23)**	**0.04**
	NV Mid	−0.54 (−1.18 to 0.11)	0.10
	NV Far	0.25 (−0.05 to 0.55)	0.11

Note: Bolded text corresponds to $P < 0.05$.

Results

One thousand forty-eight images were obtained using UWF-FA from patients with type 1 or type 2 diabetes from January 2009 to May 2018. One hundred and eleven (10.6%) images were excluded due to missing patient demographics. One hundred and thirty-eight (13.2%) images were excluded for previous laser photocoagulation treatment, 69 images (6.6%) for failed 2-dimensional projection with the Optos software, 14 images (1.3%) for originating from a camera other than Optos 200Tx or Optos California, and 65 images (9.1%) for poor image quality (eg, presence of cataract or hemorrhage) limiting biomarker evaluation. The final analysis was conducted on a total of 651 eyes from 363 patients (205 males and 158 females) (Figure 1).

Complete demographic data for the cohort is outlined in our previous manuscript.[23] Briefly, the mean age (SD) was 59.4 (13.7) years and 43.5% (158) were female. Of the 363 patients (651 eyes), 76 eyes had no DR, 92 eyes had mild non-proliferative diabetic retinopathy (NPDR), 144 eyes had moderate NPDR, 101 eyes had severe NPDR, and 220 eyes

had PDR. Eyes with PDR were excluded from DR progression analysis. The mean total follow-up time after initial UWF-FA imaging was 915 days (SD ± 714). A representative graded image is outlined in Figure 2.

Associations Between Demographics and Areas of NP and NV Relative to Changes in DR Severity

On average, females had a 0.12 mm^2 greater area of NP in the posterior pole than males (95% CI, −0.2 to −0.04; $p < 0.001$). Compared to white patients, total NP was 23.88 mm^2 greater in Black patients (95% CI, 8.31 to 39.44; $p < 0.001$). The area of NP in the far periphery was 21.73 mm^2 higher in Black individuals compared to white individuals (95% CI, 8.60 to 34.87; $p < 0.001$). Moreover, in Black patients, a change in severity was associated with a 0.73 mm^2 greater area of total NV when compared to white patients (95% CI, 0.10 to 1.37; $p = 0.02$). In Asians, the area of NP in the far-periphery was 18.10 mm^2 greater than the area observed in white patients (95% CI, 4.65 to 31.55; $p = 0.01$). Conversely, Asian patients had a 0.18 mm^2 smaller area of NV in the posterior pole compared with white patients (95% CI, −0.28 to −0.07; $p < 0.001$). With every additional year of age, the area of NP in mid-periphery seen in DR patients increased by 0.51 mm^2 (95% CI, −0.88 to −0.14; $p = 0.01$). Similar increases were seen for total NV and NV in far-periphery. With each additional year of age, the total area of NV and NV in far-periphery increased by 0.04 mm^2 (−0.06 to −0.01; $p = 0.01$) and 0.01 mm^2 (−0.02 to 0; $p = 0.01$), respectively (Table 1). Finally, area of NP in the mid-periphery of the left eye was found to be 7.61 mm^2 larger area than what was observed in the right eye (95% CI, −13.76 to −1.45; $p = 0.02$).

Association Between Changes in Areas of NP and Progression of DR Over 10 Years

Each additional year with a DR diagnosis was associated with a 10.75 mm^2 increase in the total NP (95% CI, 1.94—19.56; $P = 0.02$). Over a period of ten years this is estimated to be an increase in total area by 107.5 mm^2. Progression of DR was also associated with a 78.8 mm^2 increase in NP far-periphery over 10 years (95% CI, 16.2—141.3; $P = 0.01$) (Table 2). These findings establish an association between DR progression and increases in quantifiable areas of NP. Each additional year of diagnosis contributes to significant increases in NP areas, particularly in the far-periphery. This can be used to monitor disease progression over a 10-year span.

Areas of NP and NV Predict Changes in Assigned Unit Severity

In addition to defining associations between DR progression and increases in area of NP and NV on UWF-FA, our data demonstrate the ability to predict changes in assigned DR severity. A one unit change in severity as defined by ETDRS classification was associated with a 25.75 mm^2 increase in total area of NP (95% CI, 11.16—40.33; $p = 0.001$), 13.15 mm^2 increase in area of NP in mid-periphery (95% CI, 6.93—19.38; $p < 0.0001$), 12.29 mm^2 increase in area of NP in far-periphery (95% CI, 3.62—20.97; $p = 0.01$), and 0.05 mm^2 increase in area of NV in the posterior-pole (95% CI, 0.01—0.09; $p = 0.01$) (Table 3). Our results demonstrate the predictive value of areas of NP and NV in anticipating changes in assigned severity levels.

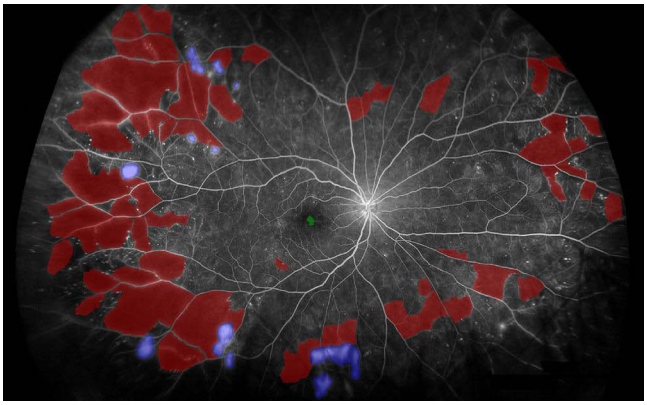

Figure 2 Example manual segmentation image of biomarkers. UWF FA of patient with PDR and manual segmentation completed. Green represents FAZ, red represents areas of nonperfusion, and purple represents areas of neovascularization. Following segmentation, biomarker areas were calculated.

Table 2 Association Between Changes in Area of Regional NP and NV with Progression of DR Over 10 Years

Biomarker	Difference in Biomarker Area over 10 years (mm^2) (95% CI)	P value
NP Total	**107.5 (19.4 to 195.6)**	**0.02**
NP Posterior	2.1 (−0.16 to 4.3)	0.07
NP Mid	25.9 (−7.3 to 59.1)	0.13
NP Far	**78.8 (16.2 to 141.3)**	**0.01**
NV Total	0.93 (−0.99 to 2.83)	0.34
NV Posterior	0.01 (−0.05 to 0.07)	0.75
NV Mid	0.58 (−1.03 to 2.12)	0.48
NV Far	0.32 (−0.16 to 0.80)	0.20

Note: Bolded text corresponds to $P < 0.05$.

Table 3 Association Between Regional Areas of NV and NP with Changes in Assigned Unit Severity

Biomarker	Difference in Biomarker area (mm^2) Relative to Severity of DR (95% CI)	P value
NP Total	**25.75 (11.16 to 40.33)**	**0.001**
NP Posterior	0.43 (−0.13 to 1.00)	0.13
NP Mid	**13.15 (6.93 to 19.38)**	**<0.0001**
NP Far	**12.29 (3.62 to 20.97)**	**0.01**
NV Total	0.37 (−0.02 to 0.75)	0.06
NV Posterior	**0.05 (0.01 to 0.09)**	**0.01**
NV Mid	0.3 (−0.04 to 0.63)	0.08
NV Far	0.06 (−.01 to 0.13)	0.07

Note: Bolded text corresponds to $P < 0.05$.

Discussion

The results of this ten-year retrospective cross-sectional study on the progression of DR show that areas of NP in the mid and far periphery and areas of NV strongly correlate with changes in DR severity over time. The duration of a DR diagnosis was associated with a larger total area of NP and NP in the far periphery, indicating the potential for using age or years with a DR diagnosis in conjunction with quantitative biomarker measures as a method for monitoring disease progression. Additionally, increases in assigned DR severity were significantly associated with an increase in peripheral regions of NP seen on UWF imaging over time.

Larger areas of NP in the mid and far periphery as well as areas of NV are strongly associated with changes in DR severity over time. As previous studies have demonstrated, areas of peripheral disease provide stronger evidence of DR severity when compared to central lesions.[27] Furthermore, we observed that the duration of DR diagnosis is associated with a larger area of total NP and NP in the far periphery. Over a 10-year period, the accumulation of NP serves as a significant predictor of DR severity. Notably, the assigned severity level is significantly correlated with all regions of NP except in the posterior pole. These findings highlight the usefulness of UWF imaging in overcoming the limitations of 7SF, which primarily covers

findings in the posterior pole and does not identify disease pathology in the far periphery. As previous studies have demonstrated, diagnoses made using UWF are on average more severe than diagnoses made using 7SF imaging.[37] Regular use of UWF imaging during initial diagnosis of DR and for follow-up can allow for more precise grading and monitoring of severity.

Clinical and demographic attributes such as sex, race, and type of DM were also associated with the areas of NP and NV. Specifically, among Black individuals, the areas of NP and NV are significantly increased. Each additional year of age was associated with an incremental increase in the area of NP. The ability to compare progression of DR relative to a standard value based on the patient's demographics may provide clinicians with more data points for tracking DR progression over time.

Interestingly, we found that DR progression is more strongly associated with NP than NV. For instance, among Black individuals, both total NV and NP in the far periphery were significantly higher, but the area observed during examination for NP in the far periphery was over 29 times larger than that for NV (21.73 vs 0.73). One possible explanation is that NP occurs earlier in the disease process and is therefore a better predictor of progression, whereas NV can lead to vitreous hemorrhage and thus is often promptly treated to cause regression when it is noted.

The current ETDRS guidelines do not provide a quantitative method for tracking DR progression.[37] Biomarkers are predictors of disease progression and are useful in identifying which patients are likely to progress rapidly and which are likely to remain stable over time. In our previous work on this cohort, a quantitative measure with a threshold area of 77.48 mm^2 was proposed to determine the risk of progression to PDR.[24] The findings of the current study contribute an additional piece to the utility of quantification to diagnosis of DR by investigating the relationship between areas of NP and NV and changes in severity over time. Coupled with the use of UWF to improve our ability to identify markers to track DR progression, biomarker quantification may be the path forward for DR disease classification and monitoring.

Given the findings of this study, a shift in clinical practice could be made towards regularly screening DR patients with UWF imaging when available and utilizing quantifiable biomarkers in high-risk areas when defining disease. Moreover, a comprehensive approach considering the type of diabetes, patient age, and years since diagnosis should be taken into account during disease diagnosis. This study illustrates the direct correlation of these factors with larger areas NP and NV, resulting in increased disease severity and a higher probability of progressing to diabetic PDR. Although not examined in this cohort, further patient stratification based on risk factors could aid in guiding treatment options and prompt early intervention for individuals with higher risk of progressing to severe disease.

Limitations

While this study and others support the shift towards UWF imaging as a standard for diagnosing and tracking DR, our work did not investigate other imaging modalities such as optical coherence tomography (OCT).[38,39] The use of OCT and OCT associated biomarkers such as disorganization of retinal inner layers (DRIL) may add prognostic value that was not elucidated in our study.[40] Additionally, this was a retrospective study, not a prospective evaluation, and imaging and treatment decisions were not standardized but based on the discretion of the treating physician and patient. Lastly, although NV was measured as one of the strongest predictors of ETDRS progression, the study population with NV was relatively small.

Conclusions

In summary, our study demonstrates the importance of UWF imaging in the diagnosis and monitoring of DR and introduces the usefulness of biomarkers of disease as quantitative predictors of disease progression.

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Disclosure

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