Published in final edited form as:

Ophthalmol Retina. 2020 January ; 4(1): 49–56. doi:10.1016/j.oret.2019.08.008.

Quantitative Ultra-widefield Angiographic Features and Associations with Diabetic Macular Edema

Alice C. Jiang^{1,2}, Sunil K. Srivastava^{1,3}, Ming Hu^{1,4}, Natalia Figueiredo¹, Amy Babiuch^{1,3}, Joseph D. Boss³, Jamie L. Reese¹, Justis P. Ehlers^{1,3}

¹The Tony and Leona Campana Center for Excellence in Image-Guided Surgery and Advanced Imaging Research, Cole Eye Institute, Cleveland Clinic, Cleveland, OH.

²Case Western Reserve University, School of Medicine, Case Western Reserve University, Cleveland, OH.

³Vitreoretinal Service, Cole Eye Institute, Cleveland Clinic, Cleveland, OH

⁴Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH

Abstract

Purpose: To examine the relationship between diabetic macular edema (DME) and quantitative ultra-widefield fluorescein angiography (UWFA) metrics of ischemia, leakage, and microaneurysms (MAs).

Design: Retrospective image analysis study

Subjects: Eyes with diabetic retinopathy that had undergone spectral-domain optical coherence tomography (OCT), UWFA, and ultra-widefield fundus photography.

Methods: OCT images were analyzed to determine the presence or absence of DME, central subfield thickness (CST), and subretinal fluid (SRF). Utilizing a semi-automated analysis platform, UWFA images were segmented for ischemia, leakage, and MAs with manual correction as needed. Clinical variables, including age, sex, race, hemoglobin A1C, blood pressure, cholesterol levels, use of blood thinners, smoking status, and lens status were also evaluated.

Main Outcome Measures: Factors associated with the presence and severity of DME

Results: A total of 304 eyes (156 OD, 148 OS) from 178 diabetic patients were analyzed in the study. Panretinal leakage index, MA count, and ischemic index were not significantly different

---

Corresponding Author: Justis P. Ehlers, MD, 9500 Euclid Avenue, i32, Cleveland, OH 44195 Phone: 216-636-0183 EHLERSJ@ccf.org.

Publisher's Disclaimer: This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosures: ACJ: None; SKS: Bausch and Lomb (C, R); Bioptigen (P); Allergan (R); Leica (C), Zeiss (C); MH: None; NF: None; AB: Genentech (C), Regeneron (R) JDB: None; JLR: None; JPE: Leica (C, P), Thrombogenics (C, R), Genentech (C,R), Roche (C), Zeiss (C), Alcon (C,R), Novartis(C,R), Aerpio (C,R), Allergan (C), Allegro (C), Regeneron (C,R)

Conflict of Interest: No conflicting relationship exists for any author

between eyes with and without DME in univariate assessment. Zonal assessments of macular MAs and macular leakage index values revealed that eyes with DME had a significantly higher MA count ($p=0.001$) and leakage index ($p<0.0001$) in the posterior pole compared to eyes without DME. Severity of macular thickening (i.e., CST) was significantly associated with macular leakage index and posterior pole MA count ($p=0.0002$ and $p=0.03$, respectively). In addition to posterior pole leakage index and MA count, DME was associated with older age ($p<0.01$), higher systolic blood pressure ($p<0.001$), and Caucasian race ($p=0.03$). Multivariate assessment confirmed independent association of presence of DME with macular leakage index and macular MA count ($p < 0.01$).

Conclusions: Quantitative measures of leakage index and MA count in the posterior pole on UWFA images were associated with the presence and severity of DME. Panretinal analyses were not as strongly linked to DME. Additional research is needed to determine the role of quantitative UWFA in predicting DME development and characterizing prognosis.

Precis

Macular leakage index and macular microaneurysm count are independently associated with the incidence and severity of diabetic macular edema (DME). Panretinal ultra-widefield metrics were not strongly linked to DME.

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic retinopathy (DR) and vision-related decreased quality of life.¹ Retinal imaging is increasingly important in the early diagnosis, treatment, and monitoring of DR and DME. Over three decades ago, the Early Treatment of Diabetic Retinopathy Study (ETDRS) established guidelines for fundoscopic grading of DR and DME, and showed that focal laser photocoagulation of clinically significant DME substantially reduced the risk of visual loss.² More recently, optical coherence tomography (OCT) has supplanted this grading and classification system, and now uses central subfield thickness (CST) and anatomic location of DME for characterization. In addition, the advent of ultra-widefield FA (UWFA) imaging systems with the capability to produce images with a 200° field of view in a single photograph, allows for visualization up to 3.2 times more retinal area compared to the conventional 7 standard field imaging implemented by the ETDRS, providing a unique opportunity for assessing panretinal vascular disease burden.^{3,4}

Compared to clinical examination, OCT is a more sensitive and specific method for objective evaluation of structural changes in DME, including macular thickness and presence of fluid.^{5,6} However image-guided metrics are needed to maximize our approach to DR and early DME where OCT may not be the optimal tool. Previous studies have examined the relationship between FA and OCT imaging features in DME,⁸ but limited studies have assessed UWFA features, in particular quantitative UWFA, and the correlation to DME. Studies that have investigated the relationship between ischemia on UWFA and DME have found varied and somewhat confounding results. Wessel et al. found a correlation between peripheral ischemia and the presence/absence of DME, while Silva et al. and Fan et al. found no significant association between non-perfusion and clinically significant DME.^{9,10, 11} One previous study quantified peripheral leakage on UWFA images of eyes with diabetic retinopathy and found a moderate correlation between peripheral leakage and the

size of the foveal avascular zone. However, the study did not evaluate the association of DME with specific quantitative leakage metrics.¹² Given the limited research of the impact of UWFA features, such as MA count, leakage index, and ischemic index on eyes with DME, further investigation is warranted.

The current study aims to characterize the relationship between the presence of DME and quantitative UWFA metrics, including ischemic index, leakage index, and microaneurysm count. Additional clinical/demographic factors were also evaluated to assess their association with the presence of DME. This initial assessment may provide further insight into the underlying pathophysiology, disease burden, and retinal vascular feature characterization which is of importance in both clinical and research applications.

METHODS

Study Population and Analysis

This retrospective study was approved by the Cleveland Clinic Institutional Review Board (IRB) and adhered to the tenets of the Declaration of Helsinki. Given the retrospective nature of this study, no informed consent was required. Eyes with diabetic retinopathy were identified that underwent angiographic assessment with UWFA using either the 200Tx and California imaging systems (Optos, Scotland, UK) and concurrent SD-OCT imaging. Exclusion criteria included prior pan-retinal photocoagulation, intravitreal injections within the last six months, poor UWFA image quality, or severe artifacts obscuring view (e.g., lashes). Additional exclusion criteria included poor SD-OCT quality or color photos of insufficient quality to grade diabetic retinopathy severity.

A chart review was also conducted for all patients for the following data: age, sex, race, hemoglobin A1C (HbA1C), hypertension, systolic blood pressure, diastolic blood pressure, high cholesterol, blood thinners, smoking, and lens status. The HbA1C and blood pressure values recorded in the chart (from any office or hospital visit) closest to the date of the UWFA were used. Clinical data with continuous values were analyzed with a one-way ANOVA. Clinical data categorical values were analyzed with chi-square tests.

Quantitative UWFA Analysis

Two UWFA image timepoints were selected for each study eye: one in the AV-transit or early venous phase and one in the late phase for quantitative analysis. UWFA images were dewarped to correct for peripheral distortion, as previously described.¹³ A semi-automated platform for angiographic feature extraction was utilized as previously described for initial analysis.¹⁴ Following initial segmentation, manual correction was performed as needed with an initial review by a trained image analyst. A second analyst performed a confirmatory read. A region of interest was identified for each metric based on the area of analyzable retina for a given feature.

Ischemia was defined as areas of significant hypofluorescence or a region of capillary non-perfusion in early-mid phase FA images. The total retinal area was delineated as the peripheral edge at which the vessels could be visualized. The ischemic index was calculated as the area of ischemia divided by the total analyzable retinal area.

MAs were defined as small circular foci which were significantly hyperfluorescent compared to surrounding choroidal background in early-mid phase FA images. MA count was defined as the number of MAs within the specified area. Leakage was defined as a region of increasing hyperfluorescence in size and intensity in the late phase angiogram compared to the AV-transit phase. Leakage index was defined as the area of leakage divided by the overall analyzable area of the retina. Zonal assessments of MA counts and leakage indices were also evaluated including two regions: the macular zone (i.e., a 3 disc diameter circular zone centered on the fovea) and the peripheral zone (i.e., all regions peripheral to the macular zone within the analyze area of the retina). Representative examples of MA and leakage segmentation in eyes with and without DME can be seen in Figure 1.

Clinical Diabetic Retinopathy Severity and DME Assessment

For each eye, the corresponding ultra-widefield color fundus photos were graded for DR severity according to the International Clinical Disease Severity Scale for Diabetic Retinopathy.² SD-OCT images were also analyzed to determine the presence or absence of DME, which was defined as the presence of any intraretinal fluid on the OCT macular cube scan. OCT scans were additionally assessed for central subfield thickness (CST) and the presence of subretinal fluid (SRF). In our patient cohort, 126 patients have two eyes included in this study. To account for the dependence of two eyes from the same patient, we fitted linear mixed effect model (LMM) and generalized linear mixed effects model (GLMM) for the continuous variable (OCT CST) and the binary categorical variables (the presence of DME and the presence of OCT SRF), respectively.

RESULTS

Demographics and Clinical Features

A total of 304 eyes (156 OD, 148 OS) from 178 diabetic patients met criteria for inclusion in this study. This included 181 eyes were from males (59.5%) and 123 eyes were from females (40.5%) with a mean age of 62.7 years $\pm$ 13.3 years. There were 232 phakic (76.3%) eyes and 72 pseudophakic (23.7%) eyes. HbA1C levels were available for 236 eyes with a mean of 8.0% $\pm$ 1.9%. Clinical DR severity grading of the eyes showed 32 eyes (10.5%) with mild NPDR, 74 eyes (24.3%) with moderate NPDR, 120 eyes with severe NPDR (39.5%), and 78 eyes with PDR (25.7%). From OCT review, 143 eyes (47.0%) had DME, while 161 eyes (53.0%) had no evidence of DME. The clinical characteristics of the patients are summarized in Table 1.

The presence of DME was associated with increased age ($p=0.007$) and higher systolic blood pressure ($p=0.008$), but not current HbA1C ($p=0.4$) or diastolic blood pressure ($p=0.7$) (Table 1). DR severity was significantly associated with the presence of DME, ($p=0.04$). In addition, eyes with DME were significantly associated with Caucasian race ($p=0.03$), but not gender ($p=0.97$), clinical diagnosis of hypertension ($p=0.62$), high cholesterol ($p=0.76$), blood thinners ($p=0.09$), smoking ($p=0.84$), or lens status ($p=0.87$) (Table 1). The presence of SRF was associated with higher systolic blood pressure (mean 144.4 mm Hg vs 134.5 mm Hg, $p=0.025$). Overall mean CST was 297.1 microns $\pm$ 100.5 microns; eyes with DME

had a mean CST of $346.6 \text{ microns} \pm 123.3 \text{ microns}$ and eyes without DME had a mean CST of $253.08 \text{ microns} \pm 38.70 \text{ microns}$.

Quantitative UWFA Parameters and DME Features

Panretinal univariate assessments showed no significant difference between eyes with DME compared to eyes without DME for total ischemic index ($p=0.51$), total aneurysms ($p=0.74$), total leakage area ($p=0.51$), and total leakage index ($p=0.11$) (Figure 2).

Quantitative zonal assessments of MA counts and leakage on UWFA demonstrated significant association with the incidence of DME. Eyes with DME had a significantly higher macular leakage index ($9.68\% \pm 7.78\%$) than eyes without DME ($5.84\% \pm 7.95\%$, $p=0.0004$). Peripheral leakage index was not associated with DME ($p=0.91$). In addition, the distribution of leakage in eyes with DME was more macular predominant (i.e. mean $52.9\% \pm 25.1\%$ of leakage was located in the posterior pole) compared to eyes without DME (i.e., $35.4\% \pm 27.5$, $p < 0.0001$) (Figure 3).

Similarly, the mean macular MA count was significantly higher in eyes with DME ($69.6 \text{ MAs} \pm 54.2$) compared to eyes without DME ($49.7 \text{ MAs} \pm 51.3$, $p = 0.003$) (Figure 4). In addition, eyes with macular predominant MA distribution ($45.5\% \pm 1.8\%$) (e.g., percentage of macular MAs out of total panretinal MAs), had a significantly higher incidence of DME compared to eyes with a more peripheral predominant distribution ($32.5\% \pm 1.6\%$, $p<0.001$) (Figure 5).

Multi-variate generalized linear mixed effects regression analysis identified central subfield thickness ($p<0.0001$), increased macular MA count ($p = 0.002$), total MA count ($p=0.05$) increased macular leakage index ($p = 0.05$), and systolic blood pressure ($p = 0.005$) to be independently associated with the presence of DME. Panretinal ischemic index was not significantly associated with the presence of DME with multivariate assessment ($p = 0.15$). When the model did not include OCT factors (i.e., CST), macular leakage index ($p=0.001$) and macular MA count ($p=0.007$) remained independently associated with the presence of DME.

In eyes with DME, severity of macular edema, as measured by CST was positively correlated with macular leakage index ($p<0.00001$, $R=0.30$) and was weakly but significantly correlated macular MA count ($p=0.03$, $R=0.09$). In addition, age, BP parameters, ischemic index, Hgb A1c values were not correlated with CST. SRF was not found to be associated with any variables when accounting for two-eye dependency on univariate assessment. Prior to correcting for 2-eye dependence, the presence of SRF was significantly associated with a higher panretinal leakage index (4.4% vs 2.9% , $p=0.03$) and, in particular, increased macular leakage index (12.8% vs 7.3% , $p=0.004$). However, multi-variate generalized linear mixed effects regression analysis identified: increased macular leakage index ($p=0.01$) and smoking history (0.04) as independently and significantly associated with SRF on OCT.

DISCUSSION

The current study demonstrates the strong association between macular zone leakage index severity and the presence of DME, as well as the association of macular zone MA count with the presence of DME. Interestingly, this study found that panretinal levels of ischemia, leakage, and MAs did not vary significantly between eyes with and without DME (Figure 2). Though not fully understood, DME arises from breakdown of the blood-retinal barrier, causing fluid and proteins to leak out of the vasculature and accumulate in the macula. Previous research has demonstrated the link between MA presence, leakage, and DME. Najeeb et al. previously found that MAs and leakage had the same spatial distribution of leakage in the retina, suggesting at least some component of leakage in DR arises from strongly hyperpermeable MAs.¹⁶ In this study, both the concordant association of increased macular zone MA count and increased macular zone leakage index with DME suggests that both mechanisms play significant roles in the pathophysiology of DME. However, severity of DME by CST was positively correlated with only leakage in the macular zone, and not with MA count in the macular zone. Further, the presence of SRF was associated with panretinal leakage index, and to a greater extent leakage index in the macular zone, but there was no association seen with either increased ischemic index or MA count in the macular zone. Both CST and SRF were significantly correlated with leakage index, but not MA count in this region. Thus, macular leakage index appears to be the most important quantitative angiographic metric associated with DME severity and possibly the incidence of SRF. This suggests that greater vascular hyperpermeability, both panretinal and in the macular zone, may overwhelm the compensatory mechanisms of the retina for fluid resorption, leading to the development of more severe intraretinal fluid and subretinal fluid accumulation. Pharmacotherapeutic approaches targeted at reducing leakage index could help to confirm the role of leakage in disease pathogenesis and progression.

Increased panretinal ischemia and panretinal ischemic index have been strongly correlated with DR severity, especially in the pathogenesis of PDR, but not to DME.¹⁵ In this study, panretinal ischemic index was not associated with DME incidence in univariate assessment. However, multivariate assessment demonstrated a trend for association of ischemic index with DME incidence when OCT factors were incorporated into the model. The strong correlation of leakage index and CST may suggest that there may be a possible independent mechanism for DME related to ischemia, but additional research will be needed with a larger dataset to better define the potential impact of ischemic index on the incidence of DME. Silva et al. and Fan et al., also did not find a significant relationship between global ischemia and clinically significant DME.^{10,11} Previously, Wessel et al. described that the incidence of DME was higher in patients with ischemia; however, when the binary classification of presence or absence of DME was removed a significant relationship between the amount of macular thickening and extent of retinal ischemia did not exist.⁹ Similarly, in the univariate assessment, posterior pole MA count was associated with the presence of DME but univariate panretinal MA count was not; although the multi-variate assessment when including OCT factors demonstrated weak association of total MA count. Additional studies are needed to determine whether peripheral MAs have an association with DME that may not be significant in small sample sizes.

Additionally, this study did not detect an association between DME and certain clinical characteristics. For instance, hyperglycemic control (as assessed by HbA1C) and hyperlipidemia has been associated with an increased risk of developing DME, but was not significantly correlated in our study.^{17,18,19} Additionally, systemic risk factors are often multifactorial and may only account for some of the risk. Such data strongly suggests that additional unidentified factors play a critical role in the development and progression of DR and DME.

We recognize that our study is not without limitations. Inherent to a retrospective, cross-sectional study, our results should be followed up by a prospective and/or interventional study. Additionally, there was no standardized acquisition protocol for UWFA images and challenges were encountered with image segmentation including low image quality, media opacities, and artifacts, leading to the exclusion of images in the initial screening. In an effort to balance these issues a large number of eyes were included in the study. One additional limitation is that both eyes of patients with sufficient quality of angiograms were included that could lead to some inherent biases. Finally, our study defined DME to be the presence of any intraretinal fluid seen on OCT, however future studies examining foveal-involving DME may also be of interest.

Despite our limitations, this study is to our knowledge first assessment of multiple factors quantitative ultra-widefield angiographic features in DME. Additional research is needed for higher order evaluation of ultra-widefield leakage parameters, including perivascular and generalized distribution. Anti-VEGF treatments for DME have been shown to decrease diffuse leakage area on FA by a mean of 40% but not have a significant impact on focal leakage.²⁰ The distribution of leakage and characterization of leakage foci on UWFA can be further analyzed with machine learning algorithms, which can process high volumes of datasets and summarize complex information. Extensive peripheral ischemia has been associated with identifying recalcitrant eyes, however given the results of this study it is reasonable to include the evaluation of macular leakage index on UWFA in treatment-resistant eyes with DME.²¹ In addition, more work is needed to better understand the driving mechanism that may be associated with increased macular leakage index and whether this could be used as a treatment guidance tool. Finally, natural history studies similar to the DRCR Protocol AA can investigate the role of leakage as a potential biomarker for predicting the development of DME in addition to treatment response.

In summary, this study demonstrates the zonal preference of increased MA and leakage in the posterior pole in eyes with DME. Total panretinal angiographic features did not correlate in eyes with DME presence. Additional research is needed to determine the role of quantitative angiographic features in the detection of DME, as well as prognosis and treatment response.

Acknowledgments

Financial Support: NIH/NEI K23-EY022947-01A1 (JPE); Research to Prevent Blindness (Cole Eye Institutional)

REFERENCES

1. Hariprasad SM, Mieler WF, Grassi M, Green JL, Jager RD, Miller L. Vision-related quality of life in patients with diabetic macular oedema. *Br J Ophthalmol*. 2008;92(1):89–92. doi:10.1136/bjo.2007.122416. [PubMed: 17584999]
2. Photocoagulation therapy for diabetic eye disease. Early Treatment Diabetic Retinopathy Study Research Group. *JAMA*. 1985;254(21):3086. doi:10.1001/jama.1985.03360210102042. [PubMed: 4057532]
3. Wessel MM, Aaker GD, Parlitsis G, Cho M, D'Amico DJ, Kiss S. Ultra-wide-field angiography improves the detection and classification of diabetic retinopathy. *Retina*. 2012;32(4):785–791. doi: 10.1097/IAE.0b013e3182278b64. [PubMed: 22080911]
4. Grading diabetic retinopathy from stereoscopic color fundus photographs--an extension of the modified Airlie House classification. ETDRS report number 10. Early Treatment Diabetic Retinopathy Study Research Group. *Ophthalmology*. 1991;98(5 Suppl):786–806. doi:10.1016/s0161-6420(13)38012-9. [PubMed: 2062513]
5. Diabetic Retinopathy Clinical Research Network DRCR, Browning DJ, Glassman AR, et al. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology*. 2007;114(3):525–536. doi:10.1016/j.ophtha.2006.06.052. [PubMed: 17123615]
6. Tan CSH, Chew MCY, Lim LWY, Sadda SR. Advances in retinal imaging for diabetic retinopathy and diabetic macular edema. *Indian J Ophthalmol*. 2016;64(1):76–83. doi: 10.4103/0301-4738.178145. [PubMed: 26953028]
7. Yeung L, Lima VC, Garcia P, Landa G, Rosen RB. Correlation between Spectral Domain Optical Coherence Tomography Findings and Fluorescein Angiography Patterns in Diabetic Macular Edema. *Ophthalmology*. 2009; 116(6): 1158–1167. doi: 10.1016/J.OPHTHA.2008.12.063. [PubMed: 19395034]
8. Özdek C, Erdiñ MA, Gürelik G, Aydın B, Bahçeci U, Hasanreisio lu B. Optical Coherence Tomographic Assessment of Diabetic Macular Edema: Comparison with Fluorescein Angiographic and Clinical Findings. *Ophthalmologica*. 2005;219(2):86–92. doi: 10.1159/000083266. [PubMed: 15802932]
9. Wessel MM, Nair N, Aaker GD, Ehrlich JR, D'Amico DJ, Kiss S. Peripheral retinal ischaemia, as evaluated by ultra-widefield fluorescein angiography, is associated with diabetic macular oedema. *Br J Ophthalmol*. 2012;96(5):694–698. doi:10.1136/bjophthalmol-2011-300774. [PubMed: 22423055]
10. Silva PS, Dela Cruz AJ, Ledesma MG, et al. Diabetic Retinopathy Severity and Peripheral Lesions Are Associated with Nonperfusion on Ultrawide Field Angiography. *Ophthalmology*. 2015;122(12):2465–2472. doi:10.1016/J.OPHTHA.2015.07.034. [PubMed: 26350546]
11. Fan W, Wang K, Ghasemi Falavarjani K, et al. Distribution of Nonperfusion Area on Ultra-widefield Fluorescein Angiography in Eyes With Diabetic Macular Edema: DAVE Study. *Am J Ophthalmol*. 2017;180:110–116. doi:10.1016/j.ajo.2017.05.024. [PubMed: 28579062]
12. Sim DA, Keane PA, Rajendram R, et al. Patterns of Peripheral Retinal and Central Macula Ischemia in Diabetic Retinopathy as Evaluated by Ultra-widefield Fluorescein Angiography. *Am J Ophthalmol*. 2014;158(1):144–153.e1. doi:10.1016/J.AJO.2014.03.009. [PubMed: 24709807]
13. Croft DE, van Hemert J, Wykoff CC, et al. Precise montaging and metric quantification of retinal surface area from ultra-widefield fundus photography and fluorescein angiography. *Ophthalmic Surg Lasers Imaging Retina*. 45(4):312–317. doi:10.3928/23258160-20140709-07.
14. Itoh Y, Petkovsek D, Kaiser PK, Singh RP, Ehlers JP. Optical Coherence Tomography Features in Diabetic Macular Edema and the Impact on Anti-VEGF Response. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(10):908–913. doi:10.3928/23258160-20161004-03. [PubMed: 27759856]
15. Jiang AC, Boss JD Srivastava SK, Reese J, and Ehlers JP. Evaluation of Diabetic Retinopathy Severity and Underlying Panretinal Ischemic Index. Poster Presentation. Association for Research in Vision and Ophthalmology Annual Meeting April 30, 2018. Honol.

16. Najeef BH, Simader C, Deak G, et al. The distribution of leakage on fluorescein angiography in diabetic macular edema: A new approach to its etiology. *Investig Ophthalmol Vis Sci*. 2017;58(10):3986–3990. doi:10.1167/iovs.17-21510. [PubMed: 28796876]
17. Bhagat N, Grigorian RA, Tutela A, Zarbin MA. Diabetic Macular Edema: Pathogenesis and Treatment. *Surv Ophthalmol*. 2009;54(1):1–32. doi:10.1016/j.survophthal.2008.10.001. [PubMed: 19171208]
18. Klein R, Klein BEK, Moss SE, Davis MD, DeMets DL. Glycosylated Hemoglobin Predicts the Incidence and Progression of Diabetic Retinopathy. *JAMA J Am Med Assoc*. 1988;260(19):2864. doi:10.1001/jama.1988.03410190112033.
19. Risks of Progression of Retinopathy and Vision Loss Related to Tight Blood Pressure Control in Type 2 Diabetes Mellitus. *Arch Ophthalmol*. 2004;122(11):1631. doi: 10.1001/archophth.122.11.1631. [PubMed: 15534123]
20. Allingham MJ, Mukherjee D, Lally EB, et al. A Quantitative Approach to Predict Differential Effects of Anti-VEGF Treatment on Diffuse and Focal Leakage in Patients with Diabetic Macular Edema: A Pilot Study. *Transl Vis Sci Technol*. 2017;6(2):7. doi :10.1167/tvst.6.2.7.
21. Patel RD, Messner LV, Teitelbaum B, Michel KA, Hariprasad SM. Characterization of ischemic index using ultra-widefield fluorescein angiography in patients with focal and diffuse recalcitrant diabetic macular edema. *Am J Ophthalmol*. 2013;155(6):1038–1044.e2. doi:10.1016/j.ajo.2013.01.007. [PubMed: 23453693]

Figure 1. Segmentation of Leakage on UWFA.

Late time point UWFA images with severe NPDR either without or with DME. Top row represents unsegmented images. Bottom row represents images with leakage segmentation. The gold ring represents the macula-centered posterior pole. The blue line delineates the total retinal area.

Figure 2. Segmentation of MAs on UWFA.

Early time point UWFA images with severe NPDR, either without or with DME. Top row represents unsegmented images. Bottom row represents images with MA segmentation. The gold ring represents the macula-centered posterior pole. The blue line delineates the total retinal area.

Figure 3. Global assessments of angiographic features on eyes with and without DME.

There was no significant difference between eyes with DME compared to eyes without DME for A) total ischemic index ($p=0.607$), B) total aneurysms ($p=0.739$), C) total leakage area ($p=0.292$), and D) total leakage index ($p=0.152$).

Figure 4. Quantitative Analysis of Leakage.

A) Leakage index. Compared to eyes without DME, eyes with DME had a significantly higher leakage index in the posterior pole ($p<0.0001$). B) Leakage distribution. Compared to eyes without DME, eyes with DME had a significantly high proportion of leakage found in the posterior pole ($p<0.0001$). Whiskers represent 10-90th percentiles.

Figure 5. Quantitative Analysis of MAs.

Compared to eyes without DME, eyes with DME had significantly higher A) macular MA count ($p=0.003$) and B) distribution of MAs found in the posterior pole ($p<0.0001$). Whiskers represent 10-90th percentiles.

Table 1.

Patient demographics.

Characteristic	DME - (n=161)	DME + (n=143)	p value
Age (years, mean $\pm$ SD)	60.2 $\pm$ 14	64.8 $\pm$ 12	0.0007 *
Male/Female	96/65	85/58	1.000
Caucasian/African American	66/89	79/54	0.03 *
OD/OS	74/69	82/79	0.89
Phakic/Pseudophakic	123/38	109/34	0.87
DR severity			
Mild NPDR	24	8	
Moderate NPDR	38	36	
Severe NPDR	56	64	
PDR	43	35	
Systolic bp (mmHg, mean $\pm$ SD)	131.0 $\pm$ 18.6	140.2 $\pm$ 22.3	0.0002 *
Diastolic bp (mmHg, mean $\pm$ SD)	74.6 $\pm$ 12.53	76.5 $\pm$ 11.1	0.1880
HbA1C (mean $\pm$ SD)	8.0% $\pm$ 2.0%	8.0% $\pm$ 1.7%	0.4
Presence of high cholesterol (# of eyes)	141	124	0.76
Use of blood thinners (# of eyes)	128	100	0.09
Smoker (C/F/N)	13/61/87	16/52/75	0.84

SD standard deviation; C/F/N current/former/never smoker; DME diabetic macular edema; NPDR nonproliferative diabetic retinopathy; PDR proliferative diabetic retinopathy.