## ARTICLE ORIGINAL

# Contribution of ultra-wide field fluorescein angiography in diabetic retinopathy in a Tunisian population

## Apport de l'angiographie à la fluorescéine ultra-grand champ dans la rétinopathie diabétique, dans une population Tunisienne

Rym Maamouri, Rim Bouraoui, Khaled El Matri , Ahmed Chebil, Asma Hassairi, Emna Regai, Yousra Falfoul, Leila El Matri

*Institut d'ophtalmologie de Tunis, Service B / Université Tunis – El Manar, Faculté de médecine de Tunis,*

**RÉSUMÉ**

**Objectif :** Évaluer l'apport de l'angiographie à la fluorescéine (AF) ultra-grand champ (UGC) chez les patients ayant une rétinopathie diabétique (RD) cliniquement non-proliférante (NP) et d'analyser l'association entre les modifications vasculaires périphériques et la présence d'œdème maculaire diabétique (OMD).

**Méthodes :** Étude rétrospective de patients diabétiques explorés par AF-UGC obtenues à l'aide d'un système de lentille contact ultra-grand champs. L'OMD avait été retrouvé à la fois sur l'AF et la tomographie par cohérence optique à domaine spectral (SD-OCT).

**Résultats :** Un total de 71 yeux de 39 patients diabétiques avec une RD cliniquement non proliférante a été inclus. La RD était cliniquement classée en RDNP severe dans 52 yeux (73%), RDNP modérée dans 15 yeux (21%) et RDNP minime dans 4 yeux (6%).

Sur l'AF-UGC, les signes de RD étaient principalement antérieurs dans 14% des cas (10/71), principalement postérieurs dans 48% des cas (34/71) et diffus dans 38% des cas (27/71). Une ischémie rétinienne était retrouvée dans 87% des yeux (62/71), prédominant dans les zones temporales supérieures. Une diffusion vasculaire périphérique était observée dans 85% des cas (60/71) et une néovascularisation pré-rétinienne était présente dans 14% des cas (10/71), changeant le stade de la RD de RDNP à RD proliférante dans 10 yeux.

Un OMD était présent sur SD-OCT dans 53% des cas. L'épaisseur maculaire centrale était significativement plus importante dans les yeux ayant des zones d'ischémie rétinienne périphérique (353 µm vs. 254 µm, p = 0,006) et l'ischémie rétinienne périphérique était associée à un œdème maculaire (97% contre 76%, p = 0,01) et une acuité visuelle basse (p <0,001). La diffusion vasculaire périphériques était associée à la présence d'une ischémie rétinienne périphérique (p <0,001) et la présence de néovascularisation rétinienne (53% vs. 35%, p = 0,01), mais elle n'était pas associée à la présence d'OMD (p = 0,449).

**Conclusion :** L'angiographie à la fluorescéine ultra-grand champ est d'un grand apport dans l'étude de la périphérie rétinienne chez les patients ayant une rétinopathie diabétique. Elle nous aide ainsi à améliorer la classification de la RD et à guider un éventuel traitement au laser. Elle permet aussi une connaissance plus approfondie de la physiopathologie de l'œdème maculaire diabétique.

**Mots-clés :** rétinopathie diabétique ; angiographie à la fluorescéine ultra-grand champ ; rétinopathie diabétique antérieure ; ischémie rétinienne périphérique ; diffusion vasculaire périphérique ; néovascularisation pré-rétinienne ; œdème maculaire diabétique

**SUMMARY**

**Aim:** To assess the contribution of ultra-wide field (UWF) fluorescein angiography (FA) in clinically non proliferative diabetic retinopathy (DR) and to study the relationship between peripheral vascular lesions and the presence of diabetic macular edema (DME).

**Methods:** Retrospective study of consecutive UWF-FA obtained using a wide-field contact lens system. DME was detected on both FA and spectral-domain optical coherence tomography (SD-OCT).

**Results**: A total of 71 eyes of 39 diabetic patients with clinically non proliferative DR (NPDR) was included. DR was clinically graded as severe NPDR in 52 eyes (73%), moderate NPDR in 15 eyes (21%) and mild NPDR in 4 eyes (6%).

On UWF-FA, DR was predominantly anterior in 14% of cases (10/71), predominantly posterior in 48% of cases (34/71) and diffuse in 38% of cases (27/71). Retinal non perfusion was present in 87% of eyes (62/71), predominating in superior-temporal areas. Peripheral vessel leakage was present in 85% of cases (60/71) and retinal neovascularization was noted in 14% of cases (10/71), upgrading DR severity from NPDR to proliferative DR in 10 eyes.

DME was present on SD-OCT in 53% of cases. Central macular thickness was significantly higher in eyes with retinal non-perfusion (353 µm vs. 254 µm, p=0,006) and retinal non-perfusion was associated with macular edema (97% vs. 76%, p=0,01) and poor visual acuity (p<0.001). Peripheral vessel leakage was associated with retinal non-perfusion (p<0.001) and retinal neovascularization (53% vs. 35%, p=0.01), but it was not associated with the presence of DME (p=0.449).

**Conclusion:** UWF-FA was of great help assessing DR and evaluating peripheral retinal lesions in order to refine DR staging and to guide laser treatment. Besides, it allows better understanding of DME pathophysiology.

**Keywords:** Diabetic retinopathy; ultra-wide field fluorescein angiography; anterior diabetic retinopathy; retinal non perfusion; peripheral vascular leakage; retinal neovascularization; diabetic macular edema

Correspondance

Khaled El Matri

Institut d'ophtalmologie de Tunis, Service B / Université Tunis - El Manar / Faculté de médecine de Tunis,

E-mail: khaled.elmatri@gmail.com

## INTRODUCTION

Diabetic retinopathy (DR) remains the leading cause of visual loss in adults (1). The prevalence of visual impairment related to DR is on the rise worldwide and particularly in North Africa and the Middle East (2). Diabetes prevalence in Tunisia was estimated to be 9.9% in 2007 (3), and would be rising to 26.6% in 2027 (4). Early diagnosis is important to prevent advanced proliferative stages, and early treatment is necessary is cases of diabetic macular edema (DME) to avoid irreversible vision loss.

Capturing a single image of the entire ocular fundus has been limited (5). To overcome the uncertainty of obtaining midperipheral angiographic information, protocols such as the seven standard fields have been utilized for creating uniform clinical research data, combining seven 30-degree-images allowing the visualization of approximately 75 degrees of the fundus (6). Standard fluorescein angiography (FA) with confocal scanning laser ophthalmoscopy (CSLO) can capture single shot fundus images of 30, 55 or 102 degrees, using a classic non-contact lens, a wide field non-contact lens or the ultra-wide field (UWF) non-contact module, respectively (7). Automatic montage assembly of traditional FA images can be obtained, combining multiple images of the posterior pole and the periphery resulting in a composite field up to 120 degrees (8). In 2005, Staurenghi et al. reported the development of an UWF contact lens compatible with the CSLO imaging system and described its utility in retinal vascular diseases (9). This contact lens system could increase the field of view up to 150 degrees in a one-shot image.

More recently, a new non-contact UWF device has been developed, utilizing an ellipsoid mirror allowing to produce approximately 200 internal degrees of view (10), however this innovative machine is not available yet in Tunisia.

The aim of our study was to assess the contribution of UWF-FA in clinically non proliferative DR and to study the relationship between peripheral vascular lesions and the presence of DME.

## METHODS

**Study design and patient selection:** A retrospective consecutive observational study of eyes with DR diagnosed in the ophthalmology "B" department at "Institut Hedi Raies

d'ophtalmologie de Tunis" over 2 years (January 2013-January 2015). All patients provided informed consent before their participation in the study. All diabetic patients had a non-proliferative DR (NPDR) based on fundus examination and colour fundus photography (Topcon 3D OCT-2000 FA plus, Tokyo, Japan) and NPDR stages were determined according to the diagnostic criteria of the early treatment diabetic retinopathy study (ETDRS). All patients underwent CSLO UWF-FA (Heidelberg engineering HRA2, Heidelberg, Germany), using Staurenghi UWF contact lens (Ocular Staurenghi 230 SLO Retina Lens; Ocular Instruments Inc., Bellevue, WA). UWF-FA was obtained according to standard protocol with intravenous injection of 5 ml of 10% sodium fluorescein. Using the standard FA with non-contact lens, we obtained composite FA images. The composite image was putted over the UWF-FA image and the resulting overlaid circle was regarded as a boundary line for the classification of the DR localization. We analysed each image evaluating the localization of DR (predominantly anterior, predominantly posterior or diffuse); and evaluating the presence of retinal non-perfusion (RNP) greater than one disc diameter, retinal neovascularization (RNV) and peripheral vascular leakage (PVL). Spectral domain optical coherence tomography (SD-OCT) (Topcon 3D OCT-2000 FA plus, Tokyo, Japan) was performed to all patients evaluating the presence of DME, defined as a central macular thickness (CMT) greater than 300 μm and/or the presence of intra/sub-retinal fluid accumulation.

Exclusion criteria were ocular comorbidities such as retinal vascular occlusions, advanced age-related macular degeneration, inherited macular diseases, intra-ocular inflammation, or macular scar of any etiology. The non-inclusion criteria were patients with clinically proliferative DR (PDR), patients with history of laser photocoagulation or intra/peri-ocular injections, and eyes with media opacity resulting in low-quality images precluding accurate evaluation of the UWF-FA.

Patients charts were then reviewed for age, gender, type and duration of diabetes, level of hemoglobin A1c (HbA1C), and Snellen best corrected visual acuity (BCVA).

**Statistical analysis:** BCVAs were recorded as decimal values and converted to the logarithm of the minimal angle of resolution (LogMAR). Pearson correlation test, paired Wilcoxon test and chi-square test were performed using

SPSS 22.0 for Windows. The paired Student's *t*-test was used to statistically evaluate changes in Log MAR BCVA and CMT at different time points. In all analyses, a *P* value <0.05 was considered to be statistically significant.

## RESULTS

### Baseline characteristics (table 1):

Our study included 71 eyes of 39 patients (20 females and 19 males). Mean age of the patients was 58 ± 12 years (range from 19 to 79 years), mean duration of diabetes was 10 years and mean HbA1C was 7.4%. Mean visual acuity was 0.30 [IQR] = 0.29 LogMAR. DR was clinically graded as severe NPDR in 52 eyes (73%), moderate NPDR in 15 eyes (21%) and mild NPDR in 4 eyes (6%). DME was present on SD-OCT in 38 eyes (53%).

**Table 1.** Demographic and clinical characteristics of patients with diabetic retinopathy (39 patients / 71 eyes)

| Parameters | Data |
|---|---|
| Mean age (years) | 58 [19 - 79] |
| Sex ration (F/H) | 20/19 |
| Type of diabetes mellitus (n = patients) | |
| *Type 1* | 3 (8%) |
| *Type 2* | 36 (92%) |
| Mean duration of diabetes  (years) | 10 [1 - 30] |
| Mean HbA1C (%) | 7.4 [7 – 8.2] |
| Mean BCVA (Median LogMAR) | 0.3 (+1.3-0) |
| DR clinical severity grade  (n = eyes) | |
| *Mild* | 4 (6%) |
| *Moderate* | 15 (21%) |
| *Severe* | 52 (73%) |
| *Proliferative* | 0 |

LogMAR= logarithm of the minimal angle of resolution

### Angiographic characteristics (table 2):

DR was predominantly anterior in 10 eyes (14%), predominantly posterior in 34 eyes (48%) and diffuse in 27 eyes (38%). RNP was present in 62 eyes (87%) (Figure 1) and it was essentially localized in the superior temporal quadrant (71%). PVL was identified in 60 eyes (85%), predominantly in the superior quadrant. Finally, RNV was present in 10 eyes (14%) and was localized in all cases beyond the limits of composite standard FA. The latter finding upgraded the DR severity from clinically NPDR to angigraphically PDR in 10 eyes (clinically severe NPDR in 8 eyes, moderate NPDR in 1 eye, and mild NPDR in 1 eye) (Figure 2,3).

**Table 2.** Ultra-wide field fluorescein angiographic characteristics in a series of 71 eyes with diabetic retinopathy

| Angiographic findings | Eyes: n (%) |
|---|---|
| Angiographic macular edema | 38 (53%) |
| Angiographic macular ischemia | 3 (4%) |
| Retinal non perfusion (RNP) | 62 (87%) |
| Retinal neovascularization (RNV) | 10 (14%) |
| Localization of DR signs | |
| - Predominantly anterior | 10 (14%) |
| - Predominantly posterior | 34 (48%) |
| - Diffuse | 27 (38%) |
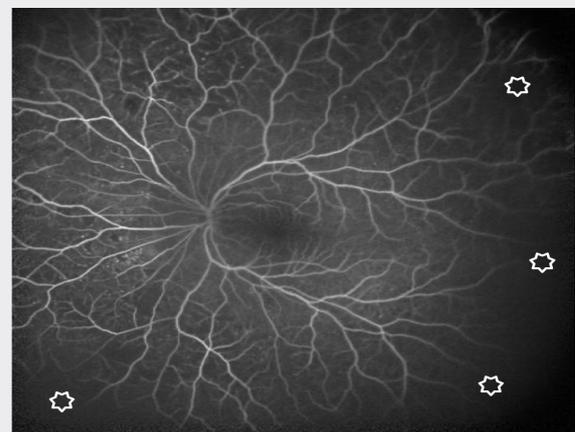


**Figure 1 :** UWF-FA of a clinicaly mild NPDR showing multiple microneurysms and masking effect of retinal hemorrhages in the periphery and areas of RNP (ischemia) in the extreme priphery (white stars), upgrading the mild NPDR into a severe NPDR with predominantly anterior DR signs.
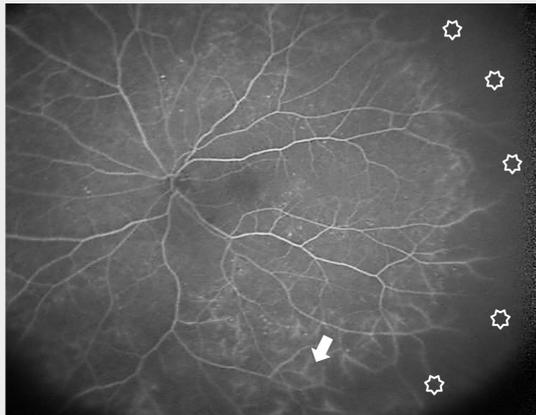
**Figure 2:** UWF-FA of a clinically moderate NPDR showing diffuse DR signs with peripheral vascular leakage (white arrow) and extensive areas of RNP in the temporal extreme periphery (white stars), upgrading the moderate NPDR into a severe NPDR with diffuse DR signs.
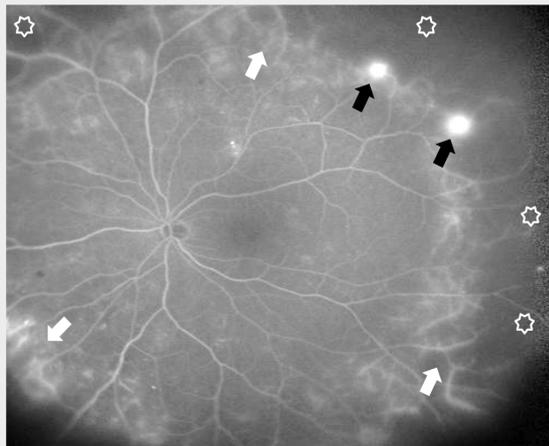


**Figure 3:** UWF-FA of a clinically mild NPDR showing PVL (white arrows), extensive areas of RNP (white stars) associated to RNV (black arrows) in the extreme periphery, upgrading the mild NPDR into a proliferative DR with predominantly anterior DR signs.

RNP was significantly associated with macular edema (97% vs. 76%, p=0.01) and poor BCVA (p<0.001); and CMT was significantly higher in eyes with RNP (353µm vs. 254µm p=0.006). No association was found between RNV and DME (p=0.07). However, PVL was associated with RNP (p<0.001) and RNV (53% vs. 35%, p=0.01), but not with DME (p=0.449).

Finally, using UWF-FA, DR was angiographically reclassified as PDR in 10 eyes (14%), severe NPDR in 52 eyes (73%), moderate NPDR in 7 eyes (10%), and mild NPDR in 2 eyes (3%).

## DISCUSSION

In the current study of diabetic patients with NPDR, UWF-FA shown effective highlighting severe peripheral lesions not detected clinically nor on composite standard FA. It could detect RNP areas in 87% of cases and more interestingly it highlighted the presence of RNV in the extreme periphery in 10 cases, upgrading the DR severity from clinically NPDR to angiographically PDR in 10 eyes. Using UWF-FA, we also noticed that DR lesions could be diffuse or predominate either anteriorly or posteriorly. DR signs were predominantly anterior in 14% of cases, predominantly posterior in 48% of cases and diffuse in 38% of cases. Anterior DR lesions may not be detected on standard imaging, wrongfully downgrading the DR severity.

PVL was associated with RNP and RNV, but it was not associated with the presence of DME; while RNP was associated with DME and poor visual acuity.

Since its introduction, UWF imaging has shown its utility in the diagnosis of DR, with a stronger sensitivity compared to conventional FA and clinical examination (11–13). According to the previous studies, areas of retinal non perfusion detected beyond the 7-standard-field ETDRS images varied from 47.9 to 73%, while the rate was observed to be up to 85% of cases in our study. Wessel et al. were the first to demonstrate, in a large retrospective study including 218 eyes with different stages of diabetic retinopathy, that UWF-FA showed 3.9 times more retinal non-perfusion and 1.9 times more retinal neovascularization comparing to the 7-standard-field ETDRS images (14).

Indeed, UWF-FA could highlight in our series the presence of RNV in the extreme periphery in 10 eyes (14%), while it was not detected on conventional imaging. The latter finding upgraded the DR severity from severe NPDR (8 eyes), moderate NPDR (1 eye) and mild NPDR (1 eye), to PDR needing urgent laser photocoagulation therapy.

Silva et al. (15) reported that there was a difference in DR

severity grading in 20% of eyes, when comparing between UWF imaging and 7-standard-field ETDRS images. Besides, Talks et al. (16) showed a 30% increase in the rate of peripheral RNV when using the Optomap UWF imaging.

Our study also revealed the presence of PVL in 60 patients (85%) and it was statistically associated with RNP areas and RNV. This angiographic finding was described in DR by Oliver and Schwartz in 2010 (17). In a series of 264 eyes with DR at different stages, they reported the presence of PVL in 41% of cases and it was associated with RNV and DME. In Kong et al. study (18), PVL was only observed in severe NPDR and PDR with a percentage of 60% and 69.4% respectively.

In our study, we found a significant association between RNP areas and DME. Indeed, 97.4% of patients with DME had areas of RNP. This association was previously reported by other authors as Wessel et al. (19) They could demonstrate that eyes presenting with RNP areas were 3.75 times more likely to have DME (p = 0.02). Moreover, Patel et al. (20) studied 148 eyes of 76 patients with type 2 diabetes mellitus and they found that 80% of patients with recalcitrant DME had areas of peripheral RNP. The aforementioned studies suggested that DME might be related to peripheral retinal ischemia and they concluded that it would be reasonable to use UWF-FA in presence of refractory DME, looking for peripheral RNP; peripheral retinal photocoagulation being a potential treatment for DME, enhancing the effect of combined intravitreal anti-VEGF injections. However, other authors, Sim et al. (21) and Silva et al. (22) didn't find any association between DME and peripheral RNP. Moreover, in a large series of 304 eyes, Jiang et al. found that panretinal vascular anomalies such as vascular leakage, ischemic index and microaneurysms count were not associated with DME; but a strong correlation was noted between DME and posterior pole vascular anomalies such as leakage index and microaneurysms count, in addition to demographic data as older age and white race, and systemic diseases such as higher systolic blood pressure (23).

In our data, the posterior part of retina was predominantly involved in 48% of cases, and diffuse DR signs were observed in 38% of the cases. More interestingly, DR lesions were predominantly anterior, almost exclusively observed in the extreme periphery using the UWF-

FA, in 14% of the eyes. Bae et al. (24) found 30% of anterior DR using an UWF-FA in patients with NPDR suggesting that this new entity was actually missed by conventional angiogram and that diabetic lesions confined in the anterior retina were more frequently noted in early stages of NPDR. Therefore, even in presence of mild to moderate NPDR on fundoscopy or conventional FA, the complementary imaging using UWF-FA can be of a great help better assessing the extreme periphery with a more precise DR grading.

In the era of non-invasive imaging, recent studies have compared UWF-FA to WF OCT-angiography (OCTA) in the assessment of retinal vascular diseases and DR severity grading and magement. Although covering a much smaller area thant UWF-FA, WF-OCTA shown to be very useful detecting DR signs including RNP and RNV (25). Couturier et al. noticed that WF-OCTA could better detect capillary non-perfusion areas, allowing a more precise follow-up of patients undergoing anti-VEGF therapy (26). Associating WF-OCTA to UWF fundus imaging might offer a non-invasive alternative for DR screening, diagnosis, monitoring and management (27).

There are some limits in our study, as its retrospective design, the lack of a control group and that we didn't measure the retinal non perfusion with the ischemic index.

The UWF Staurenghi contact lens has some disadvantages. We need the use of topical anesthesia prior to placing the contact lens, with a risk of vasovagal response. It requires the presence of a trained and skilled ophthalmologist to hold the Staurenghi lens, keeping it aligned with visual axis and the optics of the angiograph while acquiring images. Moreover, poor iris dilation or the presence of media opacity as corneal scar, cataract or vitreous hemorrhage can make FA acquisition very hard with poor-quality images. The new era of non-contact UWF imaging systems allowed to address the latter limits of the Staurenghi system. Besides, with advances in UWF retinal imaging, a stereographic projection software has been developed by Optos in order to generate retinal images with consistent angular magnification (28). It allowed a more precise assessment of retinal vascular parameters such as total retinal area, retinal vascular bed area, ischemic index and vascular density (29,30), that could be very useful in future sudies.

In conclusion, UWF-FA provides a better visualization of retinal periphery allowing precise classification and assessment of DR which may improve therapeutic indications and management of DR and DME.

## REFERENCES

1. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. Lancet. 2010; 376: 124–36.

2. Khandekar R. Screening and public health strategies for diabetic retinopathy in the Eastern Mediterranean region. Middle East Afr J Ophthalmol. 2012; 19: 178–84.

3. Bouguerra R, Alberti H, Salem LB, et al. The global diabetes pandemic: the Tunisian experience. Eur J Clin Nutr. 2007; 61.

4. Saidi O, O'Flaherty M, Mansour N Ben, et al. Forecasting Tunisian type 2 diabetes prevalence to 2027: validation of a simple model. BMC Public Health. 2015; 15: 104.

5. Rivero ME, Bartsch DU, Otto T, Freeman WR. Automated scanning laser ophthalmoscope image montages of retinal diseases. Ophthalmology. 1999; 106: 2296–300.

6. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number 12. Ophthalmology. 1991; 98: 823–33.

7. Fischer J, Otto T, Delori F, Pace L, Staurenghi G. Scanning Laser Ophthalmoscopy (SLO). In: High Resolution Imaging in Microscopy and Ophthalmology. Cham: Springer International Publishing; 2019. p. 35–57.

8. Hassenstein A, Meyer CH. Clinical use and research applications of Heidelberg retinal angiography and spectral-domain optical coherence tomography - a review. Clin Experiment Ophthalmol. 2009; 37: 130–43.

9. Staurenghi G, Viola F, Mainster MA, Graham RD, Harrington PG. Scanning laser ophthalmoscopy and angiography with a wide-field contact lens system. Arch Ophthalmol. 2005; 123: 244–52.

10. Witmer MT, Parlitsis G, Patel S, Kiss S. Comparison of ultra-widefield fluorescein angiography with the Heidelberg Spectralis(®) noncontact ultra-widefield module versus the Optos(®) Optomap(®). Clin Ophthalmol. 2013; 7: 389–94.

11. Friberg TR, Gupta A, Yu J, et al. Ultrawide angle fluorescein angiographic imaging: a comparison to conventional digital acquisition systems. Ophthalmic Surg Lasers Imaging Retina. 2008; 39: 304–11.

12. Csutak A, Lengyel I, Jonasson F, et al. Agreement between image grading of conventional (45°) and ultra wide-angle (200°) digital images in the macula in the Reykjavik eye study. Eye. 2010; 24: 1568–75.

13. Mackenzie PJ, Russell M, Ma PE, Isbister CM, Maberley DAL. Sensitivity and specificity of the optos optomap for detecting peripheral retinal lesions. Retina. 2007; 27: 1119–24.

14. 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: 785–91.

15. 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: 2465–72.

16. Talks SJ, Manjunath V, Steel DHW, Peto T, Taylor R. New vessels detected on wide-field imaging compared to two-field and seven-field imaging: implications for diabetic retinopathy screening image analysis. Br J Ophthalmol. 2015; 99: 1606–9.

17. Oliver SCN, Schwartz SD. Peripheral vessel leakage (PVL): a new angiographic finding in diabetic retinopathy identified with ultra wide-field fluorescein angiography. Semin Ophthalmol. 2010; 25: 27–33.

18. Kong M, Lee MY, Ham D-I. Ultrawide-field fluorescein angiography for evaluation of diabetic retinopathy. Korean J Ophthalmol. 2012; 26: 428–31.

19. 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: 694–8.

20. Patel RD, Messner L V, 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: 1038-1044.e2.

21. 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: 144-153.e1.

22. Silva PS, Cavallerano JD, Sun JK, Soliman AZ, Aiello LM, Aiello LP. Peripheral lesions identified by mydriatic ultrawide field imaging: distribution and potential impact on diabetic retinopathy severity. Ophthalmology. 2013; 120: 2587–95.

23. Jiang AC, Srivastava SK, Hu M, et al. Quantitative Ultra-Widefield Angiographic Features and Associations with Diabetic Macular Edema. Ophthalmol Retin. 2020; 4: 49–56.

24. Bae K, Lee JY, Kim TH, et al. Anterior Diabetic Retinopathy Studied by Ultra-widefield Angiography. Korean J Ophthalmol. 2016; 30: 344–51.

25. Sawada O, Ichiyama Y, Obata S, et al. Comparison between wide-angle OCT angiography and ultra-wide field fluorescein angiography for detecting non-perfusion areas and retinal neovascularization in eyes with diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2018; 256: 1275–80.

26. Couturier A, Rey P-A, Erginay A, et al. Widefield OCT-Angiography and Fluorescein Angiography Assessments of Nonperfusion in Diabetic Retinopathy and Edema Treated with Anti-Vascular Endothelial Growth Factor. Ophthalmology. 2019; 126: 1685–94.

27. Cui Y, Zhu Y, Wang JC, et al. Comparison of widefield swept-source optical coherence tomography angiography with ultra-widefield colour fundus photography and fluorescein angiography for detection of lesions in diabetic retinopathy. Br J Ophthalmol. 2021; 105: 577–81.

28. Tan CS, Chew MC, van Hemert J, Singer MA, Bell D, Sadda SR. Measuring the precise area of peripheral retinal non-perfusion using ultra-widefield imaging and its correlation with the ischaemic index. Br J Ophthalmol. 2016; 100: 235–9.

29. Fan W, Uji A, Borrelli E, et al. Precise Measurement of Retinal Vascular Bed Area and Density on Ultra-wide Fluorescein Angiography in Normal Subjects. Am J Ophthalmol. 2018; 188: 155–63.

30. Fan W, Uji A, Nittala M, et al. Retinal vascular bed area on ultra-wide field fluorescein angiography indicates the severity of diabetic retinopathy. Br J Ophthalmol. 2021;