Wide-Field Retinal Imaging of Diabetic Retinopathy

5

J. Fernando Arevalo, Igor Kozak, and The KKESH Collaborative Retina Study Group*

Diabetic Retinopathy and Ultra-Wide-Field Fluorescein Angiography

Diabetic retinopathy (DR) is one of the diseases in which identifying pathology in the retinal periphery is of crucial importance. Posterior pole fluorescein angiography has been integral to the management of DR, in which it can reveal microaneurysms, nonperfusion, macular edema, and neovascularization. Because much of the abnormality in DR, especially nonperfusion, can occur in the mid periphery and periphery [1], ultra-wide-field imaging may be particularly useful in the evaluation of this condition. In a previous report, Wessel et al. [2] by overlaying a 7-standard field (7SF) template on the ultra-wide-field fluorescein angiography (UWFA) found that UWFA showed 3.2 times the amount of retinal area, 3.9 times the amount of retinal nonperfusion, 1.9 times the area of neovascularization, and 3.8 times the area of panretinal photocoagulation (PRP), compared with the simulated 7SF image. Another study showed that UWFA imaged significantly more retinal area and revealed more ischemia than fluorescein angiography using conventional digital acquisition systems [3]. It is not uncommon for DR patients with prior PRP to see on UWFA large fronds of neovascularization and peripheral ischemic retina, only part of which had previous laser treatment. Frequently, most of this is located outside the 7SF. On the basis of UWFA, patients may further undergo targeted PRP to the untreated peripheral ischemic areas (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, and 18).

A small but significant proportion of patients (10 %) in the study by Wessel et al. [2] had normal 7SF fluorescein angiography with positive findings on UWFA, suggesting that UWFA may allow us to diagnose lesions previously missed by standard fluorescein angiography. Because the study was a retrospective review of all patients who underwent UWFA imaging, there may be a selection bias for patients more likely to exhibit peripheral abnormality, such that the true rate of missing abnormality with standard imaging may be lower in practice. Nevertheless, the study highlighted that UWFA demonstrates more abnormality than 7SF imaging and that the added retina visualized with UWFA can significantly change the qualitative assessment of the degree of retinopathy. The study suggested that UWFA expands our view of the periphery without significantly compromising the imaging of central abnormality because only 5.4 % of patients with clinically significant macular edema exhibited no macular edema on UWFA [2].

Prior studies suggest that mid-peripheral nonperfusion, as noted on standard fluorescein angiography, is associated with neovascularization [4]. More recently, Oliver and Schwartz [5] demonstrated that peripheral nonperfusion, which was present in 54 % of DR patients imaged by UWFA, was associated with increased risk of neovascularization, including neovascularization anterior to the equator and neovascularization posterior to the equator. Peripheral nonperfusion on UWFA was also associated with macular ischemia, although not macular edema. The group also noted a finding of late peripheral vascular leakage, which was associated both with peripheral nonperfusion and with neovascularization, especially posterior neovascularization. UWFA has been shown to demonstrate peripheral nonperfusion better

J.F. Arevalo, MD, FACS (✉)
Edmund F. and Virginia B. Ball Professor of Ophthalmology, Chairman, Department of Ophthalmology, Johns Hopkins Bayview Medical Center, Retina Division, Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
e-mail: arevalojf@jhmi.edu

I. Kozak, MD, PhD
Senior Academic Consultant, Vitreoretinal Division, King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia
e-mail: ikozak@kkesh.med.sa

I. Kozak, J.F. Arevalo (eds.), *Atlas of Wide-Field Retinal Angiography and Imaging*, DOI 10.1007/978-3-319-17864-6_5

than standard fluorescein angiography [6], and this, as well as the finding of peripheral vascular leakage, correlated to visually significant and treatable complications such as neovascularization [5]. UWFA may be useful in identifying patients who have not yet developed neovascularization or macular edema but are at increased risk to do so, based on the presence of extensive peripheral nonperfusion or vascular leakage. These patients may, in turn, warrant more frequent follow-up than might have been recommended using traditional fluorescein angiography imaging modalities.

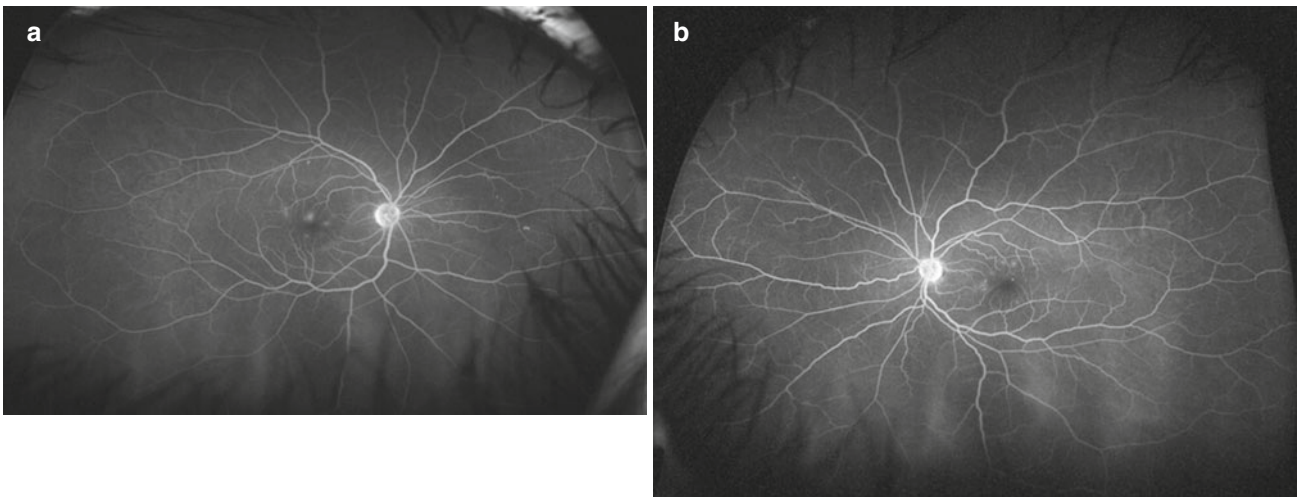

Fig. 1 (**a**) Mild nonproliferative DR. Wide-field fundus color images of the right eye of a 55-year-old woman with controlled type 2 diabetes shows few microaneurysms in the posterior pole and nasal mid periphery. (**b**) Mild nonproliferative DR. Wide-field fundus color images of the left eye of the same patient shows few microaneurysms in the posterior pole

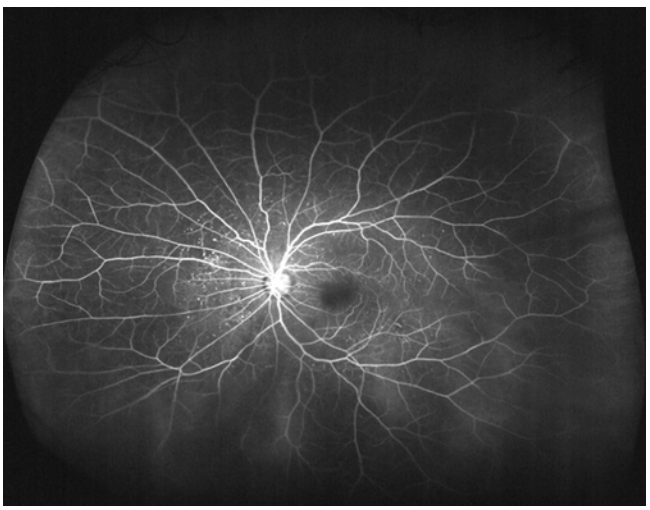

Fig. 2 Mild nonproliferative DR. Wide-field fundus color images of the right eye of a 60-year-old man with a history of primary open-angle glaucoma in both eyes shows scattered microaneurysms around the optic disc and outside the vascular arcades

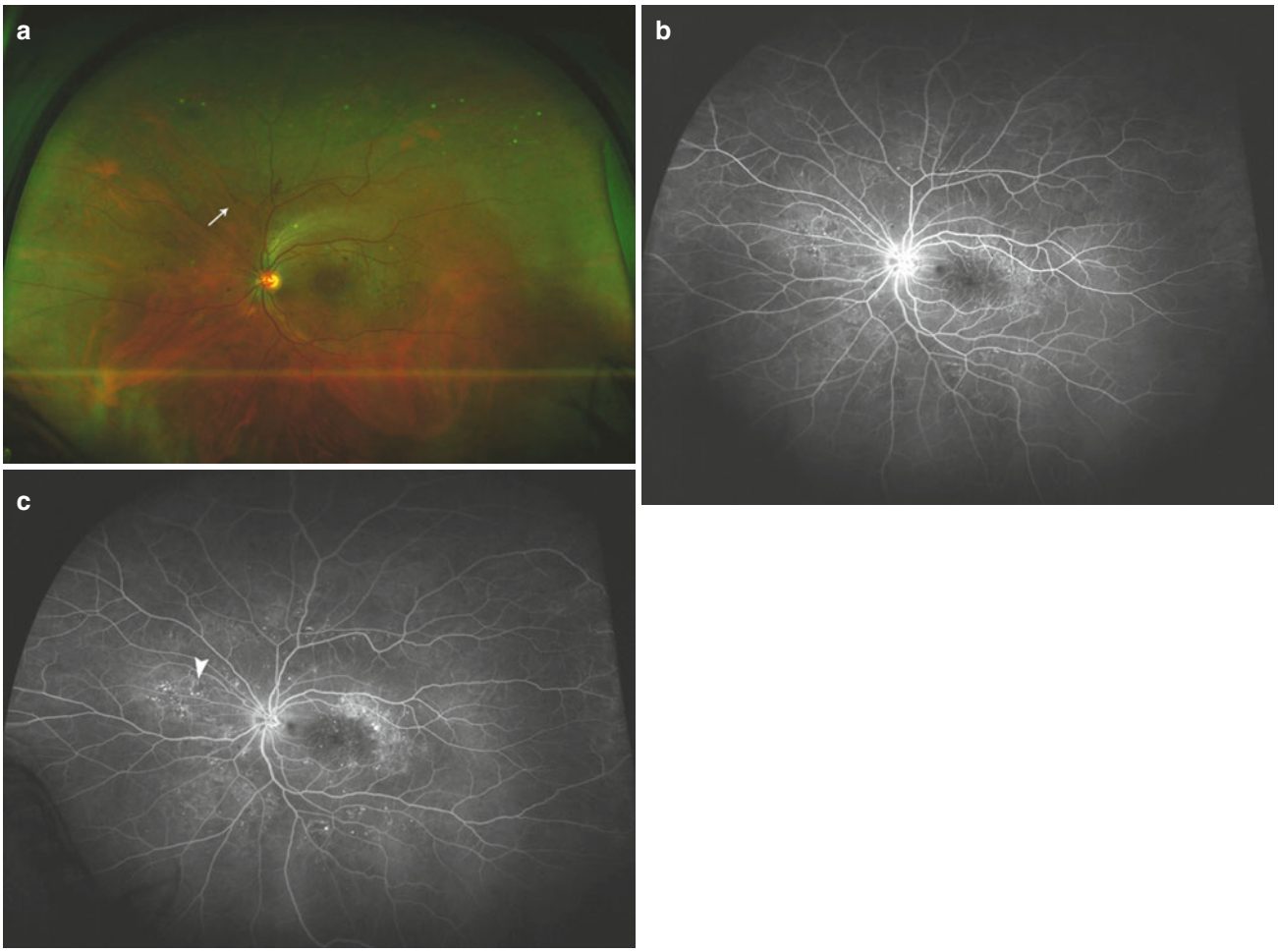

Fig. 3 (**a**) Moderate nonproliferative DR. A 56-year-old man with a history of DR and bevacizumab intravitreal injection for clinically significant macular edema in his left eye. Wide-field fundus color images of the left eye demonstrate several microaneurysms (*white arrow*). (**b**) Moderate nonproliferative DR. Wide-field early fundus fluorescein angiogram of the same eye demonstrates numerous microaneurysms and areas of capillary drop-out nasally. (**c**) Moderate nonproliferative DR. Wide-field late fundus fluorescein angiogram of the same eye demonstrates numerous microaneurysms, diffuse extramacular leak, and areas of capillary drop-out (*white arrowhead*)

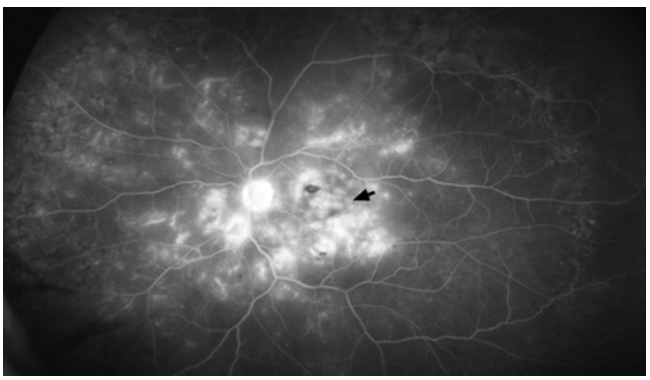

Fig. 4 Severe nonproliferative DR. A 73-year-old woman has a history of DR for 20 years and numerous intravitreal injections for clinically significant macular edema in her left eye. Wide-field fundus fluorescein angiogram of her left eye demonstrates areas of abnormal retinal pigment epithelium and severe macular edema (*black arrow*) but no neovascularization

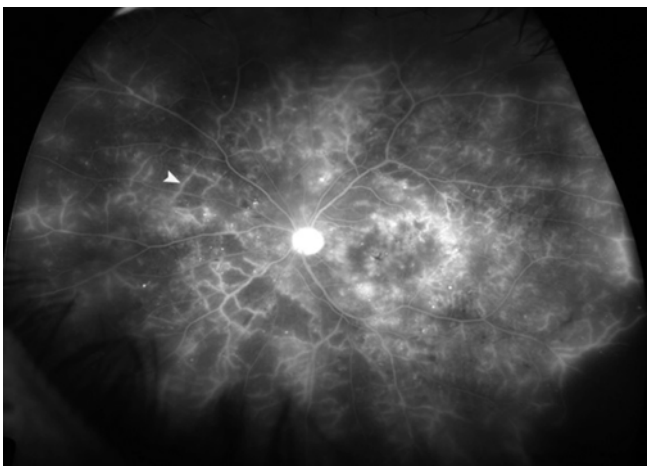

Fig. 5 Severe nonproliferative DR. A 38-year-old diabetic man with DR has slightly decreased vision in his left eye. Wide-field fundus fluorescein angiogram of his left eye demonstrates macular edema and extensive areas of retinal nonperfusion (*white arrow head*) in all quadrants but no neovascularization

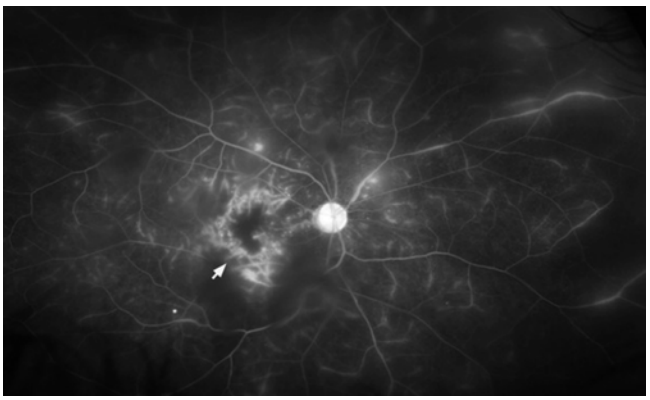

Fig. 6 Severe nonproliferative DR. A 48-year-old diabetic man has a history of DR and decreased visual acuity in his right eye. Wide-field fundus fluorescein angiogram of his right eye demonstrates sheathing of blood vessels and extensive macular ischemia (*white arrow*) without neovascularization

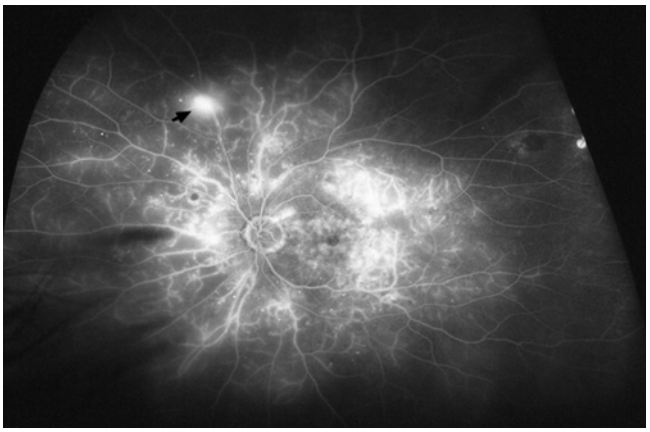

Fig. 8 PDR. A 60-year-old man with PDR in his left eye. Wide-field fundus fluorescein angiogram of his left eye demonstrates macular edema, areas of capillary nonperfusion nasally, and NVE (*black arrow*)

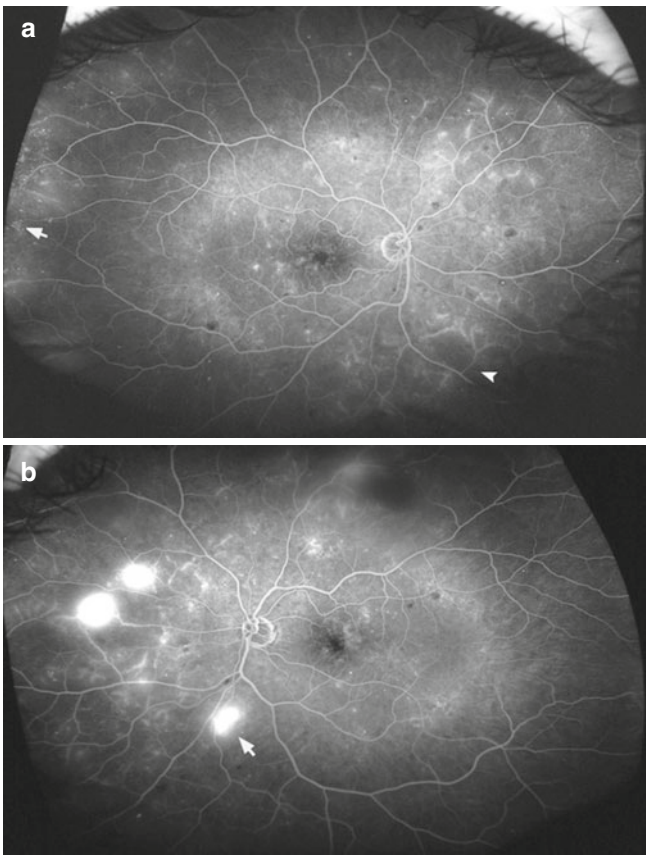

Fig. 7 (**a**) Bilateral DR. A 63-year-old diabetic man presented with DR in both eyes. Wide-field fundus fluorescein angiogram of the right eye demonstrates severe nonproliferative retinopathy with macular edema, capillary nonperfusion (*white arrowhead*), and numerous mid-peripheral and peripheral microaneurysms (*white arrow*) without neovascularization. (**b**) Bilateral DR. Wide-field fundus fluorescein angiogram of the left eye of the same patient demonstrates proliferative retinopathy with some macular edema and neovascularization elsewhere (NVE) (*white arrow*)

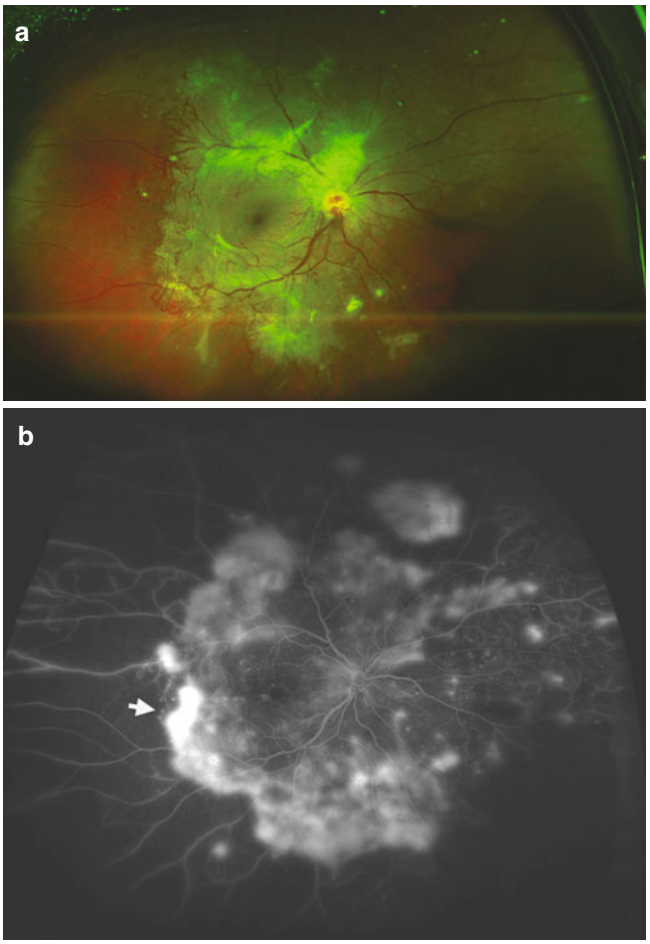

Fig. 9 (**a**) PDR. A 47-year-old diabetic woman with chronic PDR in her right eye. Wide-field fundus photography of her right eye demonstrates fibrovascular membrane with florid neovascularization. Visual acuity is 20/30. (**b**) PDR. Wide-field fundus fluorescein angiogram of the same eye demonstrates severe neovascularization (*white arrow*) and peripheral retinal nonperfusion

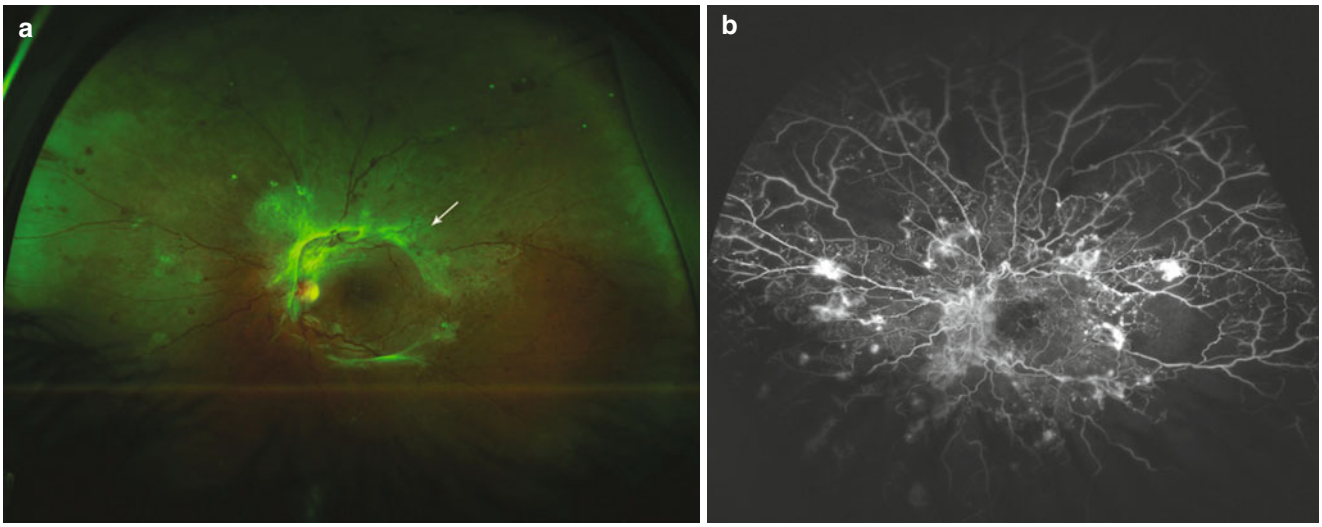

Fig. 10 (**a**) PDR. A 42-year-old diabetic woman with chronic PDR in her left eye. Wide-field fundus photography of her left eye demonstrates fibrovascular membrane with florid neovascularization (*white arrow*). Visual acuity is 2/200. (**b**) PDR. Wide-field fundus fluorescein angiogram of the same eye demonstrates severe widespread neovascularization, an island of macular ischemia, and large areas of retinal nonperfusion

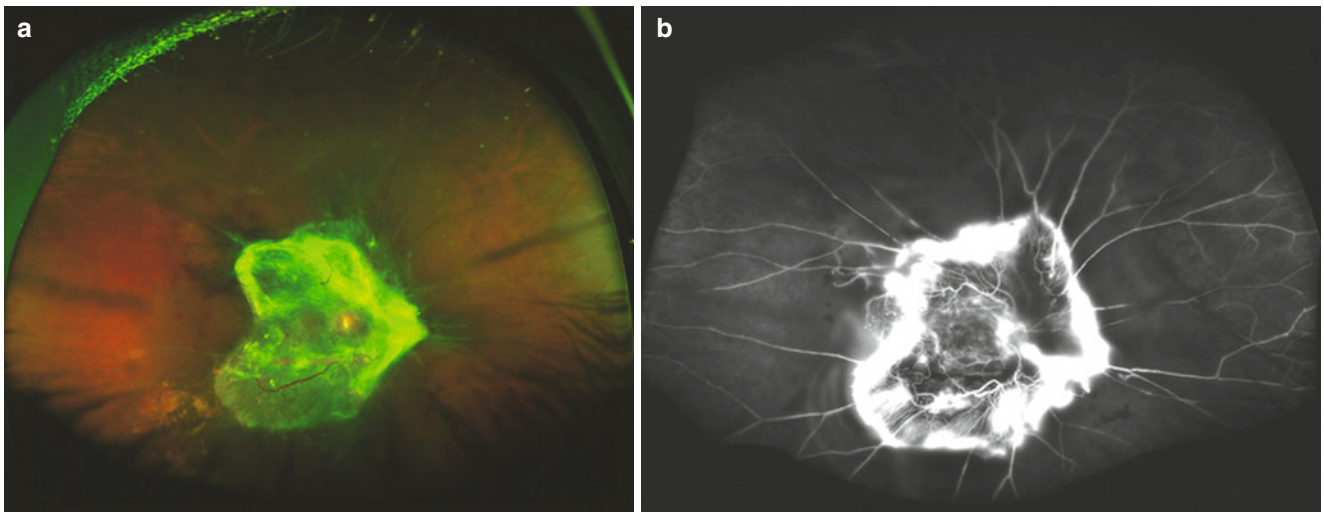

Fig. 11 (**a**) PDR with fibrovascular membrane. A 42-year-old woman with decompensated diabetes and PDR in her right eye. Wide-field fundus photography of her right eye demonstrates aggressive fibrovascular membrane and ischemic retinal vessels. (**b**) PDR with fibrovascular membrane. Wide-field fundus fluorescein angiogram of the same eye demonstrates severe neovascularization of the preretinal membrane, traction on retinal blood vessels, and extensive retinal ischemia

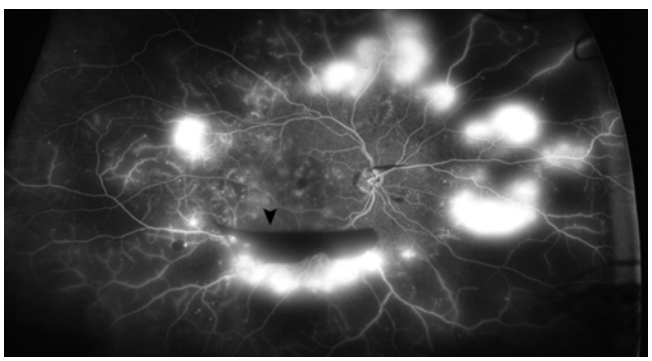

Fig. 12 Severe neovascularization with preretinal hemorrhage. A 58-year-old man with PDR in his right eye. Wide-field fundus fluorescein angiogram demonstrates extensive neovascularization with layered preretinal hemorrhage (*black arrowhead*)

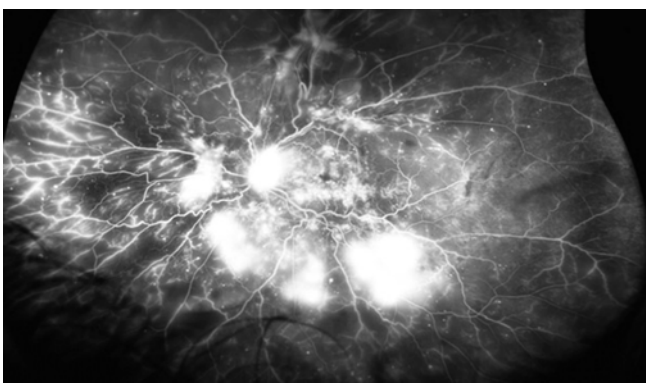

Fig. 13 Aggressive PDR. A 29-year-old woman with type 1 diabetes mellitus aggressive form of retinopathy shows neovascularization of disc (NVD), extensive NVE, and macular leakage

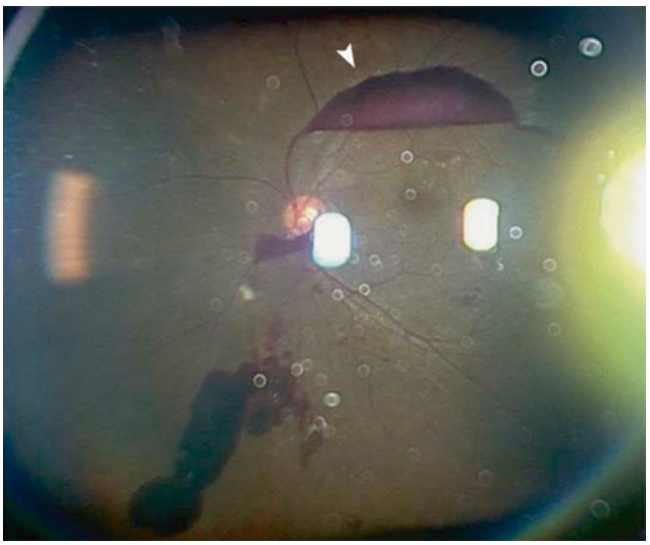

Fig. 14 Diabetic retinal hemorrhage. Wide-field biomicroscopic image of an eye with PDR and preretinal hemorrhage (*white arrowhead*). The image taken with a slit-lamp wide-field camera system is inverted

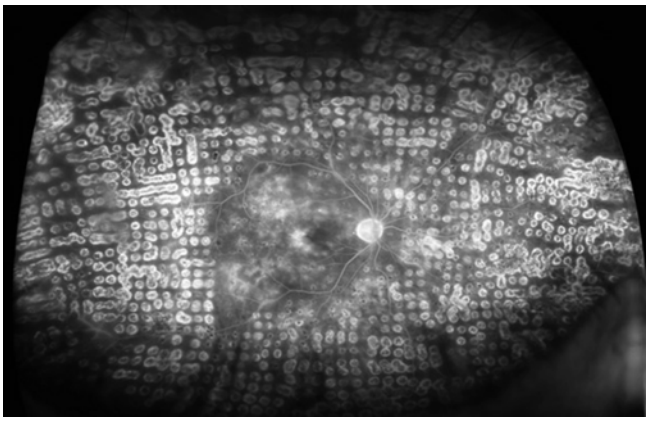

Fig. 15 PRP with conventional pattern laser. A 39-year-old man with a history of PDR after laser therapy. Wide-field fundus fluorescein angiogram of his right eye demonstrates photocoagulation spots with pattern laser

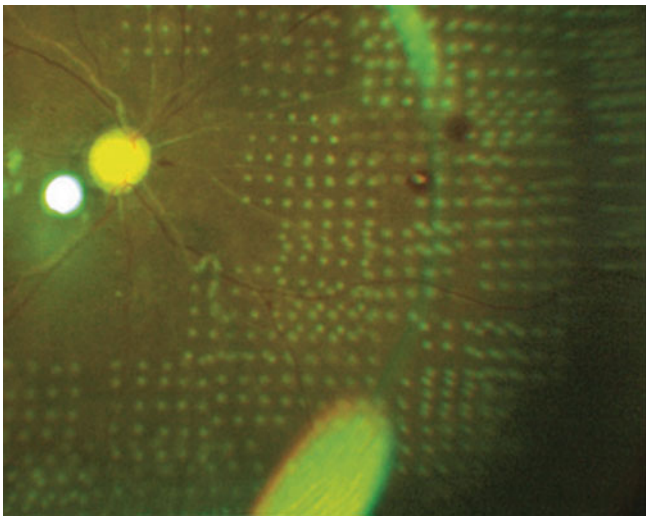

Fig. 16 PRP with navigated pattern laser. A 54-year-old man with PDR during photocoagulation with navigated laser delivery. Intraoperative view with wide-field laser contact lens shows pattern photocoagulation with 100-ms pulse duration

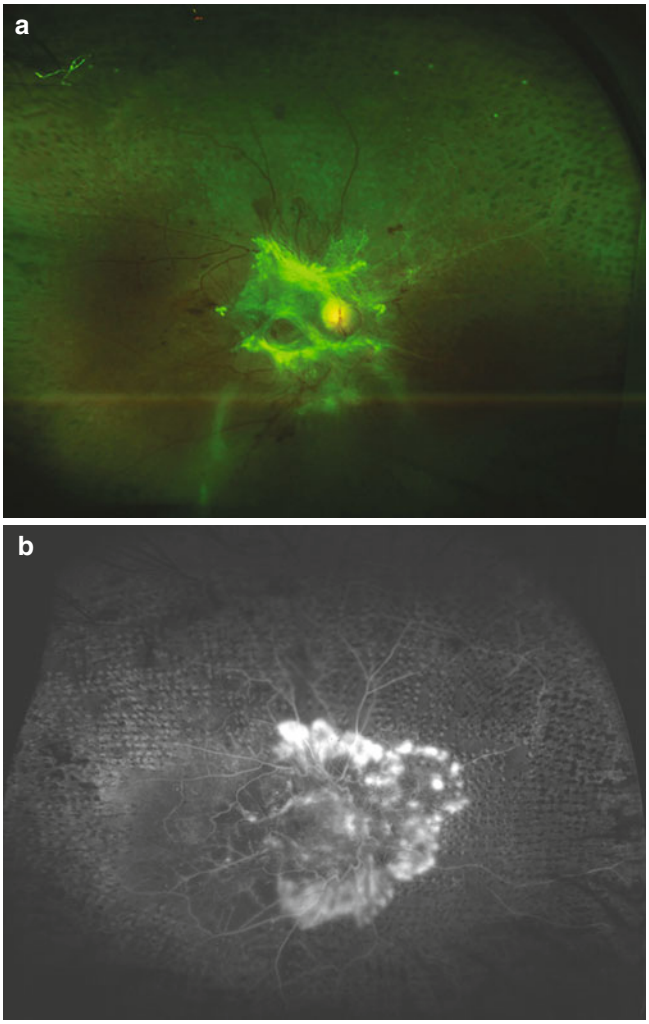

Fig. 17 (**a**) Persistent neovascularization. A 37-year-old man with PDR in both eyes. Wide-field color fundus photography of his right eye demonstrates fibrovascular membrane with persistent neovascularization in spite of previous full laser photocoagulation. (**b**) Persistent neovascularization. Wide-field fundus fluorescein angiogram of the same eye demonstrates dye leakage from persistent new vessels and old laser photocoagulation spots

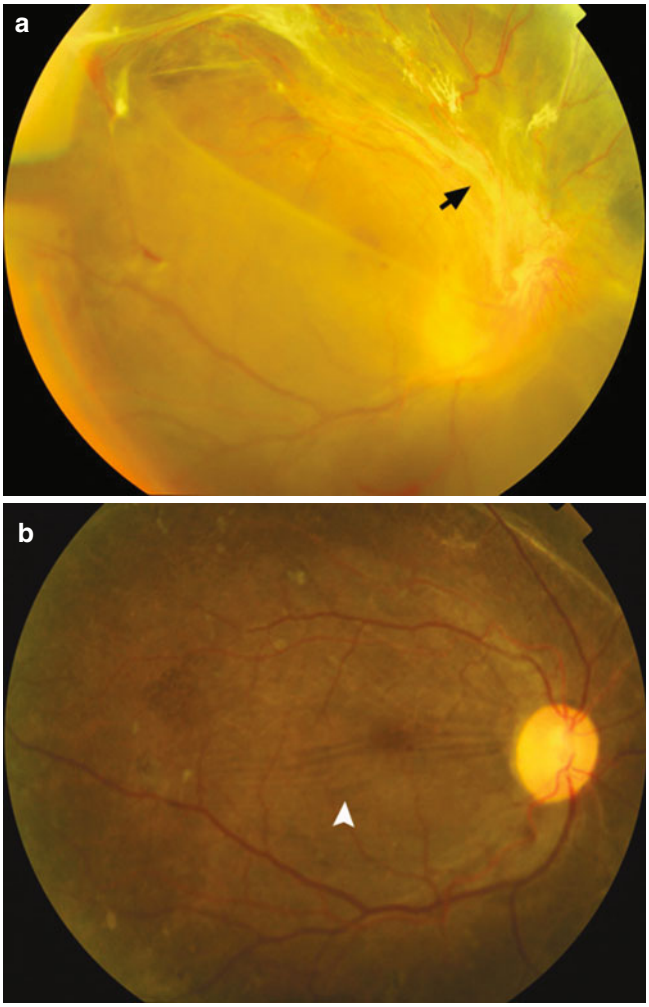

Fig. 18 (**a**) Surgical management of traction retinal detachment. A 38-year-old woman with type 1 diabetes mellitus and traction retinal detachment. Color fundus photography of her right eye demonstrates fibrovascular traction membrane with active neovascularization (*black arrow*). Visual acuity was 20/400. (**b**) Surgical management of traction retinal detachment. The same eye 1 year after pars plana vitrectomy, membrane peel, and gas tamponade shows a completely flat retina with residual internal limiting membrane wrinkling (*white arrowhead*) confirmed by optical coherence tomography (*not shown*). Visual acuity improved to 20/50

Detection and Classification of DR

Two studies have compared UWFA retinal imaging to dilated clinical funduscopic examination for the detection and classification of DR. Neubauer and colleagues [7] assessed DR severity level using both mydriatic stereoscopic funduscopy and nonmydriatic 200° UWFA images. DR and diabetic macular edema (DME) severity levels were determined based on the International Classification of Diabetic Retinopathy scale by 3 masked graders independently. In general, there was agreement between Optomap retinopathy grading and clinical assessment among the readers for the study. Sensitivity of 94 % and specificity of 100 % were demonstrated for all graders to detect more than mild DR. Grading of DME demonstrated only fair agreement between UWFA images and clinical examination.

Wilson and colleagues [8] compared UWFA images with both slit-lamp biomicroscopy examination and single- and dual-field mydriatic digital retinal photographs. Images were obtained and screened for "referable disease," defined as any of the following: ≥4 blot hemorrhages in 1 hemifield or quadrant, abnormalities of venous caliber, intraretinal microvascular abnormalities, retinal neovascularization, vitreous hemorrhage, or exudates or blot hemorrhage ≤1 disc diameter (DD) from the fovea. In comparison with slit-lamp biomicroscopy as the reference standard, UWFA images achieved a sensitivity of 83.6 % compared with 82.9 % for digital photography in the ability to identify referable disease.

One study reported at the 2011 Association for Research in Vision and Ophthalmology meeting has compared nonmydriatic UWFA retinal imaging with the Optos P200MA to clinical trial gold standard mydriatic Early Treatment of Diabetic Retinopathy Scale (ETDRS) protocol 7 standard field stereoscopic photographs [9]. The sensitivity of nonmydriatic UWFA images for detecting any DR and proliferative diabetic retinopathy (PDR) diagnosed on ETDRS photos were 99 and 73 %, respectively, with a specificity of 100 and 99 %, respectively. Despite the nonmydriatic acquisition of the UWFA images, the kappa values for agreement with ETDRS photos were similar to those reported between film and mydriatic digital images compared in multicenter clinical trials [10, 11]. There was excellent agreement between clinical-level DR severity grading on Optos 100° images and ETDRS photos as well as between grading of Optos images and results from clinical examination. Another study has demonstrated a substantial agreement for DME grading of Optos versus ETDRS images as well [12]. However, in this study, 9.3 % of 100° UWFA images were ungradable for level of DR severity.

UWFA-Guided Targeted PRP

UWFA may also directly guide the treatment of patients undergoing panretinal photocoagulation. The Diabetic Retinopathy Study (DRS) showed complications of PRP in that 10 % of patients suffer a decrease in vision after PRP and 5 % develop constriction of their visual field. Complications further included macular edema, hemorrhage, choroidal detachment, angle-closure glaucoma, and decrease in color vision and contrast [13]. By targeting PRP directly to the areas of ischemia, rather than broadly throughout the retina, we may be able to spare healthy retinal tissue and reduce the side effects of PRP while directly treating those areas most likely contributing to the hypoxic drive. Original case series of UWFA-guided targeted PRP in PDR described successful regression of neovascularization and no adverse effects [6]. Subsequent studies have reported on safety and efficacy of targeted PRP using a pattern laser delivery system [14, 15] and computer-assisted navigated laser delivery [16].

DR remains one of the most evidence-guided diseases in the field of retina. As such, it is important to note that seminal studies in DR such as the DRS and the ETDRS were conducted before the advent of UWFA. This raises important questions regarding how and when we can apply older studies toward the management of patients in an age in which we are able to visualize and image far more retinal abnormality than was previously possible. For example, PRP is generally not indicated for patients with retinopathy in the absence of neovascularization. However, our newfound ability to visualize specific areas of peripheral nonperfusion as well as to apply targeted PRP through UWFA may shift the scales regarding the risk-benefit ratio of prophylactic PRP prior to the development of neovascularization or macular edema; this remains to be investigated. Moreover, as ischemia likely drives macular edema, targeted PRP to areas of peripheral nonperfusion may also prove useful as an adjunctive therapy for macular edema; studies investigating this modality are currently under way. In general, studies comparing targeted PRP with true "panretinal" photocoagulation are necessary.

Acknowledgment *The following investigators belong to The King Khaled Eye Specialist Hospital (KKESH) Collaborative Retina Study Group: J. Fernando Arevalo, MD, FACS (PI), Saba Al Rashaed, MD, Eman Al Kahtani, MD, Sawsan Nowilaty, MD, Hassan A. Al-Dhibi, MD, Yahya A. Al-Zahrani, MD, Igor Kozak, MD, PhD, Sulaiman Al-Sulaiman, MD, Patrik Schatz, MD, Abdulelah Al-Abdullah, MD, Khalid Al Rubaie, MD, Yousef Al Dhafiri, MD, Badr Al Ahmadi, MD, Abdulaziz Al Hadlaq, MD, Majed Al Harbi, MD, Abdulaziz Al Oreany, MD, Adel Al-Akeely, MD, Mohammad Hazzazi, MD, Mohammed Talea, MD, Ghazai Al-Thobaiti, MD.

References

1. Shimizu K, Kobayashi Y, Muraoka K. Mid-peripheral fundus involvement in diabetic retinopathy. Ophthalmology. 1981;88:601–12.
2. 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.
3. Friberg TR, Gupta A, Yu J, Huang L, Suner J, Puliafito CA, et al. Ultrawide angle fluorescein angiographic imaging: a comparison to conventional digital acquisition system. Ophthalmic Surg Lasers Imaging. 2008;39:304–11.
4. Shimizu K, Muraoka K. Diabetic retinopathy. Is it a maculopathy? A super-wide fluorescein angiographic evaluation. Dev Ophthalmol. 1981;2:235–42.
5. 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.
6. Reddy S, Shwartz SD. Ultra wide field fluorescein angiography guided targeted retinal photocoagulation. Semin Ophthalmol. 2009;29:9–14.
7. Neubauer AS, Kernt M, Haritoglou C, et al. Nonmydriatic screening for diabetic retinopathy by ultra-widefield scanning laser ophthalmoscopy (Optomap). Graefes Arch Clin Exp Ophthalmol. 2008;246:229–35.
8. Wilson PJ, Ellis JD, MacEwen CJ, Priglinger SG, Kampik A, Ulbig MW. Screening for diabetic retinopathy: a comparative trial of photography and scanning laser ophthalmoscopy. Ophthalmologica. 2010;224:251–7.
9. Noble J, Silva PS, Cavallerano JD, Sun JK, Aiello LM, Aiello LP. Comparison of nonmydriatic Optos® fundus imaging with mydriatic Early Treatment Diabetic Retinopathy Study (ETDRS) 7-standard field stereo photography and clinical grading. Paper presented at the annual meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale; May 2011, 1283/A33.
10. Hubbard LD, Sun W, Cleary PA, Danis RP, Hainsworth DP, Peng Q, et al. Comparison of digital and film grading of diabetic retinopathy severity in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. Arch Ophthalmol. 2011;129:718–26.
11. Gangaputra S, Almukhtar T, Glassman AR, Aiello LP, Bressler N, Bressler SB, et al. Comparison of film and digital fundus photographs in eyes of individuals with diabetes mellitus. Invest Ophthalmol Vis Sci. 2011;52:6168–73.
12. Boucher MC, Gresset JA, Angioi K, Olivier S. Effectiveness and safety of screening for diabetic retinopathy with two nonmydriatic digital images compared with the seven standard stereoscopic photographic fields. Can J Ophthalmol. 2003;38:557–68.
13. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy: clinical application of Diabetic Retinopathy Study (DRS) findings. DRS report number 8. Ophthalmology. 1981;88:583–600.
14. Muqit MM, Young LB, McKenzie R, John B, Marcellino GR, Henson DB, et al. Pilot randomized clinical trial of Pascal TargETEd Retinal versus variable fluence PANretinal 20 ms laser in diabetic retinopathy: PETER PAN study. Br J Ophthalmol. 2013;97:220–7.
15. Muqit MM, Marcellino GR, Henson DB, Young LB, Patton N, Charles SJ, et al. Optos-guided pattern scan laser (Pascal)-targeted retinal photocoagulation in proliferative diabetic retinopathy. Acta Ophthalmol. 2013;91:251–8.
16. Kozak I, Arevalo JF, Gupta V, Chhablani J, Kim JS. Navigated targeted panretinal photocoagulation for diabetic retinopathy (paper on demand). Paper presented at the 32nd annual meeting of the American Society of Retina Specialists (ASRS), San Diego; 9–13 Aug 2014.