Advances in retinal imaging for diabetic retinopathy and diabetic macular edema

Colin Siang Hui Tan[1,2], Milton Cher Yong Chew[1], Louis Wei Yi Lim[1], Srinivas R Sadda[3]

Diabetic retinopathy and diabetic macular edema (DME) are leading causes of blindness throughout the world, and cause significant visual morbidity. Ocular imaging has played a significant role in the management of diabetic eye disease, and the advent of advanced imaging modalities will be of great value as our understanding of diabetic eye diseases increase, and the management options become increasingly varied and complex. Color fundus photography has established roles in screening for diabetic eye disease, early detection of progression, and monitoring of treatment response. Fluorescein angiography (FA) detects areas of capillary nonperfusion, as well as leakage from both microaneurysms and neovascularization. Recent advances in retinal imaging modalities complement traditional fundus photography and provide invaluable new information for clinicians. Ultra-widefield imaging, which can be used to produce both color fundus photographs and FAs, now allows unprecedented views of the posterior pole. The pathologies that are detected in the periphery of the retina have the potential to change the grading of disease severity, and may be of prognostic significance to disease progression. Studies have shown that peripheral ischemia may be related to the presence and severity of DME. Optical coherence tomography (OCT) provides structural detail of the retina, and the quantitative and qualitative features are useful in the monitoring of diabetic eye disease. A relatively recent innovation, OCT angiography, produces images of the fine blood vessels at the macula and optic disc, without the need for contrast agents. This paper will review the roles of each of these imaging modalities for diabetic eye disease.

Access this article online

Website: www.ijo.in

DOI: 10.4103/0301-4738.178145

Quick Response Code:

Key words: Diabetic macular edema, diabetic retinopathy, retinal imaging

Diabetes mellitus affects at least 171 million people worldwide, and this number is expected to increase to 366 million by the year 2030. Diabetic retinopathy (DR) is a common complication of diabetes and affects more than up to 93 million people worldwide.[1,2] In India, over 62 million people are diagnosed with diabetes,[3] and the prevalence of DR in an urban population has been reported to be as high as 18%.[4]

Both DR and diabetic macular edema (DME) affect the quality of life of a patient. Using the 25-item National Eye Institute Visual Function Questionnaire-25, Hariprasad *et al*.,[5] found that patients with Type 2 diabetes and DME had lower scores compared to control groups with DR only.

Screening for DR and DME is essential to detect early features and ensure timely intervention. Besides traditional fundus photography, newer technologies such as widefield imaging and optical coherence tomography (OCT) are now being utilized to detect and evaluate diabetic eye disease. In addition, the wide variety of treatment now available for DME requires more intensive monitoring of treatment outcomes. As a result, ocular imaging modalities will play increasingly important roles in the management of patients with diabetes. This paper will review some of the advanced imaging modalities used in the management of diabetic eye diseases.

[1]Department of Ophthalmology, National Healthcare Group Eye Institute, Tan Tock Seng Hospital, [2]Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore, [3]Department of Ophthalmology, Doheny Eye Institute, University of California, Los Angeles, CA, USA

Correspondence to: Dr. Srinivas R Sadda, Doheny Eye Institute, DEI 3623, 1450 San Pablo Street, Los Angeles, CA 90033, USA. E-mail: ssadda@doheny.org

Manuscript received: 01.10.15; Revision accepted: 31.12.15

Color Fundus Photography

For many years, conventional color fundus photography (CFP) has been the main method of evaluating the posterior pole. The classic fundus camera used × 2.5 magnification with a 30° field of view (Zeiss FF, Carl Zeiss Meditec, Dublin, CA, USA). Newer fundus cameras can capture between 30° and 55° fields of view of the retina in a single image.[6,7] By taking steered images, it is possible to cover a wider region of the retina, including the optic disc, macula, vascular arcades, and the region temporal to the macula, which can cover a 75° field of view. This formed the basis of the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system,[6,8] where a 13-level severity scale[9] was developed and modified from the Airlie House classification.[6,8] DR was classified into categories ranging from no retinopathy to severe vitreous hemorrhage.

Multiple steered images require a clinician or grader to evaluate each field on its own, and then synthesize this into an overall severity assessment for each eye. This limitation can be overcome by combining the images into a montage. A montage image, however, may have shadows or artifacts

Cite this article as: Tan CS, Chew MC, Lim LW, Sadda SR. Advances in retinal imaging for diabetic retinopathy and diabetic macular edema. Indian J Ophthalmol 2016;64:76-83.

at the boundaries where the various images overlap, which could potentially mask real pathology or obscure real lesions.

Ultra-widefield Color Fundus Photography

The limitations of conventional CFP have been addressed by the introduction of ultra-widefield (UWF) imaging devices such as the Optos 200Tx, Optos Daytona, or the Optos California (Optos Plc, Dunfermline, UK), which can image up to 200° of the retina in a single image [Fig. 1].[10] With the use of steered images, even larger regions of the retina can be visualized and then combined.

Several prospective studies comparing UWF CFP with ETDRS 7-standard field images have reported a very good correlation between both imaging modalities. In a study of 103 patients,[11] Silva *et al*. reported that the severity of DR matched in 84% of cases. When agreement within one level was evaluated, the agreement increased to 91% respectively, giving a weighted kappa of 0.85. The frequency of exact agreement between UWF CFP and ETDRS imaging for macular edema was 79%, with a weighted kappa of 0.66.

UWF color photos, however, have been shown to demonstrate more peripheral pathology which was not seen on standard ETDRS photos [Fig. 1]. Silva *et al*.,[12] reported that the use of UWF CFP increased identification of DR (38.4% vs. 33.8%, P = 0.0053) and vision-threatening DR (14.5% vs. 11.9%, P = 0.0257) compared to nonmydriatic fundus photography. In addition, the peripheral retinal lesions located outside the ETDRS 7-standard fields resulted in a more severe assessment of the level of DR in 9% of patients, including identification of neovascularization elsewhere (NVE) that were not seen on ETDRS fundus photography.[12] It has also been reported that a third of hemorrhages or microaneurysms, intraretinal microvascular abnormality and NVE were located predominantly outside the ETDRS standard fields.[13]

The peripheral lesions detected using UWF CFP have potential prognostic significance. In a study of 100 patients,[14] Silva *et al*., compared eyes with DR lesion located more centrally, and eyes that had predominantly peripheral lesions (PPL), defined as eyes where >50% of the lesion being graded was located in the peripheral field compared to the modified ETDRS field. Patients with PPL had increased the risk of DR progression over 4 years, which was independent of baseline DR severity or HbA1c levels. In addition, eyes with PPL had a 3.2-fold increased risk of ≥2 step DR progression (34% vs. 11%) and 4.7-fold increased risk for progression to proliferative DR (PDR) (25% vs. 6%). A greater extent of PRL substantially increased the risk of DR progression and progression to PDR, especially for eyes with less severe DR at baseline.

In addition to the ability to detect more retinal pathology, it has also been shown that the acquisition time using UWF imaging is significantly shorter compared to ETDRS 7-standard field photography (170 s vs. 370 s, respectively).[11,12]

Fundus Fluorescein Angiography

Fluorescein angiography (FA) has played important roles in the investigation of patients with DR. Areas of capillary nonperfusion are clearly visualized, as is enlargement of the foveal avascular zone (FAZ). In addition, FA demonstrates active leakage from microaneurysms in DME and is also helpful in confirming leakage from suspicious areas of neovascularization. Conventional FAs typically cover 30–55° of the retina. While standard fundus cameras can be steered to image different parts of the retina, the various images are captured at different phases of the angiogram. As a result of the short transit time for fluorescein, important information may be lost.

In recent years, UWF imaging technology has been applied to FA [Fig. 2]. The Optos 200 Tx[10] and California both perform UWF FA covering 200° of the posterior pole. By using a noncontact lens, widefield 102° FA images can be obtained from the Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) device as well.[15]

Studies performing UWF FA on patients with DR and other retinal vascular diseases have demonstrated large areas

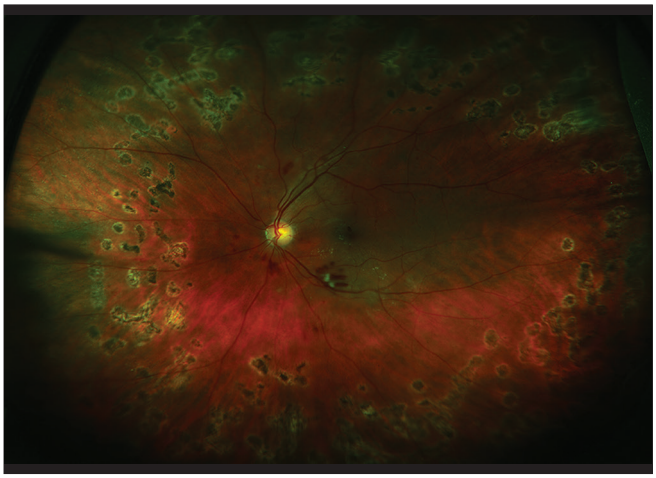

Figure 1: Ultra-widefield color fundus photograph of a patient with diabetic retinopathy and diabetic macular edema. Microaneurysms blot and flame hemorrhages are observed, while hard exudates are noted at the macula. Laser scars from previous pan-retinal photocoagulation can be seen well outside the area covered by the Early Treatment Diabetic Retinopathy Study standard field

Figure 2: Ultra-widefield fluorescein angiogram of a patient with proliferative diabetic retinopathy. Leakage characteristic of neovascularization is seen from neovascularization superiorly. Microaneurysms are seen at the macula. Areas of capillary dropout are seen inferiorly and temporally

of nonperfusion in the peripheral retina.[16-18] In some cases, these areas of nonperfusion lie outside the region covered by conventional fundus cameras. In a study evaluating UWF FA on patients with DR, Wessel *et al*. reported that 3.9 times more nonperfusion, 1.9 times more area of NVE, and 10% more retinal pathology were seen on UWF FA compared to ETDRS 7-standard field photography.[17] This has led to attempts to quantify the amount of retinal nonperfusion.

UWF images exhibit significant distortion of images at the periphery due to the translation of an image from a three-dimensional object (the eye) onto a flat, two-dimensional surface such as a monitor. Initially, there was no way to accurately quantify the areas of nonperfusion in anatomical units (e.g., mm^2). Instead, an ischemic index has been described to quantify the amount of retinal nonperfusion.[16,17,19] The ischemic index is calculated by expressing the number of pixels within regions of nonperfusion as a percentage of the total visible retina. Special stereographic projection software now exists to convert a raw UWF image to a stereographically projected image, so that actual areas of the lesion on the image can be expressed in anatomically correct units.[20]

The extent of peripheral retinal nonperfusion for DR varies widely. In one study, the ischemic index ranged from 0% to 99%, with a mean of 47%.[16] The wide range of ischemic indices has also been reported among patients with retinal vein occlusion, where mean ischemic indices of 14.8% and 25% have been reported.[19,21]

Some authors have reported significant correlations between the presence of DME and peripheral retinal ischemia.[16,17] It is believed that vascular endothelial growth factor (VEGF) production by the areas of the ischemic retina may result in vasodilation and weakening of the walls of the capillaries at the macula. This enhances the permeability of these vessels, and the resultant extravasation of both fluid and lipids results in macular edema.[16,17] Wessel *et al*. reported that patients with retinal ischemia had 3.75-fold increased the risk of having DME compared to those without retinal ischemia ($P < 0.02$).[17] That study also found that more eyes with retinal nonperfusion had DME, compared to eyes without evidence of nonperfusion. However, the authors found no association between the amount of ischemia and macular thickening. The authors speculated that only a small amount of retinal ischemia may be required for DME to develop.

In another study by Patel *et al*.,[16] 148 eyes were divided into four cohorts based on the severity of DR. The mean ischemic index among those with mild non-PDR (NPDR) (Cohort 1) was 0%, compared to 53% to 65% for those with PDR (Cohorts 3 and 4). In addition, eyes with more nonperfusion required more treatment with macular photocoagulation compared to those with smaller areas of nonperfusion. For example, eyes in Cohort 4 experienced a mean decrease of macular thickness of 7.2% compared to 25.2% for Cohort 1. The mean number of macular photocoagulation treatments required was 5.7 in Cohort 4, compared to only 2.3 for Cohort 1. In this study, 80% of eyes with recalcitrant DME showed evidence of untreated retinal nonperfusion.

Similar findings have been reported in studies of patients with retinal vein occlusion. In a prospective study of 32 patients, Singer *et al*. reported that the mean ischemic index was larger when macular edema was present compared to when it had resolved following treatment (14.8% vs. 10.3%, $P < 0.001$).[21]

However, a paper by Sim *et al*., reported no significant relationship between the presence of either peripheral ischemia or peripheral leakage and DME.[22]

The extent of peripheral retinal nonperfusion correlates in some eyes with the size of the FAZ.[22] There are, however, patients with extensive peripheral ischemia but relatively preserved FAZ, and the reasons for the disparity in ischemia centrally and peripherally remain unclear.

The findings of these earlier studies have prompted ophthalmologists to consider new approaches to the treatment of DME. Scatter panretinal photocoagulation is known to reduce the risk of retinal and iris neovascularization.[23] In addition, as a result of the finding that the presence of peripheral ischemia is associated with the occurrence of DME, some ophthalmologists have suggested selective treatment of areas of retinal nonperfusion with laser photocoagulation, a technique of targeted retinal photocoagulation. It is believed that selective treatment of these areas may reduce VEGF production, which would result in the amount of macular edema. Prospective, randomized studies, however, are required to determine if such targeted approaches for the treatment of DME are effective.

Target retinal photocoagulation has also been tried in some patients,[24-26] for the treatment of retinal neovascularization and PDR.[24,25] In a series of 28 eyes with treatment-naive PDR, Muqit *et al*. applied target retinal photocoagulation to areas of peripheral ischemia, which was guided by UWF FA images.[24] The authors reported regression of PDR in 76% of cases at 12 weeks. At 24 weeks, complete regression was seen in 37%, while partial regression occurred in an additional 33%. No patient required retreatment at 4 weeks, and only 37% required repeat laser photocoagulation at 12 weeks. In addition, there were significant reductions in central retinal thickness (12 μm over 24 weeks), and improvement of visual acuity (VA) (mean gain of 3 letters at 12 weeks, $P < 0.0001$). Similar successes have been reported among patients with retinal vein occlusion.[27] Randomized clinical trials, however, are still lacking.

The presence of retinal neovascularization and retinal nonperfusion also increases the risk of recurrent vitreous hemorrhage. In a series of 46 eyes treated with vitrectomy for vitreous hemorrhage secondary to PDR, Kim *et al*.,[28] compared eyes with recurrent vitreous hemorrhage against those that did not develop recurrent hemorrhage. Using UWF FA, eyes with recurrent vitreous hemorrhage manifested with increased frequency of peripheral nonperfusion (81.8% vs. 37.5%, $P = 0.002$), peripheral retinal neovascularization (defined as focal leakage beyond the temporal vascular arcade) (40.9% vs. 8.3%, $P = 0.01$) and late peripheral vessel leakage (defined as late venous or arterial hyperfluorescence peripheral to the temporal arcades and nasal periphery) (90.9% vs. 29.2%, $P < 0.001$). In this series, patients who were treated with additional retinal photocoagulation and anti-VEGF injections had fewer further recurrences of vitreous hemorrhage compared to those treated with vitrectomy alone.

Fundus Autofluorescence Imaging

Fundus autofluorescence (FAF) imaging is a noninvasive modality that has been used in the investigation of various retinal diseases.[29-35] Short-wavelength FAF derives its signal mainly from lipofuscin in the retinal pigment epithelial (RPE). Near-infrared (NIR) FAF, on the other hand, derives its signal from melanin, which is found in both the RPE and choroid. Melanin accumulates in the apical parts of the RPE cells and is thought to be protective of the RPE.[36]

The majority of studies have been performed using short-wavelength FAF and have reported increased autofluorescence in patients with DME.[29-32] Some authors have described various patterns of FAF, such as a single cyst of increased FAF, multicystic FAF or combined single and multicystic FAF,[29] or normal, increased FAF, single-spot increased FAF and multi-spot increased FAF [Fig. 3].[30] In a series of 151 eyes with untreated clinically significant macular edema, cystoid patterns on OCT and FA were correlated with the presence of increased FAF. In addition, the retinal sensitivity of the central subfield was decreased in eyes with single-spot FAF and multi-spot FAF, compared to eyes with normal FAF ($P < 0.05$).[30] In another study of 61 patients with DME, a higher level of FAF was associated with worsening VA, and an increase in the central macular thickness on OCT.[31] The level of FAF was higher among patients with decreased vision during follow-up visits compared to those with improved or unchanged vision.

In a study performed using NIR-FAF,[36] Yoshitake studied 121 consecutive eyes with center-involving DME. In healthy eyes, the autofluorescence signals were almost absent at the optic disc and gradually increased centrifucally with a peak at the fovea. Two patterns were described – a mosaic pattern, consisting of granular or patchy hyper- and hypo-autofluorescence at the fovea, and cystoids, where the cystoids spaces were outlined. Both the mosaic and cystoid patterns were associated with worse VA and thicker central subfield on OCT. In addition, eyes with foveal serous retinal detachments had lower levels of relative autofluorescence than those without serous fluid.

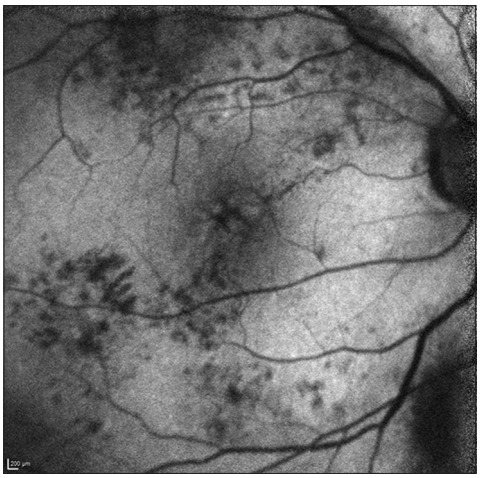

Figure 3: Fundus autofluorescence demonstrating areas of hyper- and hypo-reflectivity in a patient with severe diabetic macular edema. Multiple areas of hyperreflectivity at the fovea correspond to the presence of intraretinal cysts

Optical Coherence Tomography

OCT now plays a vital role in the diagnosis and management of retinal diseases. By producing detailed cross-sectional images of the retina, ophthalmologists can visualize changes in the anatomy caused by DME and monitor the response to treatment [Fig. 4]. Studies have shown a moderate correlation between retinal thicknesses and VA. Several morphologic patterns of DME have been observed [Fig. 4a], including diffuse retinal thickening, cystoids macular edema, serous retinal detachment, and vitreofoveal traction, which correlate with the severity of visual impairment and retinal thickness.[37] Several, such as the presence of cystoids macular edema,[38] or the loss of the external limiting membrane, have been reported to carry a worse prognosis for visual recovery.

Recent advances have also enabled the visualization of the choroid beneath the RPE [Fig. 4b], and studies have suggested that choroidal thickness may be of prognostic significance in various retinal diseases.[39-42] In DR and DME, the evidence thus far has been conflicting, with some suggesting thickening of the choroids, while others report that the choroid is thinner in diabetic eye disease.[43-45]

Optical Coherence Tomography Angiography

OCT angiography (OCTA) is a new technology where rapid scanning by newer spectral domain or swept source OCT (SS-OCT) devices allows analysis of variation of reflectivity and phase shift from blood vessels in the retina, allowing construction of microvascular flow maps. This technology enables clinicians to visualize the microvasculature of the retina and choroid without the need for an intravenous injection of fluorescein [Fig. 5].

Several studies using OCTA in patients with diabetes have reported areas with absent or sparse capillaries which correlate

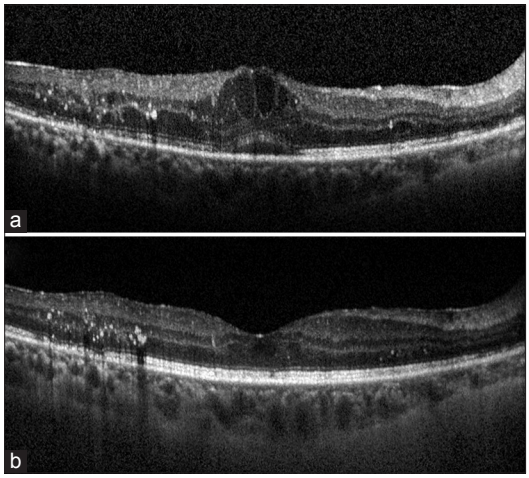

Figure 4: Optical coherence tomography scans of a patient with diabetic macular edema. (a) Pretreatment: Intraretinal cysts and retinal thickening are seen, with subretinal fluid under the fovea. (b) Following intravitreal injection of anti-vascular endothelial growth factor agents, the edema and subretinal fluid have resolved. Some areas of hyperreflectivitiy temporally correspond to the presence of hard exudates

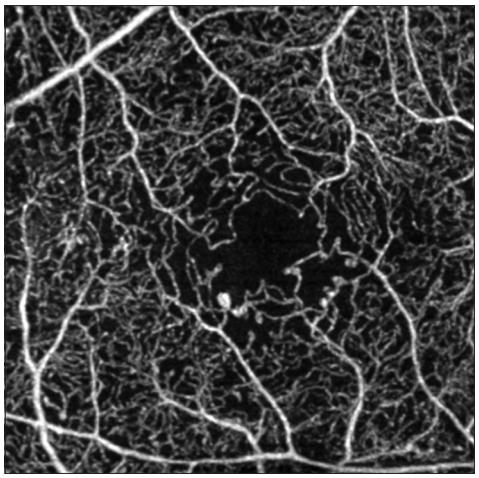

Figure 5: Optical coherence tomography angiogram of a patient with diabetic maculopathy. The foveal avascular zone is irregular with areas of disruption of the capillary network. Dilatations characteristic of microaneurysms are seen inferiorly

with regions of nonperfusion seen on FA.[46,47] In some eyes, areas of capillary loss which were obscured by leakage on FA were more clearly defined using OCTA.[47]

Diabetic eyes were also found to have loss of integrity of the vascular arcades and enlargement of the FAZ.[47,48] In one report, the mean horizontal FAZ diameter was significantly larger in eyes with DR compared to healthy controls (753 μm vs. 573 μm in the superficial layer; 1009 μm vs. 659 μm in the deep layer).[48]

Areas of neovascularization at the optic disc are also clearly visualized on OCTA, and microaneurysms may appear as focally dilated saccular or fusiform capillaries on OCTA of both the superficial and deep capillary plexus.[46] The sensitivity and specificity of OCTA for identifying all of the vascular lesions in DR has yet to be defined in large studies. For example, microaneurysms or other vessel abnormalities that feature slower or faster flow than the dynamic range of the OCTA instrument may go undetected.

Role of Swept Source Optical Coherence Tomography

While spectral domain OCT can readily visualize the various features of DR and DME, the increased scanning speed and a larger range of SS-OCT may be useful in assessing eyes with DR and DME. SS-OCT has been used to visualize a thick posterior hyaloids among eyes with diabetes compared to normal controls (0% of eyes without retinopathy, 19% of eyes with NPDR, 55% of eyes with PDR and 41% of eyes with DME).[49] There were also differences in the rates of vitreoschisis among nondiabetic eyes (27%) compared to 45% of diabetic eyes with no retinopathy, 48% of eyes with NPDR, 65% of eyes with PDR and 63% of eyes with DME.[49] SS-OCT also detected adhesions or pegs between the retina and detached posterior hyaloid in eyes with DR and DME, while this was not observed in eyes without diabetic eye disease.

Intraoperative Optical Coherence Tomography

Imaging using OCT also has the potential to influence the surgical management of complications related to DR. Performing intraoperative OCT in the operating room during the course of the surgery may provide additional information on retinal architecture that was unavailable during the preoperative scan due to media opacity. The Prospective Intraoperative and Perioperative Ophthalmic Imaging with Optical Coherence Tomography study evaluated the feasibility, utility, and safety of using intraoperative OCT during various vitreoretinal surgeries.[50] Among patients that underwent pars plana vitrectomy for dense vitreous hemorrhage secondary to PDR, intraoperative OCT revealed a variety of retinal pathologies including epiretinal membranes (60.9%), macular edema (60.9%), posterior hyaloids traction (4.3%) and retinal detachment (4.3%).[51] The surgeons reported that the findings from intraoperative OCT did influence their surgical decision making, especially when membrane peeling was performed. In addition, the presence of macular edema detected using intraoperative OCT may influence the decision to treat with anti-VEGF drugs during or soon after the surgery.

Functional Optical Coherence Tomography

Functional OCT allows noninvasive physiological assessment of retinal tissue, such as its metabolism.[52,53] A transient intrinsic optical signal (IOS) has been observed in retinal photoreceptors. Changes in retinal function, which occurs in various disease including DR, may manifest as differences in IOS detected using functional OCT.

Role of Imaging in Treatment of Diabetic Macular Edema

The standards for the diagnosis and classification of DME were established by the ETDRS, which was based on stereoscopic fundus biomicroscopy by experienced examiners. Despite being highly specific and sensitive, without additional imaging, this provided only limited information.

Imaging such as FA is useful in identifying leakage and ischemia in DME and hence brought new means to predict the onset and progression of DME.[54,55] However, FA was invasive and had risks of serious side effects such as allergies and anaphylaxis.

OCT introduced new methods for early detection of DME, monitoring disease progression as well as treatment response. With better resolution, differentiation of different retinal layers and more visualization of structural changes characteristic of DME were identified. In addition, retinal thickness, central macular thickness, and macular volume can be quantified and followed up over time. OCT provides a highly reproducible method to evaluate DME and assessing treatment response.[56,57] Currently, OCT imaging has been used as a standard imaging tool in many clinical trials such as the RESOLVE[58] study and PACORES[59] group for evaluating the effect of anti-VEGF in DME.

Role of Imaging in Predicting Outcomes in Diabetic Macular Edema

Though a major limitation of OCT is its inability to test retinal function and provide information on ischemia, some studies have showed that there is a moderate correlation between best-corrected VA (BCVA) and OCT parameters.[56] In a study to investigate the relationship between VA and central retinal thickness, the DR Clinical Research Network[60] documented a modest correlation between the BCVA and the OCT-measured central point thickness and central retinal thickness after focal laser photocoagulation. In addition, for any given amount of retinal edema, the VA was variable and not predictable. Hence, their results showed that although OCT parameters were an important clinical tool in DME evaluation, it is not a reliable surrogate to VA in assessing clinical outcomes.

Conclusion

DR and DME account for significant morbidity and visual loss throughout the world. The application of advanced retinal imaging will help to enhance our understanding of the disease progression and risk factors, and allow ophthalmologists to optimize the management of patients with diabetic eye disease.

Acknowledgments

Dr. Colin Siang Hui Tan is the Head of the Fundus Image Reading Center, National Healthcare Group Eye Institute, Singapore. He is supported in part by the National Healthcare Group Clinician Scientist Career Scheme Grant CSCS/12005. Dr. Colin Siang Hui Tan receives travel support from Bayer, Heidelberg Engineering and Novartis.

Dr. Sadda is the Director of the Doheny Imaging Reading Center, Doheny Eye Institute, USA. Dr. Sadda has served as a consultant to Allergan, Genentech, Optos, Carl Zeiss Meditec, and Alcon.

Financial support and sponsorship

Research Support from National Healthcare Group Clinician Scientist Career Scheme Grant CSCS 12/005. Conference support from Bayer, Heidelberg Engineering, Novartis. Research Support from Allegan, Genentech, Optos, and Carl Zeiss Meditec.

Conflicts of interest

There are no conflicts of interest.

References

1. Yau JW, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, *et al*. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556-64.
2. World Health Organization. Vision 2020. The Right to Sight. Global Initiative for the Elimination of Avoidable Blindness: Action Plan 2006-2011. In: International Agency for the Prevention of Blindness, editor. World Health Organization; 2007.
3. Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. Australas Med J 2014;7:45-8.
4. Raman R, Rani PK, Reddi Rachepalle S, Gnanamoorthy P, Uthra S, Kumaramanickavel G, *et al*. Prevalence of diabetic retinopathy in India: Sankara Nethralaya diabetic retinopathy epidemiology and molecular genetics study report 2. Ophthalmology 2009;116:311-8.
5. 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;92:89-92.
6. 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.
7. Li HK, Horton M, Bursell SE, Cavallerano J, Zimmer-Galler I, Tennant M, *et al*. Telehealth practice recommendations for diabetic retinopathy, second edition. Telemed J E Health 2011;17:814-37.
8. Diabetic retinopathy study. Report Number. Design, methods, and baseline results. Report Number. A modification of the Airlie House classification of diabetic retinopathy. Prepared by the diabetic retinopathy. Invest Ophthalmol Vis Sci 1981;21(1 Pt 2):1-226.
9. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS report number. Early treatment diabetic retinopathy study research group. Ophthalmology 1991;98 5 Suppl: 823-33.
10. Friberg TR, Gupta A, Yu J, Huang L, Suner I, Puliafito CA, *et al*. Ultrawide angle fluorescein angiographic imaging: A comparison to conventional digital acquisition systems. Ophthalmic Surg Lasers Imaging 2008;39:304-11.
11. Silva PS, Cavallerano JD, Sun JK, Noble J, Aiello LM, Aiello LP. Nonmydriatic ultrawide field retinal imaging compared with dilated standard 7-field 35-mm photography and retinal specialist examination for evaluation of diabetic retinopathy. Am J Ophthalmol 2012;154:549-59.e2.
12. Silva PS, Cavallerano JD, Tolls D, Omar A, Thakore K, Patel B, *et al*. Potential efficiency benefits of nonmydriatic ultrawide field retinal imaging in an ocular telehealth diabetic retinopathy program. Diabetes Care 2014;37:50-5.
13. 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.
14. Silva PS, Cavallerano JD, Haddad NM, Kwak H, Dyer KH, Omar AF, *et al*. Peripheral lesions identified on ultrawide field imaging predict increased risk of diabetic retinopathy progression over 4 years. Ophthalmology 2015;122:949-56.
15. 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.
16. 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;155:1038-44.
17. 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.
18. Tan CS, Sadda SR, Hariprasad SM. Ultra-widefield retinal imaging in the management of diabetic eye diseases. Ophthalmic Surg Lasers Imaging Retina 2014;45:363-6.
19. Tsui I, Kaines A, Havunjian MA, Hubschman S, Heilweil G, Prasad PS, *et al*. Ischemic index and neovascularization in central retinal vein occlusion. Retina 2011;31:105-10.
20. 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.
21. Singer M, Tan CS, Bell D, Sadda SR. Area of peripheral retinal nonperfusion and treatment response in branch and central retinal vein occlusion. Retina 2014;34:1736-42.
22. Sim DA, Keane PA, Rajendram R, Karampelas M, Selvam S, Powner MB, *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.

23. Gaucher D, Fortunato P, LeCleire-Collet A, Bourcier T, Speeg-Schatz C, Tadayoni R, *et al.* Spontaneous resolution of macular edema after panretinal photocoagulation in florid proliferative diabetic retinopathy. Retina 2009;29:1282-8.
24. 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.
25. Reddy S, Hu A, Schwartz SD. Ultra Wide Field Fluorescein Angiography Guided targeted retinal photocoagulation (TRP). Semin Ophthalmol 2009;24:9-14.
26. Takamura Y, Tomomatsu T, Matsumura T, Arimura S, Gozawa M, Takihara Y, *et al.* The effect of photocoagulation in ischemic areas to prevent recurrence of diabetic macular edema after intravitreal bevacizumab injection. Invest Ophthalmol Vis Sci 2014;55:4741-6.
27. Singer MA, Tan CS, Surapaneni KR, Sadda SR. Targeted photocoagulation of peripheral ischemia to treat rebound edema. Clin Ophthalmol 2015;9:337-41.
28. Kim DY, Kim JG, Kim YJ, Joe SG, Lee JY. Ultra-widefield fluorescein angiographic findings in patients with recurrent vitreous hemorrhage after diabetic vitrectomy. Invest Ophthalmol Vis Sci 2014;55:7040-6.
29. Pece A, Isola V, Holz F, Milani P, Brancato R. Autofluorescence imaging of cystoid macular edema in diabetic retinopathy. Ophthalmologica 2010;224:230-5.
30. Vujosevic S, Casciano M, Pilotto E, Boccassini B, Varano M, Midena E. Diabetic macular edema: Fundus autofluorescence and functional correlations. Invest Ophthalmol Vis Sci 2011;52:442-8.
31. Chung H, Park B, Shin HJ, Kim HC. Correlation of fundus autofluorescence with spectral-domain optical coherence tomography and vision in diabetic macular edema. Ophthalmology 2012;119:1056-65.
32. Bessho K, Gomi F, Harino S, Sawa M, Sayanagi K, Tsujikawa M, *et al.* Macular autofluorescence in eyes with cystoid macula edema, detected with 488 nm-excitation but not with 580 nm-excitation. Graefes Arch Clin Exp Ophthalmol 2009;247:729-34.
33. Heussen FM, Tan CS, Sadda SR. Prevalence of peripheral abnormalities on ultra-widefield greenlight (532 nm) autofluorescence imaging at a tertiary care center. Invest Ophthalmol Vis Sci 2012;53:6526-31.
34. Tan CS, Heussen F, Sadda SR. Peripheral autofluorescence and clinical findings in neovascular and non-neovascular age-related macular degeneration. Ophthalmology 2013;120:1271-7.
35. Holz FG, Steinberg JS, Göbel A, Fleckenstein M, Schmitz-Valckenberg S. Fundus autofluorescence imaging in dry AMD: 2014 Jules Gonin lecture of the Retina Research Foundation. Graefes Arch Clin Exp Ophthalmol 2015;253:7-16.
36. Yoshitake S, Murakami T, Horii T, Uji A, Ogino K, Unoki N, *et al.* Qualitative and quantitative characteristics of near-infrared autofluorescence in diabetic macular edema. Ophthalmology 2014;121:1036-44.
37. Kothari AR, Raman RP, Sharma T, Gupta M, Laxmi G. Is there a correlation between structural alterations and retinal sensitivity in morphological patterns of diabetic macular edema? Indian J Ophthalmol 2013;61:230-2.
38. Kim BY, Smith SD, Kaiser PK. Optical coherence tomographic patterns of diabetic macular edema. Am J Ophthalmol 2006;142:405-12.
39. Tan CS, Ouyang Y, Ruiz H, Sadda SR. Diurnal variation of choroidal thickness in normal, healthy subjects measured by spectral domain optical coherence tomography. Invest Ophthalmol Vis Sci 2012;53:261-6.
40. Tan CS, Cheong KX, Lim LW, Li KZ. Topographic variation of choroidal and retinal thicknesses at the macula in healthy adults. Br J Ophthalmol 2014;98:339-44.
41. Tan CS, Ngo WK, Cheong KX. Comparison of choroidal thicknesses using swept source and spectral domain optical coherence tomography in diseased and normal eyes. Br J Ophthalmol 2015;99:354-8.
42. Tan CS, Cheong KX. Macular choroidal thicknesses in healthy adults – Relationship with ocular and demographic factors. Invest Ophthalmol Vis Sci 2014;55:6452-8.
43. Kim JT, Lee DH, Joe SG, Kim JG, Yoon YH. Changes in choroidal thickness in relation to the severity of retinopathy and macular edema in type 2 diabetic patients. Invest Ophthalmol Vis Sci 2013;54:3378-84.
44. Querques G, Lattanzio R, Querques L, Del Turco C, Forte R, Pierro L, *et al.* Enhanced depth imaging optical coherence tomography in type 2 diabetes. Invest Ophthalmol Vis Sci 2012;53:6017-24.
45. Vujosevic S, Martini F, Cavarzeran F, Pilotto E, Midena E. Macular and peripapillary choroidal thickness in diabetic patients. Retina 2012;32:1781-90.
46. Ishibazawa A, Nagaoka T, Takahashi A, Omae T, Tani T, Sogawa K, *et al.* Optical coherence tomography angiography in diabetic retinopathy: A prospective pilot study. Am J Ophthalmol 2015;160:35-44.
47. Hwang TS, Jia Y, Gao SS, Bailey ST, Lauer AK, Flaxel CJ, *et al.* Optical coherence tomography angiography features of diabetic retinopathy. Retina 2015;35:2371-6.
48. Freiberg FJ, Pfau M, Wons J, Wirth MA, Becker MD, Michels S. Optical coherence tomography angiography of the foveal avascular zone in diabetic retinopathy. Graefes Arch Clin Exp Ophthalmol. 2015 Sep 4. [Epub ahead of print].
49. Adhi M, Badaro E, Liu JJ, Kraus MF, Baumal CR, Witkin AJ, *et al.* Three-dimensional enhanced imaging of vitreoretinal interface in diabetic retinopathy using swept-source optical coherence tomography. Am J Ophthalmol 2016;162:140-9.
50. Ehlers JP, Goshe J, Dupps WJ, Kaiser PK, Singh RP, Gans R, *et al.* Determination of feasibility and utility of microscope-integrated optical coherence tomography during ophthalmic surgery: The DISCOVER Study RESCAN Results. JAMA Ophthalmol 2015;133:1124-32.
51. Ehlers JP, Dupps WJ, Kaiser PK, Goshe J, Singh RP, Petkovsek D, *et al.* The prospective intraoperative and perioperative ophthalmic imagiNg with optical coherence tomography (PIONEER) Study: 2-year results. Am J Ophthalmol 2014;158:999-1007.
52. Zhang Q, Lu R, Wang B, Messinger JD, Curcio CA, Yao X. Functional optical coherence tomography enables *in vivo* physiological assessment of retinal rod and cone photoreceptors. Sci Rep 2015;5:9595.
53. Drexler W. Cellular and functional optical coherence tomography of the human retina: The cogan lecture. Invest Ophthalmol Vis Sci 2007;48:5339-51.
54. Cunha-Vaz J. Measurement and mapping of retinal leakage and retinal thickness – Surrogate outcomes for the initial stages of diabetic retinopathy. Curr Med Chem 2002;2:91-108.
55. Cunha-Vaz J, Bernardes R. Nonproliferative retinopathy in diabetes type 2. Initial stages and characterization of phenotypes. Prog Retin Eye Res 2005;24:355-77.
56. Buabbud JC, Al-latayfeh MM, Sun JK. Optical coherence tomography imaging for diabetic retinopathy and macular edema. Curr Diab Rep 2010;10:264-9.
57. Romero-Aroca P. Managing diabetic macular edema: The leading cause of diabetes blindness. World J Diabetes 2011;2:98-104.
58. Massin P, Bandello F, Garweg JG, Hansen LL, Harding SP, Larsen M, *et al.* Safety and efficacy of ranibizumab in diabetic

macular edema (RESOLVE Study): A 12-month, randomized, controlled, double-masked, multicenter phase II study. Diabetes Care 2010;33:2399-405.

59. Arevalo JF, Sanchez JG, Fromow-Guerra J, Wu L, Berrocal MH, Farah ME, *et al*. Comparison of two doses of primary intravitreal bevacizumab (Avastin) for diffuse diabetic macular edema: Results from the Pan-American Collaborative Retina Study Group (PACORES) at 12-month follow-up. Graefes Arch Clin Exp Ophthalmol 2009;247:735-43.
60. Diabetic Retinopathy Clinical Research Network, Browning DJ, Glassman AR, Aiello LP, Beck RW, Brown DM, *et al*. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology 2007;114:525-36.