INTRODUCTION

In the United States, diabetic retinopathy (DR) remains the leading cause of new onset vision loss in working-age adults and it is projected that by 2050 the number of Americans with DR and vision threatening DR will increase to 16 million and 3.4 million, respectively.1 Advances in treatment of diabetic eye disease, including laser photocoagulation2 and anti-vascular endothelial growth factor therapy,3 have improved visual outcomes over the last few years. However, in order to achieve optimal visual outcomes, accurate retinal evaluation is critical to identify the presence and severity level of DR so that timely and appropriate interventions can be initiated.4

The risks for progression, visual loss, and response to treatment in patients with varying levels of DR severity have been established based on DR grading algorithms and results from seminal clinical trials, including the Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study (ETDRS). These studies were performed over 25 years ago.2, 5-9 In these trials, DR presence and severity were determined by evaluating 35mm slide photographs capturing 30-degree retinal fields taken according to a defined protocol after pupil dilation.10–11 These sets of images are referred to as ETDRS-protocol 7 standard field, stereoscopic photographs (ETDRS photos) and have been widely accepted as the gold standard for detecting and/or classifying DR. For each patient, a series of 7 pairs of stereoscopic fundus images and 1 pair of external images per eye are captured according to a defined protocol (at least 32 images per eye).

Standard ETDRS photos require the use of 35mm slide film for the best possible image resolution, although recent studies have demonstrated excellent agreement between high-quality standardized digital images and film images.12-14 These validation studies provide the support for the use of digital images instead of 35mm slides, which now are difficult to get processed and can be onerous in terms of handling and storage. Because of their excellent agreement

ABSTRACT

Current ultra-wide field (UWF) retinal imaging systems utilize scanning laser ophthalmoscope technology combined with an ellipsoidal mirror to capture up to 200 degrees of the retina in a single image. When compared with mydriatic ETDRS-protocol, 7 standard field photographs and clinical examination, nonmydriatic UWF images appear to have excellent agreement in allowing the detection and classification of diabetic retinopathy (DR), although larger, definitive validation studies are still forthcoming. UWF imaging and angiography allow visualization of peripheral retinal nonperfusion, vascular leakage and neovascularization in patients with DR that may not be captured on 7 standard fields. Prospective randomized controlled trials are needed to evaluate whether modified laser treatment algorithms based on improved visualization of the retinal periphery might improve patient outcomes. Nonmydriatic UWF imaging has potential applications for ocular diabetic telehealth programs, but validation of newer, more portable, and more affordable UWF imaging models is needed.

KEYWORDS: Diabetes, Macular edema, Ocular telehealth, Optos, Ultra-wide field angiography, Peripheral nonperfusion

REVIEW

Ultra-wide Field Retinal Imaging in Detection, Classification, and Management of Diabetic Retinopathy

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INTRODUCTION

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with film images and substantial advantages in terms of ease of transfer and viewing, digital images are now in routine use in most clinical trials evaluating diabetic retinopathy outcomes.

There are additional challenges related to the ETDRS photographic protocol, including the need for pharmacologic pupil dilation in order to obtain adequate quality images when using many camera systems at this time. The availability of an experienced and highly trained photographer is also essential to consistently acquire valid photographic fields and quality. Patients must reliably alter their gaze positions to enable capturing images that meet ETDRS field definitions. Currently, there are no defined criteria for evaluating peripheral retinal lesions outside the standard 7 fields, and this is likely due to the technical difficulty of obtaining peripheral retinal images with these devices. Several alternatives to ETDRS photos for evaluating DR have been proposed. These include the use of nonmydriatic retinal cameras,15–16 fewer non-stereoscopic retinal fields (with multi-image montages and wider retinal fields),17–20 and digital video imaging.21–23 The introduction of ultrawide field (UWF) retinal imaging with the Optos P200MA (Optos Plc, Scotland, UK), allows all 7 ETDRS fields to be imaged within a single, high-resolution (11–14 microns), 100- or 200-degree image that approximates the image quality obtained with 35 mm film. The application of UWF imaging to the detection and grading of DR severity are discussed in further detail below.

ULTRA-WIDE FIELD IMAGING FOR DETECTION AND CLASSIFICATION OF DIABETIC RETINOPATHY

The Optos P200MA retinal imaging system uses scanning laser ophthalmoscope technology combined with an ellipsoidal mirror that forms a virtual scanning head within the patient’s eye.24 When 100-degree fields are taken using the high-resolution imaging mode, an image resolution of up to 11 microns is achieved. The retinal field image can also be enlarged to cover up to 200 degrees of the retina in a single image while maintaining substantial resolution (14 microns) to further evaluate retinal lesions located in the far periphery. A single 200-degree field images approximately 82% of the retina. During image acquisition, two lasers of different wavelengths (green 532 nm and red 633 nm) simultaneously scan the entire retina and a composite image is formed. The optical properties of the ellipsoidal mirror create a virtual scan point located posterior to the patient’s iris plane, allowing a substantial portion of the retina to be imaged (Figure 1).

Using the Optos V2 Vantage Dx image review software, the reviewer is able to adjust different image parameters including contrast, gamma/brightness, and magnification. In addition, red and green wavelength images can be evaluated independently, allowing the evaluation of lesions located at different anterior-posterior locations. This feature enables the detection of subtle peripheral lesions that might otherwise be missed in the composite color image.

FIGURE 1 During image acquisition, a virtual scan point located posterior to the patient’s iris plane is created, allowing for up to 200 degrees of the retina to be captured in a single image. (Reprinted with permission of Optos, PLC, Dunfermline, United Kingdom.)

UWF RETINAL IMAGING FOR DETECTION AND CLASSIFICATION OF DR

Two studies have compared UWF retinal imaging to dilated clinical fundoscopic examination for the detection and classification of DR. Neubauer and colleagues published a consecutive series of 51 eyes from 51 study participants in whom DR severity level was assessed using both mydriatic stereoscopic fundoscopy and nonmydriatic 200-degree UWF images. DR and diabetic macular edema severity levels were determined based on the International Classification of Diabetic Retinopathy scale by three masked graders independently.25 Between 5.9 and 9.8% of UWF images in this study could not be graded because they did not adequately cover the central 60 degrees of retina and both the macula and optic nerve head. There was agreement between Optomap retinopathy grading and clinical assessment with unweighted kappas of 0.68, 0.68, and 0.51 among the three readers for the study, respectively. Sensitivity of 94% and specificity of 100% were demonstrated for all graders to detect more than mild DR. Of eyes judged to have proliferative DR (PDR) on clinical examination, only one eye was graded by a single grader to have less than PDR (Severe NPDR) on the UWF images. Grading of DME demonstrated only fair agreement between UWF images and clinical examination, with unweighted kappas of 0.20, 0.27, and 0.25 for the three graders.

Wilson and colleagues compared UWF images to both slit lamp biomicroscopy examination and single and dual field mydriatic digital retinal photographs from 380 patients (759 eyes). Images were obtained and screened...
lesions than are covered by the standard ETDRS fields, the same image. Thus, although the wider image area may include a substantially larger field of view and, due to the spherical curvature of the eye, UWF images were ungradable for level of DR severity.

One study reported at the 2011 Association for Research in Vision and Ophthalmology meeting has compared nonmydriatic UWF retinal imaging with the Optos P200MA to clinical trial gold standard mydriatic ETDRS-protocol 7 standard field stereoscopic photographs. The sensitivity of nonmydriatic UWF 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 UWF 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. There was excellent agreement between clinical-level DR severity grading on Optos 100-degree images and ETDRS photos (Kw = 0.81, K = 0.69), as well as between grading of Optos images and results from clinical examination (Kw = 0.79, K = 0.65). There was substantial agreement for diabetic macular edema grading of Optos versus ETDRS images as well. These levels of agreement are similar to other, previously validated nonmydriatic imaging systems that are widely used in multiple telemedicine programs for diabetic retinopathy. However, in this study, 9.3% of 100-degree UWF images were ungradable for level of DR severity.

Compared to standard retinal photography, UWF images include a substantially larger field of view and, due to the spherical curvature of the eye, UWF images can exhibit both focused and blurry areas within the same image. Thus, although the wider image area may potentially allow clinicians to identify more peripheral lesions than are covered by the standard ETDRS fields, the ability to grade different parts of the retina may vary according to the degree of ocular curvature and extent of image blur. Due to this technical limitation, ungradable images with nonmydriatic wide field imaging have been reported in up to 11% of eyes. The selective use of mydriatic image capture in these cases may potentially improve the rate of ungradable images due to increased retinal illumination and increased depth of focus.

ULTRA-WIDE-FIELD FLUORESCIN ANGIOGRAPHY AND DETECTION OF PERIPHERAL RETINAL NON-PERFUSION AND NEOVASCULARIZATION

Capillary non-perfusion in DR is frequently located in the midperiphery. After evaluating 74 eyes with DR, Shimizu and colleagues reported an association between more extensive peripheral vascular non-perfusion and neovascularization of the retina and the optic disc. A similar finding was observed in patients with central retinal vein occlusion. Tsui and colleagues found that the relative percentage of nonperfused to perfused retina correlated with the development of retinal neovascularization. Multiple studies have documented the upregulation of vascular endothelial growth factor (VEGF), along with numerous other factors promoting capillary hyperpermeability, in patients with active PDR and significant capillary non-perfusion.

Fluorescein angiography has remained an integral part of the clinical evaluation of diabetic eye disease, including the documentation of areas of capillary dropout and nonperfusion as well as detection of leakage from retinal neovascularization. In the ETDRS, fluorescein angiography was included in the study protocol to identify sources of fluorescein leakage in macular edema and to guide the application of laser burns in macular photocoagulation treatment.

Conventional fundus cameras cover 45 to 60 degrees of field in one exposure. To image the peripheral fields of the retina, the subject must redirect their gaze and this can result in image distortion caused by increased optical astigmatism. Moreover, the far periphery of the retina is not visualized. Special montaging software may be used to generate images of up to 140 degrees of the retina using traditionally acquired images. However, these frames are not captured simultaneously and therefore any comparison is not exact. Wide-angle angiography using contact lenses and coaxial illumination is able to capture up to 150 degrees of the retina, but image acquisition is technically demanding.

UWF fluorescein angiography (UWFA) using the Optomap can acquire high-resolution, non-contact, full-field angiographic data in a single 100- or 200-degree frame. The ability to obtain UWFA allows the ready visualization of peripheral nonperfusion and vascular leakage (Figure 2). UWF imaging of the far periphery may also capture areas of neovascularization that are not included within the ETDRS 7 standard fields (Figure 3).

Friberg and colleagues demonstrated that UWFA images on the Optos P200A captured a wider field area (8.7 ± 1.6 disc diameters (DD)) compared to conventional imaging systems (3.4 ± 0.76 DD) (P < .001). In addition, areas of retinal nonperfusion were better visualized with the Optos (16.9 ± 15 vs. 3.4 ± 4.26 sectors), although overall image quality was better using the conventional system.

Wessel and colleagues compared areas of retinal pathology seen in UWFA with those visualized in a simulated overlay of the area withinconventional ETDRS standard 7-field imaging. The UWFA images captured 3.9 times more area of retinal nonperfusion and 1.9 times more neovascularization than that seen within the ETDRS standard 7-field overlay. In this study, 22 eyes (10%) had retinal pathology (13 eyes with nonperfusion
and 9 eyes with peripheral retinal neovascularization) that was only present anterior to the border of the simulated ETDRS standard 7-field.

Some studies have also suggested a possible association between peripheral non-perfusion and the presence of diabetic macular edema.\textsuperscript{29,39,40} Kimble and colleagues found that capillary nonperfusion was detected in 84% of patients with clinically significant macular edema and non-proliferative retinopathy.\textsuperscript{39} UWFA has been utilized to address this issue by Oliver and Schwartz who evaluated angiographic characteristics of 264 eyes of 143 patients. Although this study did not find an overall association between peripheral nonperfusion and macular edema, late leakage from peripheral retinal vessels [peripheral vessel leakage (PVL)] was associated with macular edema in eyes without peripheral nonperfusion.\textsuperscript{41} PVL was also found to be significantly related to both neovascularization and peripheral retinal nonperfusion in their study population.

**UWF IMAGING AND TARGETED RETINAL PHOTOCOAGULATION**

Another potential application of UWF imaging, and the subsequent increased ability to routinely identify areas of peripheral nonperfusion, is the use of UWF images to target photocoagulation to areas of peripheral retinal nonperfusion or neovascularization. Panretinal laser photocoagulation (PRP), which creates widespread chorioretinal scarring in the retinal periphery in order to salvage the visually important central retina, was established as the gold standard for treating PDR over 25 years ago.\textsuperscript{42} The mechanisms by which PRP exerts its effects may include decreasing VEGF production and inducing the release of angiostatin, which is a potent inhibitor of retinal neovascularization. PRP may also increase oxygen diffusion from the choroid by thinning
the retina and locally reducing the oxygen consumption by the metabolically active outer retina.\textsuperscript{43–44} Although the treatment is highly effective, well-documented potential side-effects of PRP include visual field loss, development or worsening of macular edema, and decreased color vision, night vision, and contrast sensitivity.\textsuperscript{45} The side-effects are generally associated with higher numbers of laser burns in an eye. Thus, there is ongoing interest in developing methods to reduce the overall extent of treatment required for effective regression of ocular neovascularization.

The concept of central versus peripheral targeted laser photocoagulation for PDR was reported by Blankenship in 1988.\textsuperscript{46} In this study, 50 eyes with high-risk characteristic PDR received PRP with treatment randomly assigned to either a central or peripheral distribution. Six months after treatment, there was complete regression of neovascularization at the disc in 38% of the central versus 47% of the peripheral PRP-treated eyes. Visual field constriction with the I-4e isopter was present in 39% of the central but only 29% of the peripheral PRP-treated eyes. Worsening of pretreatment macular thickening was significantly more common in eyes that received central PRP whereas decreased macular thickening post-treatment was more common in peripheral PRP-treated eyes. These results suggested that peripherally targeted PRP is effective in regressing neovascularization and might partially reduce side-effects such as visual field loss and worsening of pretreatment macular edema.

More recently, targeted retinal laser photocoagulation (TRP) has been proposed to treat specific areas of retinal non-perfusion with the goal of using less energy and sparing relatively better-perfused tissue from laser-induced tissue scarring. Reddy and Schwartz reported regression of neovascularization in two patients with PDR following Optos UWF guided TRP.\textsuperscript{47} A larger, prospective, nonrandomized study assessed outcomes after pattern scan delivered TRP after UWFA imaging in 28 eyes with treatment-naïve PDR. In a single session, 1500 burns were applied to areas of retinal capillary non-perfusion and retinal ischemia that were identified on 200 degree steered UWFA images. PDR regression with reduced NV leakage was seen in 76% of eyes at 12 weeks.\textsuperscript{48} Repeat TRP was needed in 10 eyes (37%) by 12 weeks. At 6 months, complete PDR regression was seen in 10 eyes (37%) and partial regression in an additional 9 eyes (33%). Central macular thickness decreased by an average of 12.1 microns over the 24-week follow-up period, and visual acuity (+3 letters, \( p < 0.0001 \)) and central visual fields (+1.26 dB, \( p = 0.01 \)) also improved over 24 weeks post-TRP.

The possibility that reducing the number of laser burns with a TRP strategy may reduce laser side-effects while maintaining treatment efficacy is appealing. However, given the small sample sizes and nonrandomized nature of the current TRP-related reports, larger, prospective randomized trials will be needed to determine whether targeted laser treatments for PDR based on UWF imaging are truly as efficacious as and safer than standard PRP treatment.

**IMPLICATIONS FOR TELEHEALTH PROGRAMS FOR DIABETIC RETINOPATHY**

The rapid growth of the diabetic population both in the United States and worldwide demands increasing use of resources to triage and care for individuals affected by diabetes who are at risk for vision loss from diabetic eye complications. Telehealth programs for diabetic retinopathy evaluation and triage may allow clinicians to deal with the increased need for diabetes eye care providers by enabling access to their services remotely by disadvantaged populations that would otherwise be underserved. A digital imaging system that can rapidly acquire retinal images of comparable quality to ETDRS-protocol photographs through non-mydriatic pupils would be highly useful in this effort. UWF imaging using a scanning laser compared to traditional fundus photography offers the potential advantage of being less affected by pupil size and media opacities such as cataracts.\textsuperscript{49,50} Moreover, the ability to capture a large percentage of the retina in a single, UWF 100 or 200 degree image enables the utilization of imagers who do not have to be trained and certified in the acquisition of highly defined, specific retinal fields. The digital nature of these images readily allows remote storage and access, enabling image review by specialists in DR and diabetic macular edema grading in a highly efficient manner and the ability to triage cases for subsequent locally delivered care.

Historically, major barriers for the routine use of UWF imaging systems in telehealth programs have included the substantial capital outlay required for the imaging equipment, being much greater than for traditional retinal cameras. Similarly, the large footprint needed for most UWF imaging machines can be a detracting factor. Both of these issues may be ameliorated by the introduction of newer, smaller and presumably cheaper UWF models that are currently being introduced into the marketplace. Additional validation studies will be needed to assess whether images from these newer models will have the same high levels of agreement with ETDRS-protocol photographs for DR severity level grading as did the first-generation machines.

**CONCLUSION**

Current UWF retinal imaging systems use scanning laser ophthalmoscope technology combined with a proprietary ellipsoidal mirror can capture up to 200 degrees of the retina in a single image while maintaining high resolution of 11–14 microns. When compared with both
mydriatic ETDRS-protocol 7 standard field stereoscopic fundus photographs and clinical examination, early studies suggest that nonmydriatic UWF images have excellent agreement in detecting and accurately classifying diabetic retinopathy severity level. Data from larger, definitive validation studies in cohorts with a wide range of diabetic retinopathy severity across a diversity of sites are as yet unavailable. UWF color images and UWF angiographic studies may also provide advantages of improved visualization of peripheral retinal pathology, and may demonstrate key lesions such as neovascularization and nonperfusion that are only observed to a more limited extent or missed completely in 7 standard ETDRS fields. Adequately large prospective randomized controlled trials will be needed to evaluate whether laser treatment algorithms modified based on improved visualization of the retinal periphery have clinical benefit and improved patient outcome. Non-mydriatic UWF imaging has potential applications for ocular diabetic telehealth programs, but validation of newer, more portable, and more affordable UWF imaging equipment will be required before widespread applicability to remote diabetic retinopathy assessment and patient triage.

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