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Ultra-wide-field imaging in diabetic retinopathy

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ABSTRACT

Since 1991, 7-field images captured with 30–50 degree cameras in the Early Treatment Diabetic Retinopathy Study were the gold standard for fundus imaging to study diabetic retinopathy. Ultra-wide-field images cover significantly more area (up to 82%) of the fundus and with ocular steering can in many cases image 100% of the fundus ("panretinal"). Recent advances in image analysis of ultra-wide-field imaging allow for precise measurements of the peripheral retinal lesions. There is a growing consensus in the literature that ultra-wide-field imaging improves detection of peripheral lesions in diabetic retinopathy and leads to more accurate classification of the disease. There is discordance among studies, however, on the correlation between peripheral diabetic lesions and diabetic macular edema and optimal management strategies to treat diabetic retinopathy.

1. Introduction

Fundus imaging is an integral element in the diagnosis, management and follow up of retinal and choroidal diseases. Flash fundus photography was introduced in 1886. Since then, significant advances have occurred in the field of fundus imaging. Conventional fundus cameras take single-field fundus images from the optic nerve and macula with a 20° to 50° of field of view. Single-field fundus photography images cover the most vital part of the fundus where the ocular diseases are most prevalent. However, with single field fundus images, a significant proportion of the fundus remains uncovered. A wide variety of the fundus lesions including those related to hereditary, ischemic, degenerative, inflammatory and neoplastic diseases occur in fundus periphery. Therefore, it is very important to have rapid and efficient methods for imaging the fundus periphery.

To address the limitations of single-field images, a montage image of 30° images was developed which consisted of combining images of disparate fields with small areas of overlap to facilitate alignment. Seven standard field image of the Early Treatment Diabetic Retinopathy Study (ETDRS) has been the gold standard for the detection and classification of diabetic retinopathy (DR) since 1991 (ETDRS, 1991). The sensitivity and specificity of single-field fundus photography interpreted by trained readers in different studies varied from 61% to 90% and from 85% to 97%, respectively, when compared with the stereophotographs of 7 standard fields (Williams et al., 2004). Montage images have been found reliable for the assessment of DR, however, they are not as convenient for patients and photographers as single field photography; acquisition is time-consuming and they require skilled photographers and pharmacological pupil dilation. The optimal imaging modality would be able to take a panoramic view with a single shot while being non-contact and non-mydriatic.

2. Wide-field imaging systems

According to the Diabetic Retinopathy Clinical Research network (DRCRnet), fundus photography with a field that is 100° or more is considered ultra-wide-field (UWF) (DRCRnet, 2016). In 1975, Oleg Pomerantzeff developed a wide-angle camera system using a fiber optic scleral transillumination and a contact lens to take fundus images up to 148° (Pomerantzeff, 1975). The Staurenghi lens (Ocular Staurenghi 230 SLO Retina Lens; Ocular Instruments Inc, Bellevue, WA, USA) is a contact lens system that provides a 150° field of view for fundus imaging and is designed to be used in conjunction with scanning laser ophthalmoscope (SLO) imaging systems. Retcam (Clarity Medical Systems) is a contact imaging system that gives a maximum field of view of 130°. This technology has a portable camera with a fiberoptic cable light source and is particularly useful for the imaging of pediatric patients (Witmer & Kiss, 2013). It has limitations in adults with nuclear sclerosis or with pseudophakia due to significant artifacts.

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Currently, two non-contact wide-field imaging devices are the most popular wide-field imaging systems worldwide (Ghasemi Falavarjani, Scott, et al., 2016; Ghasemi Falavarjani, Wang, Khadamy, & Sadda, 2016; Nagiel, Lalane, Sadda, & Schwartz, 2016). The Spectralis (Heidelberg Engineering, Heidelberg, Germany) is a noncontact ultra-wide-field SLO that takes a wide-field of view of 102° (as measured from the center of the pupil) in a single non-steering shot with the addition of a wide-angle lens attachment. Optos (Optos, Dunfermline, United Kingdom) is also a non-contact SLO technology that is able to take 200° field of view of the retina (as measured from the center of the eye). This field of view is equivalent to 82% of the retinal surface compared to 15% offered by a single 45 degree image. A recent study reported direct comparison of wide-field images obtained with a Spectralis with those from an older Optos instrument (P200Tx) before image distortion was autocorrected and visualization of the inferior and superior periphery were enhanced (Witmer, Parlitsis, Patel, & Kiss, 2013). The study showed that both instruments are excellent modalities to illustrate the peripheral retina, however, on a single non-steered image, the Optos captured a larger view of the retina temporally and nasally, while the view was larger in the superior and inferior views with Spectralis. Thus far, there have been no comparative studies evaluating the field of view depiction of the latest generation Optos devices and the Spectralis.

Native Optos UWF images have significant non-linear warp at the periphery as a result of digital projection of a three dimensional surface to two-dimensional image, a problem actually inherent to any widefield imaging system. The angle of view differs for the lesions when moving from the center of the image toward the periphery, and when stereographically projected, more peripheral structures will appear to be larger. Therefore, when calculating the size of the lesions (e.g. the areas of non-perfusion, etc), the relative image magnification should be corrected accordingly. Stereographic projection software on the latest Optos instruments is able to address the problem of image warp. The size and location of peripheral lesions can now be calculated in anatomically correct physical units (Tan et al., 2015). Also, a recent update to Optos software allows creation of a single montage image from multiple steered ultra-wide-field images. This montage image is able to show the entire retina (“panretinal”). Singer et al. (Singer et al., 2016) evaluated the extent of the peripheral retinal vasculature in normal individuals using montage images from Optos FA and showed a significant difference in distance from the optic disc to the periphery based on the quadrant (with temporal being larger than inferior being larger than superior being larger than nasal) and age (shorter in older individuals). Despite these advances, obtaining high-quality UWF images still require good patient cooperation, and image quality and field of view may be affected by artifacts from the eyelids and lashes.

3. Ultra-wide-field imaging in diabetic retinopathy

3.1. Grading of DR

International classification of DR severity divides eyes with DR into non-proliferative and proliferative stages, with and without macular edema (Wilkinson et al., 2003). Visualization of the peripheral retina using UWF imaging affects the detection of DR lesions and usually leads to more precise grading of disease compared to non-UWF images. Price et al. (Price, Au, & Chong, 2015) compared the Optomap UWF color images with ETDRS seven-standard field view images. Fifteen percent of images received a higher DR severity grade in Optos images. Wessel et al. (Wessel, Aaker, et al., 2012) compared DR severity grading between Optos UWF FA and ETDRS seven-standard field FA images. They also classified DR at a higher retinopathy level in the UWF view. Also, detection of retinal non-perfusion and neovascularization was higher in UWF images. Similarly, Talks et al. (Talks, Manjunath, Steel, Peto, & Taylor, 2015) reported 25% and 12% more peripheral neovascularization in Optos UWF color images than standard two-field and seven-field color fundus imaging, respectively, in patients referred from a UK DR screening service. Silva et al. (Silva et al., 2013) reported that DR severity between Optos UWF color images and ETDRS 7-standard film photographs matched in 80% of eyes. Also, the DR severity was within 1 level in 94.5% of eyes. In the same study, UWF images and dilated fundus examination matched in 58.8% of eyes and were within 1 level in 91.2%. They showed that in 10% of eyes, the DR assessment by Optos UWF was more severe than what would have been determined based on the ETDRS fields alone. Manjunath et al. (Manjunath et al., 2015) showed that Optos UWF color images detected more proliferative diabetic retinopathy (PDR) and severe non-proliferative diabetic retinopathy (NPDR) than did clinical examination. Rasmussen et al. (Rasmussen et al., 2015) found that non-mydriatic Optos UWF color images matched mydriatic UWF color images with exact agreement in 96.8% and one-level agreement in 100.0%. However, steered color images with dilated pupils resulted in higher grading in 12% of eyes.

3.2. Predominantly peripheral lesions

Predominantly peripheral lesions (PPL) has been defined as microaneurysms, hemorrhages, venous beading, intraretinal microvascular abnormalities, and new vessels elsewhere (NVE) in eyes with DR with more than 50% of the graded lesion located outside the seven standard ETDRS fields (Silva et al., 2015). Silva et al. (Silva et al., 2015) assessed the rates of 2-step or more progression and progression to PDR in 200 eyes of 100 patients with DR and showed that the risk of progression of the DR over 4 years was associated with the presence and increasing extent of predominantly peripheral lesions. Eyes with PPLs had a 3.2-fold increased risk of 2-step or more DR progression and a 4.7-fold increased risk for progression to PDR compared with eyes without PPLs. These findings remained significant after multivariate analysis for diabetes duration, diabetes type, gender, hemoglobin A1c levels, and baseline DR severity.

3.3. Diabetic macular edema and peripheral ischemia

Diabetic macular edema (DME) is the leading cause of visual impairment in DR (Bhagat, Grigorian, Tutela, & Zarbin, 2009). The pathogenesis of DME is complex and not completely understood as presence and severity of DME does not typically correlate to DR stages, however, vascular endothelial growth factor (VEGF) appears to have a key role in the development of DME. (Bhagat et al., 2009) Previous studies using conventional fluorescein angiography have suggested that peripheral retinal ischemia may be linked to DME via increased production of VEGF. (Mansour, Pulido, & Arevalo, 2015)

Recent studies have evaluated the role of UWF FA imaging in eyes with DME. In a retrospective analysis of Optos UWF FA images of patients with DR, Wessel et al. (Wessel, Nair, et al., 2012) found a significant correlation between DME and peripheral retinal ischemia and reported that eyes with retinal ischemia had 3.75 times higher rate of macular edema compared with those without retinal ischemia. Oliver and Schwartz (Oliver & Schwartz, 2010) evaluated the correlation of the peripheral retinal lesions with DME. They found that peripheral non-perfusion was associated with anterior and posterior neovascularization but not with macular edema. Peripheral vascular leakage was associated with peripheral non-perfusion and posterior neovascularization but not with DME. However, they reported a strong association between peripheral

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vascular leakage and focal macular edema in eyes without peripheral non-perfusion.

Ischemic index (ratio of the retinal ischemic area to the total retinal surface in UWF FA images) has been advanced to be a reliable indicator for the ischemic condition of the retina in various retinal vascular diseases including central retinal vein occlusion and sickle cell retinopathy (Ghasemi Falavarjani, Scott, et al., 2016; Ghasemi Falavarjani, Wang, et al., 2016; Tsui et al., 2011). Patel et al. (Patel, Messner, Teitelbaum, Michel, & Hariprasad, 2013) reported a correlation between recalcitrant DME with higher ischemic index and greater severity of DR. Eyes with higher ischemic indices had less reduction in central macular thickness and greater number of macular photocoagulation treatments. Sim et al. (Sim et al., 2014) evaluated the association between peripheral ischemic index and peripheral leakage index in Optos UWF FA images, and central macular thickness in DR. They found moderate correlations between the foveal avascular zone area and the peripheral ischemic index, and between the peripheral leakage index and foveal avascular zone area. However, they did not find a significant correlation between macular thickness and peripheral ischemia. Similarly, Silva et al. (Silva et al., 2015) could not find an association between non-perfusion area and ischemic index, and clinically significant DME.

3.4. Targeted retinal laser photocoagulation

Targeted laser photocoagulation (TRP) refers to the selective application of laser only to areas of non-perfusion detected by FA to reduce the level of VEGF produced by the ischemic retina while minimizing side effects of laser. Reddy et al. (Reddy, Hu, & Schwartz, 2009) reported regression of PDR in 2 cases after TRP. Muqit et al. (Muqit, Marcellino, et al., 2013) evaluated the effect of UWFFA-guided TRP in 28 eyes with PDR. At 12 weeks, PDR regression occurred in 76% of patients, and complete disease regression was achieved in 37% at 24 weeks. They found significant reductions in central retinal thickness as measured with optical coherence tomography, over time. The same group conducted a randomized clinical trial to compare the effect of TRP with standard panretinal photocoagulation (PRP) and minimally traumatic PRP (using barely visible spots) on central retinal thickness (ten eyes in each group). Despite similar rates of PDR regression in the 3 groups, a significant reduction in central retinal thickness was found in TRP and minimally-traumatic PRP group (Muqit, Young, et al., 2013). A phase I/II, multicenter, randomized, study of the efficacy and safety of ranibizumab injection monotherapy verses a combination therapy of ranibizumab plus Optos UWFFA-guided TRP in patients with center involving diabetic macular edema (DAVE study, ClinicalTrials.gov Identifier: NCT01552408) is ongoing.

4. Conclusion

A growing body of evidence suggests that UWF imaging plays a major role in the diagnosis, classification and management of DR. Almost all published studies reported improvement in DR classification using UWF imaging. However, the role of UWF FA-guided TRP in the management of DR remains to be defined. Also, controversy remains regarding the role of peripheral non-perfusion in the pathogenesis of DME.

Diabetic Retinopathy Research Network protocol AA has been designed to evaluate the role of the imaging of the retinal periphery using UWF images on the ability to assess the DR and predict rates of DR worsening over time in comparison with the 7 standard field images (DRCRnet, 2016). The primary objectives of the study are to assess the association of PPLs with DR progression over time, redefine DR severity grading level considering the findings in the peripheral retina, compare mydriatic 200° UWF digital photographs to mydriatic modified 7-field stereoscopic digital photographs for the assessment and grading of DR, and to determine the association between extent and location of non-perfusion on UWFFA and DR and DME severity and worsening over time. The secondary objectives are to explore the association of the prevalence and severity of cardiovascular disease or diabetic nephropathy at baseline and the incidence of these findings over time (4 years) with the severity and location of classic NPDR lesions and the extent of peripheral non-perfusion on UWFFA images. The study is a prospective, observational longitudinal study with the goal of at least 175 participants with PPLs and at least 175 participants without PPLs. The study is ongoing and the results are expected to be released in 2020 and will help to clarify the role of UWF imaging in the management of DR.

5. Financial interest

Dr. Sadda is a consultant for Carl Zeiss Meditec, Optos, Allergan, Genentech, Alcon, Novartis and Roche. He receives research funding from Carl Zeiss Meditec, Optos, Allergan and Genentech. He also receives honoraria from Carl Zeiss Meditec, Optos and Allergan. Other authors have no financial interest.

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