Ultra-widefield retinal imaging in the management of diabetic eye diseases

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Ultra-widefield (UWF) imaging has made a significant impact on the practice of ophthalmology in recent years, especially among retina specialists. Devices such as the Optos 200Tx (Optos, Dunfermline, U.K.) now allow imaging of up to 200° of the posterior pole in a single field of view (Figures 1 and 2). In contrast, the fields of view in conventional imaging devices are limited to between 30° and 55° of the posterior pole. Montages of several fields, such as those used in ETDRS seven-field imaging, have significant limitations, including inconvenience to patients as well as artifacts at the borders of the overlapping images.

Several imaging modalities are available to ophthalmologists using UWF devices, including pseudo-color images, fluorescein angiography (FA), and fundus autofluorescence (FAF). These have been shown to be of relevance to many diseases including diabetic retinopathy, retinal vein occlusion, age-related macular degeneration (AMD), uveitis, and retinal dystrophies. For example, the pattern of peripheral FAF abnormalities has been shown to vary among patients with neovascular and non-neovascular AMD, and it is possible that the presence of a particular type of abnormality may be a prognostic indicator for progression of the disease.

Diabetic retinopathy (DR) is a common complication of diabetes mellitus, affecting up to 93 million people worldwide, and is estimated to be responsible for up to 17% of total blindness. Diabetic macular edema (DME) is a common cause of vision loss among diabetics and has been shown to have considerable impact on patients’ quality of life. In the United States, DME occurs in 30% of adult diabetics who have had the dis-
The prevalence varies with the severity of diabetic retinopathy: 3% among those with mild nonproliferative DR, 38% among those with moderate to severe nonproliferative DR, and increasing to 71% for those with proliferative diabetic retinopathy.

Because the clinical features of DR occur throughout the posterior pole, UWF imaging is of particular importance managing this disease. Silva et al recently reported that the severity of DR assessed using widefield imaging and ETDRS photography matched in 80% of eyes and remained within 1 level in 94.5% of eyes (weighted kappa 0.74). Even more importantly, in 10% of eyes, UWF FA has been shown to demonstrate additional peripheral pathology such as nonperfusion and retinal neovascularization that would have been missed on corresponding ETDRS seven-field imaging (Figure 1).

Even though DME occurs at the macula and is adequately imaged using conventional devices, recent studies suggest that UWF imaging may play an important role in assessing and managing patients with DME. Several studies have demonstrated an association between peripheral retinal nonperfusion and the occurrence of both neovascularization and DME. This is believed to be mediated by the production of vascular endothelial growth factor (VEGF). We know that retinal ischemia stimulates VEGF production. VEGF is a potent vasodilator that weakens the walls of the capillaries at the macula, which enhances vascular permeability and causes leakage of proteins, lipids, and fluid, resulting in the formation of DME. It has been shown that retinal photocoagulation reduces the levels of VEGF in the eye, and it is possible that laser photocoagulation may have a beneficial effect on control of DME.

A study by Wessel et al found that 26.3% of eyes with peripheral ischemia on UWF FA had DME, compared to 8.7% among eyes without ischemia ($P < .001$). Moreover, eyes with ischemia had 3.75 times higher odds of having DME compared to those without ischemia. Patel et al reported that among a cohort of 76 patients (148 eyes) with recalcitrant DME, the mean ischemic index — the amount of retinal nonperfusion expressed as a percentage of the total area of visible retina — was 47%, with a range of 0% to 100%. The extent of the peripheral nonperfusion varied with the cohort, being 0% for those with mild nonproliferative DR and ranging from 53% to 65% among patients with proliferative DR. Patients with larger areas of nonperfusion had more recalcitrant DME and required a larger number of macular photocoagulation treatments. Patients in cohort 4, defined as active proliferative DR with or without prior panretinal photocoagulation, experienced the smallest decrease in central macular thickness (7.2%) after treatment and required an average of 5.7 macular photocoagulation treatments. Patel et al also reported differences among patients with focal and diffuse DME. The mean ischemic index was higher for eyes with diffuse compared to focal DME (ischemic index 64% vs 41%). In addition, 69% of eyes with untreated nonperfusion had diffuse DME, while the remaining 31% manifested with focal DME.

Not all studies, however, have found a relationship between peripheral nonperfusion and macular edema. Sim et al reported no relationship between DME and either peripheral ischemia or peripheral leakage. Wessel et al also reported no correlation between the presence of peripheral nonperfusion and central macular thickness on optical coherence.
The authors suggested that perhaps only a small amount of retinal ischemia is required to cause DME and that macular thickening may be related to local, structural, and anatomical factors rather than the amount of VEGF present. These findings, while requiring further study and validation, are interesting because they suggest that not all regions of peripheral nonperfusion contribute equally to DME. Additional studies are required to determine which regions of the retina may contribute more significantly to the formation of macular edema and whether it is possible to distinguish these regions reliably using current imaging modalities.

The results of recent studies have generated proposals on new ways to treat DME. Patients with recalcitrant DME may benefit from targeted retinal photocoagulation to areas of retinal nonperfusion. This would theoretically address the major underlying driver of the DME and perhaps reduce the frequency of anti-VEGF injections or macular laser photocoagulations required, while sparing areas of peripheral retina that remain perfused. Another proposal is the use of combination therapy: using anti-VEGF injections to block existing VEGF molecules, while performing targeted retinal photocoagulation to reduce VEGF production from areas of nonperfusion. It is possible that such combination therapy may enhance the durability of treatments and reduce the number of treatments that patients require.

While there is still much to be learned, it seems clear that UWF imaging, in particular UWF angiography, is of considerable importance to assess retinal pathology among patients with DR and DME and indeed other retinal vascular disorders such as retinal vein occlusion.

REFERENCES


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