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Editorial

Need for a New Classification of Diabetic Retinopathy

The classification of diabetic retinopathy (DR) is important for documenting the disease status of an individual patient and following changes over time. In the clinical setting, it is commonly used to provide an estimate of the severity of the disease and therefore can help guide the clinician in determining appropriate treatment or follow-up intervals. Recent industry-supported trials have suggested that the initiation of antivascular endothelial growth factor (VEGF) therapy to reduce the DR classification level may be correlated with a reduction in rates of vision-threatening disease; longer follow-up studies are needed. The classification of DR is also used to determine eligibility in clinical trials and may be of value to assess comparability of results from different trials because they may have different DR classification levels for entry and exclusion. Finally, pharmaceutical companies measure DR classification levels in their clinical trials to assist applications for FDA approval.

The DR classification most commonly used is the Diabetic Retinopathy Severity Score (DRSS). This classification traces back to the Airlie House Meeting in Virginia in 1968.[1] It is based on seven-field stereoscopic film-based fundus photographs (later it was determined that seven-field digital photographs as well as four widefield digital photographs were equivalent). Levels are categorized from 10 (no retinopathy) to 85 (advanced proliferative diabetic retinopathy).

What are the advantages of the DRSS? It is a reproducible and validated mean to classify and assess the severity of DR and has been, for almost half a century, used in landmark clinical trials such as the Diabetic Retinopathy Study (DRS), Early Treatment Diabetic Retinopathy Study, Diabetes Control and Complications Trial (DCCT), Epidemiology of Diabetes Interventions and Complications Study (EDIC), and DRCR Protocol I clinical trials. It is made possible by the ease with which the posterior fundus can be photographed. It is well suited for natural history studies to assess the stability, progression, or regression of DR.

Despite the advantages of the DRSS as a classification scheme, it is generally too complicated for use in the clinical setting, although some simplified and condensed versions of the scale have been described. By contrast, the DRSS is widely used in clinical trials. The current scoring system is based on only about 30% of the ocular fundus, and recent studies have shown that changes outside this area are important in predicting future events.[2] It should be recalled that when the DRSS was formulated, optical coherence tomography and ultra-widefield and other current multimodal imaging were not available. Fluorescein angiography is not a part of the DRSS; the published data from the Early Treatment Diabetic Retinopathy Study demonstrated that fluorescein angiography only marginally increased the predictive value.

Although changes in DRSS levels have shown some correlation with a risk of future development of diabetic macular edema (DME), at present, optical coherence tomography (OCT) scans have been established as the most commonly used parameter for decisions about treatment of DME. This is despite the fact that the correlation of OCT measured central subfield thickness with visual acuity is disappointing.[3] Recently, a new OCT classification of DME has been introduced and may prove helpful for reading centers, but it may be too complex for widespread deployment into the clinical arena.[4]

As described above, the DRSS has been validated in eyes not exposed to an ocular treatment (note that DRSS cannot be used for changes in eyes with previous panretinal laser), but does the DRSS apply to eyes treated with anti-VEGF therapy? There is currently interest in the treatment of eyes with advanced levels of DRSS with anti-VEGF, even in eyes with no DME or neovascular complications, so this is an important question. There are data that show that anti-VEGF treatment improves the appearance of the fundus (i.e., the DRSS staging).[5] However, after anti-VEGF therapy, it is uncertain if DRSS

R. Tadayoni: consultant: Alcon, Moria, Zeiss, Allergan, Bayer, Genentech, Novartis, Roche, and Thea. R. Tadayoni: consultant and stock options: Oculis. M. S. Ip: consultant: Novartis, Genentech, Allergan, Regeneron, RegenxBio, Apellis, Aerie, Alimera, Amgen, Cell Lineage Therapeutics, Clearside, and OCCURX. L. Jampol: grant from the National Eye Institute through the Jaeb Center for Clinical Research.

adequately reflects the true underlying disease status. Indeed, it has been shown in at least one prospective study that the appearance of the fundus and thus the DRSS staging can improve after anti-VEGF treatment without significant reperfusion of the retina.[6] Importantly, if an eye is a "native" DRSS level (e.g., 43), we speculate that this eye is different from an eye that was treated with anti-VEGF at higher levels, for example, Level 53 and was "induced" to the lower Level 43. Thus, we believe there may be a difference between a "native" eye and an "induced" eye of the same DRSS level,[7,8] and if the vascular bed (on UWF-FA) in these two types of eyes is different, then the natural course and response to further treatment of these two categories of eyes may also be different. This example highlights the fallibility of a DR classification system that relies on only one imaging modality (i.e., color fundus photographs). We suspect that the health of the retinal neurons, glial cells, and endothelial cells is vastly different in these two "Level 43" patients. There is also literature that suggests that DR is actually a neuropathy and that the fundus changes measured by the DRSS may be secondary changes.[9] Thus, the DRSS, as a DR classification scheme, may have limited utility when monitoring the underlying disease process, particularly in eyes that have been treated with anti-VEGF medication.

As a result of the shortcomings of relying on only one imaging modality to classify DR, the authors believe that the integration of other information (e.g., multimodal imaging) could improve the diagnostic and predictive power over the current DRSS; a newer classification scheme should be developed. Ultra-widefield imaging (color or pseudocolor fundus, fluorescein angiography, and others), structural OCT, OCT angiography, and other imaging techniques could be incorporated. Psychophysical testing could also be used. Examples of some other modalities that could be incorporated include: microperimetry, adaptive optics of photoreceptors or blood vessels, and microaneurysm count and microaneurysm area assessment from color images, fluorescein angiography, or OCT angiography.

Such a new DR classification is needed for a more accurate assessment of the progression or regression of DR, response to anti-VEGF therapy (as well any future treatments for DR and DME), and prediction of visual outcomes. Other subspecialties within ophthalmology, such as glaucoma, are using artificial intelligence to assist in the interpretation of large data sets, whether unimodal or multimodal, to measure severity and predict outcomes. Can we use artificial intelligence and deep learning techniques to evaluate multimodal images of DR to help quantitate the severity of DR and the response to our treatments? Studies presently underway by the DRCR Retina Network (e.g., protocols AA and W) will give us large data sets of additional information in regard to progression or regression of fundus changes and visual outcomes. Artificial intelligence should help in analyzing these data. Indeed, a number of international organizations are planning reclassifications of DR based on multimodal information with the assistance of artificial intelligence. We eagerly await these proposals.

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