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Editorial

Updating the Staging System for Diabetic Retinal Disease

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Diabetic retinal lesions were first observed in 1856, but more than a century passed before a diabetic retinopathy (DR) severity scale was developed to gauge future risk of vision-threatening disease. This system enabled clinicians to effectively monitor and treat patients with DR and provided a research tool that would revolutionize DR management. Over the ensuing 5 decades, understanding of the natural history of DR, recognition of neurodegeneration as an important aspect of diabetic pathology, availability of imaging tools to identify early changes in the diabetic retina, and methods for assessing aspects of retinal function that do not rely solely on visual acuity have all substantially improved. These advances support the need for an updated diabetic retinal disease (DRD) staging system to incorporate relevant advances and provide prognostic information necessary to better address early disease, disease progression, development and use of therapeutic interventions, and treatment effectiveness.

Given the well-established complexity of diabetic pathways and pathology, it is likely that the most accurate systems may require a diversity of new information to be included in an updated staging system for diabetic retinal disease.

Disease staging systems are vital for clinical care and research. They must correlate closely with clinically important end points and are, ideally, easy to understand and use. They should reflect disease pathophysiology, serve as end points for clinical research, and reliably predict future events of medical importance. For decades, the Early Treatment Diabetic Retinopathy Study (ETDRS) DR severity scale has served as the major staging system for care and research of DR because of its ability to predict patient outcomes, including progression to vision-threatening complications.[1] However, both the ETDRS and the simpler, international DR grading scale[2] have limitations (Table 1). Neither is quantitative or linear, and they evaluate only the vascular component of DR existing within the posteriorly located 7 standard photographic fields without regard to the retinal periphery. They do not incorporate pathophysiologic or neurodegenerative changes that occur before development of clinically evident retinopathy.[3] They are also not well suited to document progression or regression of neovascularization in eyes with proliferative DR. From a staging standpoint, ETDRS scoring was not developed for assessing effectiveness of interventions that improve DR severity, specifically with regard to visual function. Thus, studies to confirm that regression of DR severity in the setting of treatment, such as anti−vascular endothelial growth factor injections, is associated with more favorable long-term functional outcomes have been limited. These scales also do not adequately define severity stages for diabetic macular edema (DME), which is a common cause of vision loss in diabetic patients. Although groups such as the DRCR Retina Network have established treatment algorithms for DME based on central retinal thickness measurements, these variables have not been fully incorporated into DR severity scale paradigms. Diabetic macular edema occurs in eyes throughout the DR severity spectrum and can worsen and improve independently of changes in DR severity.

Diabetic retinal disease involves loss of central and peripheral retinal capillary plexus vessel density and neurosensory changes, such as loss of inner retinal neurons and gliosis, as well as the classic, clinically evident lesions. Advanced imaging tools such as ultrawide-field photography, spectral-domain OCT, OCT angiography, and adaptive optics scanning laser ophthalmoscopy can interrogate the peripheral[4] as well as central retina and the retinal neurovascular unit including blood vessels, Müller and astrocyte glial cells, and neurons. Basic research has broadened our understanding of molecular pathways and systemic factors that lead to the development and worsening of DRD. Artificial intelligence tools can identify novel aspects of DRD extracted from retinal imaging.[5]

These new insights, methodologies, and approaches make this an opportune time to update the DR severity scale and incorporate it into a new staging approach for DRD. The comprehensive inclusion of additional assessments should improve our ability to diagnose early-stage disease and predict disease progression and visual loss,[6] thereby optimizing vision outcomes across all stages of

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Table 1. Limitations of the ETDRS and International DR Severity Scales and Goals for the Development of an Updated DRD Staging System

Limitations of the ETDRS and International DR Severity Scales	Goals for the Development of an Updated DRD Staging System
Do not evaluate the neural retina	Include evaluation of neural retinal pathology in DRD to elucidate early degenerative changes that may accompany or precede vascular lesions and to determine how neural abnormalities are correlated with visual function loss
Do not visualize the peripheral retina	Understand if peripheral retina is important for predicting future outcomes in eyes with DRD, because this may change whether we should routinely evaluate peripheral nonperfusion and lesions to best stage risk of DRD worsening for research and clinical efforts
Do not include molecular, pathophysiologic, or neurodegenerative changes that occur before the development of clinically evident retinopathy	Explore early changes in DRD that may lead to better characterization of preclinical abnormalities and therapeutic target development
Do not incorporate measures of systemic health	Include systemic health context (e.g., measures of glycemic control, blood pressure, and blood lipids) in the DRD staging system because these influence future anatomic and visual outcomes in persons with diabetes
Not well suited to document worsening or improvement of retinal neovascularization in eyes with PDR	Revise the PDR scale to describe key levels for both worsening and improvement of PDR. This will enable better characterization of eyes with PDR in natural history and under treatment for research and clinical purposes.
Do not address regression of DR severity in the setting of treatment	Clarify how improvement of ETDRS DR severity level during treatment with diabetes control, anti-VEGF, or steroids affects outcomes to understand whether such therapies modify underlying disease
Do not adequately incorporate severity stages for DME that are currently being used to drive care and evaluation of eyes with DME	Include severity stages for DME that specify involvement of the macula because this information is now incorporated into commonly used treatment algorithms
Are not directly tied to visual outcomes other than those based on best-corrected central visual acuity	Understand how additional aspects of functional vision, such as visual fields, contrast sensitivity, metamorphopsia, and low luminance acuity, change in DRD. This may facilitate development of therapies addressing DRD severity levels that do not directly affect central visual acuity and provide additional registrable end points for regulatory approval.
Are not quantitative	Aim to develop a staging system and severity scales that can be used to quantitate DRD pathology for easier use in clinical research
Difficult to use in practice	Develop a revised staging system that is easy to use in practice

DME = diabetic macular edema; DR = diabetic retinopathy; DRD = diabetic retinal disease; PDR = proliferative diabetic retinopathy.

retinopathy. A more inclusive severity scale might also provide enhanced phenotypic characterization for the development of disease progression biomarkers and correlation with retinal and vitreous proteomics, genetic, and epigenetic markers. Sophisticated biostatistical methods may be needed to evaluate and incorporate information from complex 'omics approaches as well as from artificial intelligence investigations that have the potential to identify wholly novel features on retinal imaging that are associated with DRD prognosis but that have not previously been detectable by human grading. The rigorous evaluation of variables for possible inclusion in a revised severity scale might confirm new therapeutic targets and pathways that are not currently addressed by the ETDRS scale.

Development of an updated DRD staging approach can benefit from prior efforts in nonophthalmic fields. The classification of cancers has evolved from a histologic morphology-based approach to semi-automated image analysis and patient-specific molecular diagnosis. These advances provide faster and more accurate histologic analysis and enabled patient-specific therapies based on molecular mechanisms such as expression of hormone receptors. The staging of preclinical type 1 diabetes now enables more specific diagnosis of asymptomatic, preclinical immune dysfunction, and possible treatment at that stage to prevent overt diabetes.[7] Systems biology approaches have revealed broad metabolic and inflammatory pathways that contribute to diabetic nephropathy and retinopathy.[8,9] Advances in understanding interactions between components of the neurovascular unit from the stroke and neurodegeneration fields also provide insights for DRD.

Validation is a critical component of developing the staging system and should be based on carefully defined, clinically relevant outcomes performed using rigorous and statistically valid methodologies. Clearly, a revised staging system must address risk of visual loss; however, such a system may also include quality of life/autonomy outcomes or predict prognosis and response to therapy. The development process should be able to add and subtract variables in a dynamic and adaptive manner, and the new staging system will require validation in prospective cohorts of patients. Large datasets with rigorous phenotyping of natural history and treatment response will be needed to systematically and comprehensively test variables for inclusion in the DRD staging system with each proposed revision. A collaboration of industry partners with federally funded organizations such as the DRCR Retina Network to pool previously collected clinical information, biosamples, and retinal images from relevant past and future DRD studies would substantially advance this challenging effort.

Figure 1 shows a proposed schematic for a multidimensional DRD severity scale. Ideally, an updated staging system will address retinal, neural, and vascular

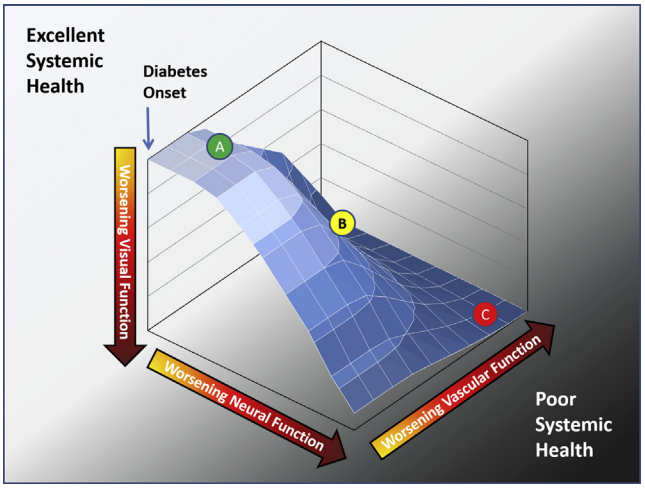

Figure 1. Schematic demonstrating relationships between retinal, neural, and vascular pathology with visual function for consideration in a revised severity scale for diabetic retinal disease (DRD). Background shading represents the context of systemic health status including, but not limited to, variables such as glycemic control, blood pressure, lipids, and the presence of comorbidities. **A,** Eye with excellent vision and minimal to mild retinal, neural, or vascular abnormalities in a patient with good systemic health. **B,** Eye with moderate vision loss, for example, from diabetic macular edema, and combined neurovascular disease in an individual with some systemic health issues. **C,** Eye with late-stage disease, for example, from a macular traction retinal detachment, and severe vision loss in a patient with poor overall systemic health.

pathology and their contributions to visual function in the context of systemic influences such as diabetes type, glycemic control, blood pressure, renal disease, and anemia. Although a multidimensional scale may initially seem cumbersome, it can address changes in parameters that do not necessarily progress in tandem or in the same temporal sequence. This comprehensive approach may reveal phenotypic variability that is not resolved by the ETDRS scale and may yield patient-specific information to guide treatments with the greatest chance of benefit. Visual fields, microperimetry, contrast sensitivity, metamorphopsia testing, and color vision have all been demonstrated to show deficits in patients with diabetic eye disease, but validation testing for use as outcomes for regulatory purposes is still under way. Nonetheless, features of retinal function will be important in assessing the ultimate integrity of the neurovascular unit. Patient-reported outcomes may help to understand the qualities of vision that are important to individuals.

Regulatory acceptance of a revised staging system and its validation based on end points of clinical importance will be critical. Developing a revised DRD staging system will require collaboration with regulatory agencies on important outcome measures for disease progression, visual function changes, and quality of life. Methods for quantification and establishing reproducibility will need to be predefined. The iterative process for testing, validation, and understanding the path to regulatory approval as an end point for clinical trials will likely highlight important areas for future research.

Any revised severity scale or staging system should have features that allow broad use. One or more severity scales with different levels of granularity to address different purposes, such as natural history outcomes versus treatment response, may be necessary. A simplified DRD staging system for routine clinical care would encourage widespread use. However, given the well-established complexity of diabetic pathways and pathology, it is likely that the most accurate systems may require a diversity of new information to be included in an updated staging system for DRD. In this case, computerized support could provide an easy-to-use interface for providers while still leveraging the power of extensive and complex data.

We propose it is an appropriate time to start developing a revised, multidimensional DRD severity scale that can be used to better define DRD, stage individual risk for disease worsening, predict and measure response to therapy, and support clinical trials evaluating novel therapies while having a readily usable interface for both researchers and clinicians. The road toward developing, testing, and implementing an updated staging system for DRD will necessitate involvement of multiple stakeholders, including scientists, clinicians, regulatory agencies, and patients. The ultimate test of the system's value will lie in demonstrating measurable benefits to patients with diabetes and improvement in functional outcomes for this vulnerable population.

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