Approach for a Clinically Useful Comprehensive Classification of Vascular and Neural Aspects of Diabetic Retinal Disease

Michael D. Abramoff,[1–5] Patrice E. Fort,[6,7] Ian C. Han,[1,2] K. Thiran Jayasundera,[6] Elliott H. Sohn,[1,2] and Thomas W. Gardner[6,7]

[1]Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, Iowa, United States
[2]Stephen A. Wynn Institute for Vision Research, University of Iowa, Iowa City, Iowa, United States
[3]Department of Electrical and Computer Engineering, University of Iowa, Iowa City, Iowa, United States
[4]Iowa City VA Health Care System, Iowa City, Iowa, United States
[5]Department of Biomedical Engineering, University of Iowa, Iowa City, Iowa, United States
[6]Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan, United States
[7]Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan, United States

Correspondence: Michael D. Abramoff, Department of Ophthalmology and Visual Sciences, University of Iowa, 200 Hawkins Drive PFP 11205, Iowa City, IA 52242, USA; michael-abramoff@uiowa.edu.

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The Early Treatment Diabetic Retinopathy Study (ETDRS) and other standardized classification schemes have laid a foundation for tremendous advances in the understanding and management of diabetic retinopathy (DR). However, technological advances in optics and image analysis, especially optical coherence tomography (OCT), OCT angiography (OCTa), and ultra-widefield imaging, as well as new discoveries in diabetic retinal neuropathy (DRN), are exposing the limitations of ETDRS and other classification systems to completely characterize retinal changes in diabetes, which we term diabetic retinal disease (DRD). While it may be most straightforward to add axes to existing classification schemes, as diabetic macular edema (DME) was added as an axis to earlier DR classifications, doing so may make these classifications increasingly complicated and thus clinically intractable. Therefore, we propose future research efforts to develop a new, comprehensive, and clinically useful classification system that will identify multimodal biomarkers to reflect the complex pathophysiology of DRD and accelerate the development of therapies to prevent vision-threatening DRD.

Keywords: classification, retina structural, diabetes functional, biomarkers imaging, neurodegeneration

Diabetic retinopathy (DR) is one of the most important causes of blindness worldwide and is the complication most feared by people with diabetes mellitus (DM).[1–3] DR is classically thought to result from microvascular changes in the retina, with microaneurysms—a result of ischemia due to capillary occlusion and nonperfusion—widely considered to be the first clinical sign of DR,[4,5] and pericyte loss considered as the earliest detectable histologic microvascular changes from diabetes in the retina.[6–11] Traditionally, retinal microvasculopathy has been seen as the pivotal initiating event,[12,13] followed by secondary inner retinal degeneration, termed retinal diabetic neuropathy (DRN).[14,15] Patients with DR may be asymptomatic, even in late stages of the disease, so early detection of the signs of DR is critical to limit visual loss from DR, especially now that numerous treatment options—laser, anti-vascular endothelial growth factor agents, and steroids[16,17]—are available. Therefore, the Preferred Practice Pattern by the American Academy of Ophthalmology and other standards worldwide recommend that every person with DM undergo regular screening for DR and be treated if vision-threatening DR develops.[3,18] Once DR is clinically apparent, it follows a well-defined progression[13] and may lead to visual loss and blindness from diabetic macular edema (DME) or proliferative DR (PDR) if undetected and untreated.[19]

Moreover, as we describe below, diabetes causes not only the classically recognized microvasculopathy and macular edema in the retina but also a neurodegeneration.[20] Therefore, rather than use the term DR, we will use the term diabetic retinal disease (DRD) to integrate the retinal microvasculopathy and retinal neuropathy caused by diabetes. Additionally, because the retina is an extension of the brain embryologically, the same interaction between microvasculopathy and neuropathy as a result of diabetes can be expected to occur there, even though so far, the only place where this interaction has been studied in the central nervous system is in the retina.[21]

Disease progression can be mitigated by intensive control of hypertension, hyperglycemia, and hyperlipidemia, but less than 20% of patients with type 2 diabetes have all three risk factors within target ranges.[22] Although current ocular treatments address vision-threatening DME and PDR, repeated anti-vascular endothelial growth factor (VEGF) injections reduce/improve retinopathy severity in less than one-third of eyes treated for 2 years.[16] Given the limited options for treatment of NPDR, we have recently discussed the role of adaptive and maladaptive pathophysiological mechanisms that occur across the course of DR.[23] These range from adaptive changes in autoregulatory responses to flickering light and hyperoxia in eyes without clinically evident retinopathy, to early decompensation in eyes

with nonproliferative retinopathy, and to overt, but often anatomically localized, decompensation of the blood–retinal barrier that leads to DME and neovascularization and fibrosis that represent aberrant wound repair and are classified as PDR.[23]

In the broader context of diabetes, these ocular processes parallel the insidious decline of function in other organ systems, and retinal dysfunction can be examined in a similar fashion. For example, in the renal system, progressive diabetic changes include glomerular hyperfiltration and renal hypertrophy, followed by glomerular sclerosis, mesangial expansion, and interstitial fibrosis. The early changes are clinically asymptomatic, but represent key opportunities to intervene. Renal function can be restored via improved diabetes control, treatment of hypertension, management of fluid overload, and angiotensin-converting enzyme or angiotensin receptor inhibition. Likewise, retinal function can be modified by control of systemic risk factors, anti-VEGF therapy, or laser treatment. Physicians recognize the benefits of preventing renal failure, but the means to prevent retinal failure[24] are currently limited because of incomplete understanding of retinal pathophysiology in diabetes, and by lack of quantitative measures of retinal function to follow during treatment.

The Current, Standard Structural DR Grading Systems Reflect Signs of Only Vasculopathy of the Posterior Pole Imaged by White Light Reflectance

DR is almost unique in medicine because screening and management are well established, in large part due to the use of standardized classification schemes. These standardized classification schemes are crucial because they enable a multidisciplinary approach where different medical specialists, including retina specialists, general ophthalmologists, optometrists, internists, endocrinologists, and family care physicians use the same language to optimize patient care. Furthermore, they enable clear endpoints for both pharmaceutical treatment studies and diagnostics devices, and minimize inter- and intraobserver variability of both management and scientific research.[25] The foundational studies that showed improved outcomes with screening and optimal management of patients with DR[26–28] used standardized classification schemes, starting with the Airlie House classification established in 1968.[29] This system developed into the classification system used in the Diabetic Retinopathy Study (DRS), which began in 1971 as the first randomized clinical trial in ophthalmology,[30] and laid the foundation for the Early Treatment Diabetic Retinopathy (ETDRS) grading scheme, the most widely used classification system for DR.[26–28,31] However, because of its complexity and unwieldiness for clinical use, the ETDRS was later condensed into the International Clinical Diabetic Retinopathy and Diabetic Macular Edema grading scheme (ICDR), with a total of 5+2 stages.[32] The existence of well-established classifications schemes for DR has also led to the development of automated algorithms for fundus image-based screening of DR.[33,34]

Despite their importance in helping to establish grading and management for DR, these foundational studies are now decades old and based on the available structural information of the retina at the time: seven-field stereo fundus color slide photography. Fundus color imaging is a process whereby a two-dimensional (2D) representation of the three-dimensional (3D), semitransparent retinal tissue projected onto the imaging plane is obtained using reflected visible white light.[25] It is an additive process whereby reflections from all wavelengths of visible light across all retinal depths are superimposed, and thus the depth of a structure cannot be resolved. Fundus imaging of the posterior pole has been the accepted standard to grade DR for decades and relies on a 20° to 50° field of view for each field. The standardized seven-field images allow hemorrhages, microaneurysms, exudates, cotton-wool spots, intraretinal microvascular abnormalities, and neovascularization, as well as retinal thickening, to be recognized, staged, and quantified in terms of size, number, and location. Therefore, ETDRS grading is also based on microvascular changes in the posterior pole as imaged by seven-field color fundus photography. However, lesions outside the view of standard seven-field photography do not represent aspects of DR microvasculopathy, or are not imaged as part of fundus photography, and thus do not contribute to the above-described grading schemes. Moreover, functional changes due to DRD, such as delayed implicit times and visual field defects, are missing from these schemes.

While the ETDRS classification system was originally developed for retinal images on slide film only, equivalence to digital imaging has been established.[31] We contend that current classification schemes are limited because they do not encompass the function and structure of the entire retina. By necessity, any assessment of the retina in DRD is a sample. This is so because DRD affects the retina from the molecular and gene expression scale all the way to macroscopic lesions such as hemorrhages, and beyond structure to function. It is impossible now and in the foreseeable future to image the entire retina structurally and functionally at a molecular resolution. However, we contend that extending the sample as currently represented by ETDRS to three dimensions, a larger field of view, and lesions beyond retinal microstructure is now required. This point was recently emphasized by the NEI/FDA Diabetic Retinopathy Clinical Trial Design and Endpoints Workshop,[35] at which there was widespread agreement on the need for development of new clinical trial endpoints to enable the treatment of DR prior to the onset of vision-threatening stages. At present, the Food and Drug Administration (FDA) has expressed interest primarily in functional endpoints for clinical trials, but clinical care also depends on corresponding structural measures.

Existing DR Grading Systems Do Not Include Ultra-Widefield Imaging, Optical Coherence Tomography, or Functional Metrics

As discussed above, the ETDRS grading covers approximately 75° of the posterior pole, so it does not incorporate peripheral changes and lesions, or subclinical changes such as disruption of the inner retinal layers (see below).[25–29,32–34] New imaging techniques have become available, including scanning laser ophthalmoscopy (SLO),[36,37] which has the potential to image a much wider field of view, and optical coherence tomography (OCT), which measures interferometry of infrared light induced by changes in refractive index in the retina.[25,38,39]

Specifically, OCT has become the standard clinical imaging tool in retinal disease, including in DR. It is widely available, does not require pupil dilation, uses low-intensity light, and allows high-resolution 3D volumetric images to be obtained in a few minutes.[25,40,41] Rather than use reflectance of light, it uses interferometry of low-coherence infrared light to resolve the depth of optical interfaces in the near-transparent retina. In the neuroretina, differences in density of optical interfaces, which are displayed as intensities in typical OCT images, correspond to the transitions between tissues in the retina as seen on histology.[25] The nerve fiber layer and ganglion cell

Investigative Ophthalmology & Visual Science

layer are thus imaged clearly in this manner. However, in the outer retina, differences in intensity on the OCT image do not always correspond to known histologic features, and can be the subject of intense debate.[42,43] OCT enables a detailed view of the various retinal layers in vivo, and is now the clinical standard for the reliable and repeatable quantification of retinal thickness, significantly enhancing our ability to diagnose and treat DME.[17,44] While initial studies applying OCT for DME primarily utilized total retinal thickness measurements for diagnosing DME and monitoring treatment response, the resolution of current OCT technology enables quantitative and qualitative analysis of the individual retinal layers, providing greater insight into structure–function relationships in normal and diseased states. Recent work in DME, for example, has correlated visual acuity with disorganization of the inner retinal layers,[45] photoreceptor length,[46] and the status of the external limiting membrane.[47] However, DME does not appear to be associated with changes in the choroid.[48] As discussed below, OCT also allows high-resolution quantification of the neuroretina in diabetes, which has shown that neurodegeneration precedes DR microvasculopathy.[20]

OCT angiography (OCTa) is a recently developed, readily available OCT technique that allows in vivo imaging of the retinal capillary beds in a patient-friendly manner without contrast dye.[49] OCTa utilizes amplitude or phase decorrelation technology, with high-frequency and dense volumetric scanning, to detect movement and thereby visualize perfused blood vessels of the retina and choroid, including the superficial and deep capillary plexus at depth-resolved levels.[50] OCTa can accurately detect areas of capillary nonperfusion in patients with DR, as confirmed by nonperfusion of the same region on traditional fluorescein angiography (FA).[51] FA requires intravenous injection of dye and has a mortality of 1:220,000[52]; thus OCTa is a safer, noninvasive technique to detect DR microvasculopathy and identify areas of diminished vascular flow in both the superficial and deep capillary plexuses.[4,49,51] The advantage of using OCTa-derived capillary perfusion density is that these lesions may precede the clinically visible microaneurysms, which are traditionally used in studies to link functional DRN to DR, by years.[26,53] Despite its advantages over FA, numerous limitations of OCTa as a relatively nascent technology currently exist. For example, a single spectral-domain OCTa scan typically covers maximally 6×6 mm^2, not enough to cover the entire macula. Manual quantification of capillary perfusion density from even a single OCTa scan, let alone multiple scans, by human experts is extremely time-consuming and likely to have substantial noise as well as low intra- and interobserver reproducibility. Thus, we and others have developed single-field and multifield OCTa protocols with subsequent widefield OCTa registration, selective segmentation of capillary plexus networks,[54–56] and selective quantification of superficial and deep capillary density.[57]

Diabetic retinopathy is traditionally considered a disease of the posterior pole, primarily early in the disease course. However, recent advances in imaging technology have allowed for improved evaluation of peripheral pathologic changes. Ultra-widefield retinal imaging is a relatively new tool to assess the progression of DR with up to a 200° field of view in a single image, allowing visualization of more than 80% of the retina.[58] Covering the entire field of the retina can be achieved but requires a combination of multiple images of the patient gazing in the cardinal directions. This approach has been used in conjunction with FA to evaluate the peripheral retinal vasculature.[59] Limitations due to the spherical nature of the eye and the flat representation of the fundus image have led to the development and validation of methods to account for distortions.[60] Among these studies, follow-up work defined a specific method to accurately measure retinal lesions in the peripheral region, properly accounting for image distortions.[61] A major limitation of ultra-widefield imaging is that it measures reflectance of retinal structures at narrow bands around specific wavelengths (488, 532, and 633 nm) rather than from multi-wavelength white light. Thus, the resulting images are pseudocolor images, with each color representing the reflectance for that narrow band. Many tissues do not have high reflectance at these specific wavelength bands. According to some authors, ultra-widefield imaging, with or without FA, may lead to significant underestimation of DR levels in 10% to 20% of patients when compared to the standard seven-field ETDRS images.[37,62] In another study, a single ultra-widefield image captured aspects of DR such as nonperfusion, neovascularization, and panretinal photocoagulation scars that were underestimated in the standard seven-field ETDRS images and missed in 10% of cases.[63] Similarly, a subsequent study, using three widefield Optomap (Dunfermline, Scotland) images, reported neovascularization outside of the standard seven-field images in 11% of cases with neovascularization.[64] These studies thus suggest that ultra-widefield imaging may detect more severe DR or a higher rate of neovascularization relative to standard field imaging. The clinical significance of these findings remains unclear, as no studies to date have shown that the detection of these peripheral lesions impacts visual outcomes. However, subsequent studies have suggested that lesions in the peripheral retina are strongly associated with disease progression, as demonstrated by a 4.7-fold increased risk of progression to PDR over 4 years, independent of baseline severity and hemoglobin A1c (HbA_{1c}).[36] Further study is needed to determine the other factors involved in disease progression, including the possible effects of aging and other cardiovascular risk factors, on progressive ischemia. There is conflicting data regarding any association between peripheral lesions as detected by ultra-widefield imaging and DME. While a correlation between DME and peripheral ischemia demonstrated by nonperfusion area has been suggested by Wessel et al.,[63] a subsequent study by Silva et al.[36] found no association. Currently, several studies to determine whether ultra-widefield images can contribute to grading and risk assessment of DR are under way,[65] including the Diabetic Retinopathy Clinical Research (DRCR) Network Protocol AA.

Beyond OCT and ultra-widefield photography, numerous methods exist to assess the relationship between retinal vasculature, structure, and function. However, at this time, there is no published report incorporating retinal function and its association with peripheral retinal lesions into a classification scheme. The closest to a functional study involves monitoring oxygen saturation and retinal ischemia using ultra-widefield FA and demonstrated a correlation between oxygen saturation and ischemic regions as a function of DR severity.[66] Multiple studies have tried to use functional imaging, especially measurement of hemoglobin oxygen saturation, to assess DR pathology and progression/grading.[66–68] Other methods have been tested, including multi-wavelength fundus ophthalmoscopy,[67] photoacoustic ophthalmoscopy, flavoprotein autofluorescence,[69] and OCT-based oximetry. The last method may be the most promising, as it has better depth resolution than multi-wavelength fundus ophthalmoscopy and does not require direct contact with the surface of the eye as does photoacoustic ophthalmoscopy.[70,71] A combination of photoacoustic ophthalmoscopy and OCT has been proposed to allow for simultaneous visualization of retinal vasculature structure and measurement of hemoglobin oxygen saturation. However, it is still unclear how this technology will allow further assessment of DR and its progression. Several alternatives to FA-based imaging of retinal

Investigative Ophthalmology & Visual Science

vasculature exist that can be performed without addition of a contrast agent. These include the retinal functional imager (RFI) or laser speckle flowgraphy (LSFG). Similar to functional OCT, RFI technology allows for visualization of retinal structure as well as measurements of blood flow and oximetry.[72–74] Measurement of blood flow using LSFG is based on scattering of laser light on the ocular fundus, and correlates strongly with absolute blood flow measured by more standard methods.[75] Changes in retinal and choroidal blood flow in patients with DME have recently been reported using this method. However, it is unclear if LSFG is sensitive enough to discriminate between patients with less advanced DR.[76] Another technique currently in development for measuring retinal function relies on the pupillary response to infrared light stimuli as a surrogate for midperipheral retinal ischemia,[77] and is currently being tested in an observational prospective clinical trial (NCT01546766). Finally, one of the only non–vasculature-based functional imaging assessments being developed is based on the transient intrinsic optical signal (IOS) and may be a promising alternative to ERG for objective measurement of retinal function.[78] In this method, also referred to as functional OCT, sequential images are recorded before and after light stimulus using high-speed, ultra-high-resolution OCT, allowing for concurrent structural and functional assessment of the retina (Tso EY, et al. *IOVS* 2007;48:ARVO E-Abstract 1951).[78,79] While not tested yet for DR, functional OCT could be a sensitive approach to explore and assess the impact of diabetes on the neuroretina.

DR Grading Systems Do Not Incorporate Recent Findings on DRN Metrics

Current DR classification schemes do not incorporate recent improvements in retinal imaging technology and methods of assessing retinal function. Another limitation is that current DR classification schemes are based primarily on microvascular changes and do not incorporate recent findings of structural DRN in diabetes.

There is extensive evidence that diabetes is accompanied by degeneration of the inner retina, a neurodegeneration that we and others call retinal sensory neuropathy, or DRN.[20,80,81] DRN is characterized by structural (e.g., neural apoptosis, ganglion cell loss, reactive gliosis, and thinning of the inner retina) and functional (electroretinogram [ERG], dark adaptation, contrast sensitivity, color vision, and microperimetric and perimetric psychophysical testing) deficits of the retina.[82–86] Central visual acuity, another aspect affected by DRN, is not affected in early DR and may be normal before clinical DR develops.[87] The functional consequences of progressive DRN, especially in the absence of clinically appreciable DR, have been gaining attention.[84–86,88] Progressive DRN has been recognized to affect visual outcome after successful treatment of DME.[89] In addition, while current therapies for DR such as monthly intravitreal anti-VEGF agents[90] and steroids are highly successful clinically, there is evidence of the former causing or accelerating retinal neurodegeneration in rodents.[91] Published clinical trials of anti-VEGF agents have not included tests of visual function that could provide a signal for potential deleterious effects of chronic VEGF suppression in persons with diabetes. The study discussed in more detail below showed that people with no or minimal DR have an average progressive neuroretinal (nerve fiber layer, ganglion cell layer, inner plexiform layer) thickness loss of 0.54 μm per year due to DRN.[20] While seemingly small, to put this in perspective, in a large study of patients with glaucoma, the average decline in neuroretinal thickness from early (<6-dB perimetric loss) to severe glaucoma (>12-dB loss) is 6 to 16 μm.[92] If DRN were to progress linearly at a rate of 0.54 μm per year over 10 years, it would result in a neuroretinal loss of 5.4 μm, thus of the same magnitude as severe glaucomatous damage. Of note, this would occur irrespective of the presence of microvascular DR. While patients with glaucoma receive treatment and regular perimetric examinations to anticipate and prevent visual loss,[93] such studies are not employed routinely for people with diabetes.

Recent studies by our group show that DRN precedes the microvasculopathy of DR, both in humans with diabetes and in mouse models of type 1 and type 2 diabetes,[20] and that DRN may occur in the absence of any characteristic microvascular damage, including pericyte loss, generally considered the earliest sign of DR.[6,94] In fact, we have claimed that one causal factor in the development of DR is DRN.[95] Specifically, we have shown that DRN precedes microvasculopathy and clinical DR in people with type 1 diabetes but minimal to no DR; postmortem donor eyes of DM patients with no detectable microvasculopathy; and two different mouse models of DM, with microaneurysms being the earliest sign of clinical DR[4] and pericyte loss the first sign of histologic DR microvasculopathy.[6] Even more recently, we found in a study of diabetic lipoprotein-associated phospholipase A2 (Lp-PLA_2) knockout mice, that absence of Lp-PLA_2 (mimicking the vasculoprotective effect of an Lp-PLA_2 inhibitor) prevents pericyte loss and other signs of DR microvasculopathy (Jiao C, et al. *IOVS* 2017;58:ARVO E-Abstract 5195). However, absence of Lp-PLA_2 did not prevent DRN, strengthening our conclusion that early DRN is independent of DR microvasculopathy.

Currently, there is evidence that DRN may be an early biomarker for the development of DR microvasculopathy, but we do not know whether it develops independently, or in parallel.[95] If indeed DRN is confirmed to be a causal factor in DR, this offers an entirely new perspective on the pathogenesis of diabetes complications in the retina and would represent a paradigm shift from the current focus on early detection and treatment of the vascular component of DR to early recognition of neurodegeneration.[3,18] Indeed, we have emphasized that diabetes progressively impairs the entire retinal neurovascular unit.[23]

In light of the existing evidence for DRN, we prefer to use the term diabetic retinal disease (DRD) rather than DR to encompass all retinal complications of diabetes, including both vasculopathy (DR and DME) and neuropathy (DRN), unless further evidence demonstrates that DRN is just an early biomarker for DR.

Next Steps

Fundus photography and OCT imaging demonstrate structural abnormalities that have accumulated from years of diabetes, but technology now exists to move beyond structural to molecular phenotyping of the disease, as in other fields of medicine. For example, breast cancers were once classified solely by their morphologic features of the grade (ductal, lobular, mixed, or metaplastic) and stage (in situ, invasive, metastatic), but today, sophisticated molecular classification guides treatment and determines prognosis.[96] Similarly, the current retinal imaging tools used in diabetes are akin to light microscopic assessment of tumors—they reveal the pathologic consequences of longstanding diabetes but not the pathophysiological processes that lead to them. Therefore, an extended retinopathy classification based on additional structural lesions will not achieve the type of advance that is now widespread in other fields of medicine. We recently proposed that DR requires a similar evolution from a scheme based solely on

Investigative Ophthalmology & Visual Science

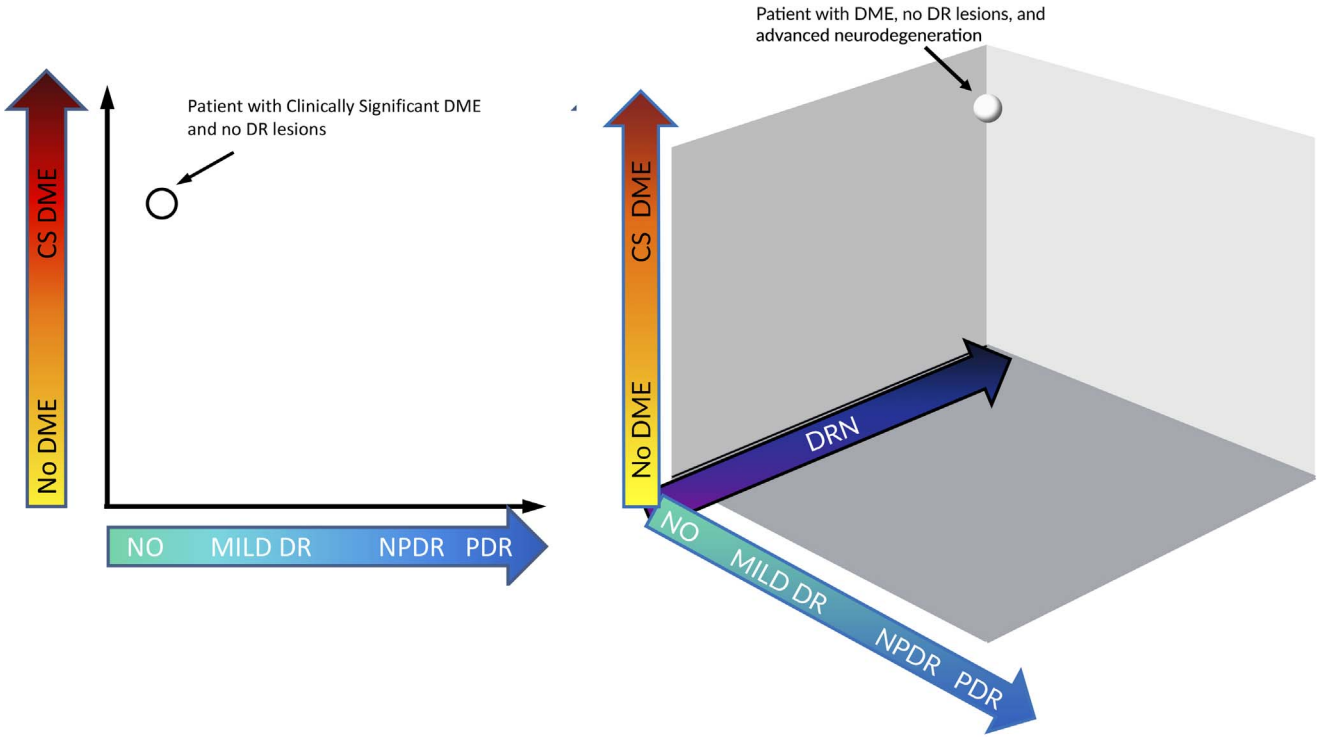

Figure. Dimension or axes in classification systems for diabetic retinopathy. *Left*: Current two-dimensional classification systems such as ETDRS, ICDR, and Eurodiab use two axes, one for diabetic macular edema (DME) severity and one for diabetic retinopathy (DR) proper (from no DR to proliferative DR [PDR]). In such a system, a patient can have extensive DME without any microaneurysms or hemorrhages. *Right*: Potential three-dimensional classification that includes estimated DRN damage in addition to the familiar two axes. In such a system, a patient can have extensive DME without any microaneurysms or hemorrhages, and early DRN.

late-stage structural lesions to one based on clinical pathophysiological and molecular phenotyping.[97] That is, a combination of structural assessment of DR, DME, and DRN via fundus imaging and OCT imaging should be combined with functional assessment of the macula and midperipheral retina, such as perimetry or electrophysiology. Molecular phenotyping in diabetes can be achieved by analysis of aqueous/vitreous fluid for relevant proteins, lipids, and/or metabolites, as is already done in other areas within ophthalmology such as inherited retinal dystrophies or glaucoma.[98] Indeed, the development of anti-VEGF therapy for DR was launched by the use of vitreous protein analysis,[99] and subsequent development of plasma kallikrein as a therapeutic possibility also arose from vitreous proteomic analysis.[100,101] Thus, the means to determine which drugs might best suit specific patients has not been established, but this is technically possible.

In addition, the cellular pathology of human DR must be better defined so that clinical features can be interpreted accurately. So far, despite the unique features of human disease, very little data have been collected from human donors, limiting our understanding of the molecular mechanisms of DR.[102] Complementary in-depth molecular studies can now be performed using vitreous and retina from human donors, which will give us key information about the mechanisms of human disease and potential markers of disease progression. If achieved, these approaches will provide clinically effective, patient-specific classification and selective treatment, as well as spur the development of new therapeutic approaches.

Requirements for a Clinically Useful Classification of Vascular and Neural Aspects of Diabetic Retinal Disease

The ETDRS classification has been the standard for decades, and until a new classification is developed and agreed upon, clinicians and researchers should continue to refer to the ETDRS in the course of validating any new classification scheme. It is widely recognized in the field of DR that the ETDRS classification, being based solely on microvascular structural lesions, by definition, fails to evaluate the majority of the retina. Therefore, the ETDRS classification system needs to be expanded to cover the entire spectrum of DRD based on the new insights discussed previously, starting from our classification schemes for DR and DME. An advantage of this approach would be continuity from a system that is currently in worldwide use, and the metrics can be obtained with devices that are commonly used.

It is important to understand the concept of the dimensionality, or axes, of classification schemes (Fig.). Specifically, DR is currently actually classified along two axes (dimensions) of disease severity: one axis for the DR vasculopathy (e.g., moderate DR) as well as one axis for DME (e.g., center-involved DME). These axes are almost independent and thus cannot be combined; some patients with moderate DR may have no center-involved DME, while some patients with clinically significant macular edema may have only mild DR.[17,32] In other words, having a specific stage along the DR axis reveals little about the specific stage along the DME axis.

Classification systems that have fewer axes are attractive because they are simpler to assess clinically and they make

Table. Tests of Retinal Function and Structure for Potential Inclusion Into Multimodal Retinal Assessment

	Functional Metric	Structural Metric
Macula	Frequency doubling perimetry; contrast sensitivity; multifocal ERG	Fundus photographs; OCT quantification of total and segmental neuroretinal thickness; quantification of neuroretinal integrity; OCTa capillary flow
Midperipheral retina	60-4 perimetry	Fundus photographs; OCT quantification of total and segmental neuroretinal thickness; quantification of neuroretinal integrity; OCTa of capillary flow
Peripheral retina	Full-field ERG	Widefield SLO/fundus imaging (Optos/Zeiss)

management decisions more straightforward. Our knowledge of the relationship between DRN and DR is still limited.[95] DRN may simply be an early sign of subsequent DR, which would allow both DRN and DR to be classified along the same axis. On the other hand, DRN could be fully independent of DR, such that a patient with PDR can have no DRN, and a patient with DRN may have moderate DR, which would require a separate axis for DRN. Similarly, peripheral lesions as detected on ultra-widefield imaging may be early biomarkers of DR according to ETDRS, or these may be independent. For example, some patients with PDR according to ETDRS grading may have neovascularization limited to the posterior pole, without visible peripheral lesions. Until we know more about the relationships within DRD, between DRN, classic DR, DME, presence of lesions on ultra-widefield imaging, capillary perfusion on OCTa, and so on, it will not be possible to determine the number of necessary axes for DRD classification systems. A clinically useful classification scheme should have the fewest number of axes until additional ones have been shown to be relevant.

Any new axis that is incorporated must be derived from robust metrics that yield clinically meaningful prognostic information on the patient's condition with minimal intra- and intervisit as well as inter- and intraobserver variability. Devices to estimate these metrics should be widely available and generate results that are easy to communicate so that physicians from different disciplines can understand the impact of DRD on visual disability. We postulate that a classification of DRD that is simple and easily understood could by itself improve outcomes in persons with diabetes. The need for such a classification is greatest for assessment of patients with no, mild, or moderate retinopathy because they constitute the majority of persons with diabetes. We propose that longitudinal multimodal measures of both macular and peripheral retinal integrity be conducted in studies that are robustly powered. Candidate studies may include those illustrated in the Table.

Studies on the relationship between ETDRS and peripheral lesions on ultra-widefield imaging are ongoing and will be essential for integration into the DRD classification scheme. Functional analysis of the neuroretina in patients with diabetes has become more defined over the last 50 years with ERG, color vision, contrast sensitivity, and various visual field paradigms. However, these tests have not advanced diabetic classification schemes and patient care, in part because they are cumbersome, are time-consuming, and require expensive equipment and therefore are impractical for busy practices. Furthermore, longitudinal studies to test the predictive ability of the tests have not been conducted. Ideal potential tests should have a short time limit for performance, such as 5 to 7 minutes, and the data output should be standardized, quantitative, and immediately interpretable. Structure and function tests should assess corresponding regions of the retina, macula, and midperiphery. Determining what functional and/or additional structural data should be added to a new classification scheme will likely need sufficiently powered, longitudinal, multi-institutional study examining multiple metrics.

In summary, we propose that research should focus on understanding the temporal and spatial relationships between existing and novel metrics and biomarkers toward a new, comprehensive, and clinically useful classification system of DRD.

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