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Translational Science Review

Clinical Evidence of a Photoreceptor Origin in Diabetic Retinal Disease

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Clinical Relevance: Although diabetes is associated with a classic microvascular disease of the retina, it is also increasingly being recognized as a cause of retinal neuropathy. Preclinical evidence suggests that retinal neuropathy in diabetes manifests in part as photoreceptor dysfunction, preceding the development of vascular features in experimental models. It remains unknown whether such findings are relevant to patients with diabetes.

Methods: Here, we review 4 lines of clinical evidence suggesting that diabetes-associated photoreceptor pathology is linked to the development of retinal microvascular disease.

Results: First, a major population-based investigation of susceptibility loci for diabetic retinopathy (DR) implicated a photoreceptor protein product as a protective factor. Next, electroretinography and other studies of visual function collectively show that rod and/or cone-derived abnormalities occur decades before the development of vascular features of DR. Third, protection from DR seemingly develops in patients with coincident retinitis pigmentosa, as suggested by several case series. Finally, based on anatomic features, we propose that the beneficial effect of macular laser in DR occurs via ablation of diseased photoreceptors.

Conclusions: The evidence we present is limited due to the small patient populations used in the studies we cite and due to the lack of methodologies that allow causative relationships to be inferred. Collectively, however, these clinical observations suggest that photoreceptors are involved in early diabetic retinal disease and may in fact give rise to the classic features of DR.

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Diabetic retinopathy (DR) is widely recognized by its hallmark microvascular abnormalities, which are often implicated as root causes of vision loss in this disease. However, diabetes is also associated with various forms of retinal neuropathy, including inner retinal thinning and inner retinal dysfunction in the absence of visible vascular lesions.[1,2] Collectively, these disease phenotypes are termed diabetic retinal disease (DRD).[3] The mainstay of current therapy for DR is directed against VEGF or allied pathways and is aimed at reducing complications of tissue ischemia. Though these approaches are effective for most patients, many remain poorly responsive. Moreover, anti-VEGF therapies may not be useful for treating nonvascular features of DRD, such as inner retinal thinning or field loss.[4]

Understanding the early pathophysiology of DRD, including the earliest cell targets of diabetes in the retina, is crucial to developing next-generation therapies. Although DRD visibly damages the inner retina, photoreceptors are highly distinctive in their metabolic properties and may therefore be uniquely susceptible to metabolic disturbances of diabetes.[5] Because some organs, such as the retina, have increased vulnerability to diabetes compared with other organs, including the brain, many have hypothesized the presence of local susceptibility factors. Such a factor in the retina may indeed be the photoreceptor, whose activity constitutes the bulk of retinal adenosine triphosphate demand and ranks among the highest of bodily tissues in terms of adenosine triphosphate usage per unit mass.[6–8]

Preclinical experimental evidence strongly suggests that the pathophysiology of photoreceptors and/or their codependent cell type (retinal pigment epithelium [RPE] cells), as well as the extracellular space between them (i.e., the subretinal space), likely initiates ensuing vascular pathologies that characterize at least the early stages of DR.[9–19] Here, we focus predominantly on clinical data suggesting a central photoreceptor role in the pathogenesis of diabetic eye disease. We review evidence from population-based studies to identify susceptibility loci, from electroretinography (ERG) and visual function testing, and from studies of patients with diabetes and coexisting photoreceptor dystrophic disease. We also draw on a proposed photoreceptor-centric model for the mechanism of action for macular laser photocoagulation, the traditional mainstay of treatment for diabetic macular edema (DME).

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Population-Based Studies of Susceptibility Loci

Several case series suggest that heritable factors could influence the onset and severity of DR. An early example includes a 1982 study of monozygotic twins with diabetes that showed a high rate of concordance among noninsulin-dependent diabetes (NIDDM) patients with respect to retinopathy severity, whereas twins with insulin-dependent diabetes (IDDM) showed lower concordance rates.[20] Though many subsequent attempts were made at finding heritable factors associated with DR, most have failed to show any meaningful associations.[21] One of the handful of studies showing a putative molecular association points to photoreceptor-related processes.[22]

The Medalist trial, which studied individuals who survived $\geq$50 years with type 1 diabetes, was aimed at identifying a hypothesized "protective endogenous factor" associated with people who do not have advanced retinopathy, nephropathy, or neuropathy. Diabetic retinopathy severity scores in this cohort showed an unexpected pattern with 35% of the cohort showing either no or mild DR and 50% of the cohort showing proliferative DR (PDR).[22] Far fewer than expected patients had intermediate stages such as moderate or severe nonproliferative DR (NPDR). A proteomics-based screen was performed on a subset of patients who donated their eyes postmortem. Retinal and vitreous samples from 6 eyes of 4 individuals in the no/mild NPDR group were compared with 11 eyes from 6 individuals in the PDR group. Using tandem mass spectrometry coupled with liquid chromatography, retinol binding protein 3 (RBP3, also known as interphotoreceptor binding protein) was found to be elevated by 1.6-fold and 1.9-fold in retinal and vitreous samples, respectively, from the individuals with a low burden of DR compared with those with PDR. These results were then validated by examining vitreous samples from a much larger cohort, combining Medalists, non-Medalist participants with diabetes, and a comparison cohort without diabetes. Retinol binding protein 3 levels inversely correlated to the presence of diabetes and severity of DR, with median levels of 5.42 mg/ml in the no diabetes group, 2.20 mg/ml in the no/mild NPDR group, 1.91 mg/ml in the moderate NPDR group, and 0.95 mg/ml in the PDR group.[22]

In an independent clinical study, reduced levels of RBP3 were also linked to worsening severity of DR. Vitreous proteomics showed that RBP3 levels were indirectly associated with DR severity, with a more than fourfold reduction in samples from PDR patients compared with control samples from patients without diabetes who underwent macular hole repair, and a corresponding approximately twofold reduction in NPDR samples compared with the same control group. Concurrent western blot analyses of retinal tissues obtained from postmortem donated tissues corroborated these data, with a more than twofold reduction in retinal RBP3 protein concentration comparing tissues from donors with diabetes but not DR to those without diabetes.[23] In follow-up analyses, elevated vitreous RBP3 in Medalists with a low DR burden correlated to improved imaging markers of photoreceptor health as well as to lower vitreous concentrations of canonical DR-related cytokines such as interleukin-12 and tumor necrosis factor-α.[24]

Retinol binding protein 3 is a 135 kDa glycoprotein that is almost exclusively produced in and secreted by photoreceptors. It plays a vital role in the visual cycle as it binds and transports cis and trans retinol between photoreceptors and the RPE. In addition, this protein may participate in fatty acid transport to the photoreceptor and provide trophic support for these cells. Inherited loss of RBP3 results in a retinitis pigmentosa (RP) phenotype.[25] Its mechanism of action in DR is currently being investigated.

Visual Function Testing

ERG measures the mass response of the neural retina to light stimulation. Standardized parameters for ERG were defined by the International Society for Clinical Electrophysiology of Vision, and involve multiple variables, including pupil dilation, dark adaptation, light adaptation, background and stimulus luminances, and recording times. Of dozens of ERG studies in patients with diabetes adhering to the International Society for Clinical Electrophysiology of Vision standards, the vast majority report abnormalities that localize to the inner retina, including losses of b-wave amplitude or oscillatory potential amplitudes and latencies, and these changes are summarized in 2 excellent recent reviews.[26,27] Other studies of visual function, such as abnormalities in the multifocal ERG that predict the later site of microaneurysm formation, and reduction in contrast sensitivity also implicate early neural contributions to DR.[28,29] There are also, however, compelling ERG data to support early photoreceptor dysfunction in diabetes.

Examination of ERG a-wave parameters in dark-adapted and light-adapted conditions can help isolate rod and cone responses, respectively. In 1 notable small case series, rod- and cone-derived a-waves showed reduced sensitivity parameters in a diabetes cohort compared with healthy controls, with no corresponding changes in maximal a-wave amplitudes, b-wave amplitudes, or implicit times.[30] These findings were reproduced by a similarly-designed study nearly 25 years later.[31] The latter study also demonstrated that patients with mild visible retinopathy had even greater reductions in the dark-adapted a-wave sensitivity, suggesting a direct relationship of photoreceptor-derived defects to DR/diabetes mellitus (DM) severity. Compared with healthy controls, a-wave latencies are increased in patients with diabetes and no DR in both light-adapted[32,33] and dark-adapted conditions.[34]

Flicker stimulation ERG, like light-adapted testing, preferentially measures cone-pathway responses. Studies using a portable ERG device, designed for DRD screening, show increased implicit times and decreased amplitudes with 30 Hz flicker stimulation, with greater severity of these defects with respect to increasing DR stage.[35,36] Recently, a pioneering group of electrophysiologists tested the effects of flicker stimulus given outside of the International Society for Clinical Electrophysiology of Vision parameters. Rather than using standardized 30 Hz white light flicker,

they varied the stimulus temporal frequency between 6 Hz and 100 Hz. Interestingly, when testing patients with diabetes and no manifest retinopathy, they found impaired responses at the higher frequency range compared with healthy controls. Because responses were normal among patients with diabetes at the lower frequency range, the diabetes-associated defects were interpreted to originate from cone photoreceptors themselves.[37] In fact, the sensitivity of the flicker ERG in detecting amplitude losses in patients with diabetes increases as the stimulus frequency is increased, with an average of 32% and 41% losses of flicker amplitude in patients with DM but without DR and patients with mild DR compared with healthy controls, respectively.[38]

Photoreceptor function can also be interrogated using psychophysical measurements.[39] For example, patients with diabetes have long been known to have delays in dark adaptation kinetics.[40,41] Bavinger et al[42] describe impaired rod recovery using dark adaptometry among patients with diabetes and no DR, with even greater impairments in those with DR. Cone recovery was also found to be abnormal at greater severities of DR. Acquired color vision deficits are also known to occur commonly in diabetes.[39] An analysis from the ETDRS showed that nearly half of its 2701 cohort of DR patients had some color vision abnormality, with the most common defect being on the tritan spectrum (blue-yellow defects).[43] More recently, chromatic perimetry was used to demonstrate sensitivity losses among patients with DR and also among patients with diabetes and no DR.[44] Interestingly, sensitivity losses were greater when a blue stimulus was used, consistent with the tritanomalous pattern identified in the ETDRS.

Taken together, these studies of visual function suggest that photoreceptor abnormalities occur early in diabetes and therefore could lead to both classic vascular changes and to the inner retinal abnormalities identified by imaging and ERG.

Focal Laser

Macular photocoagulation is an effective treatment for DME and was the first-line therapy for this disease before the anti-VEGF agents. The ETDRS, which studied 3928 patients with DR, showed that in cases of DME involving or threatening the foveal center, eyes receiving immediate focal laser were about half as likely as those assigned deferred laser to develop vision loss of $\geq$15 letters, with sustained effects for 3 years.[45]

The mechanisms by which focal laser reduces macular edema are debatable. One hypothesis posits that laser mechanically coagulates the microaneurysms that are presumed to be sites of extravascular leakage. Indeed, the ETDRS protocol mandated argon laser treatment with spot sizes of 50 to 100 microns and durations of $\leq$100 ms, with the aim to achieve "definite whitening" around identified microaneurysms or fluorescein-guided leakage sites. The protocol also dictated that investigators attempt to directly treat and ablate larger microaneurysms (i.e., >40 microns in diameter). Notably, these exact laser settings are still widely used for modern macular photocoagulation therapy. However, macular laser for DME more often involves focal or grid treatment within areas of retinal thickening. In these circumstances, the reduction in edema cannot be readily attributed to sealing a vascular leak. Moreover, on OCT imaging, laser defects tend to occur within the very outer retina while entirely sparing the inner retina, including any layer in which any of the retinal vascular plexuses reside (Fig 1).

Therefore, based on these anatomic features of photocoagulated eyes, mechanisms that are centered on photoreceptor physiology are more plausible than direct effects on the retinal vasculature regarding the beneficial effects of focal laser in DME. The simplest explanation may be that the photoreceptor outer segment is the primary source of VEGF secretion. The presence of microaneurysms, diffuse thickening, or angiographic leakage patterns may only indicate which clusters of photoreceptors are most hypoxic, and ablating these cells provides a beneficial effect in terms of reducing local VEGF concentrations. Therefore, conventional guidelines that instruct clinicians to target areas of macular thickening or large microaneurysms might have instead been guiding laser treatment selectively toward diseased photoreceptors, while avoiding the relatively healthy ones. Another straightforward explanation is that the ablation of a subset of photoreceptors will reduce oxygen demands in the setting of a diabetes-compromised vascular supply, and therefore improve local oxygen supply to the remaining cells of the macula. Indeed, experiments done nearly 4 decades ago showed that in cat and macaque retinas treated with laser photocoagulation, local oxygen tension was higher than that compared with nontreated retinas.[46,47] Finally, the laser may selectively destroy photoreceptors affected by increased oxidative stress, dysmetabolism induced by hyperglycemia, or several other proposed pathophysiologic sequelae of diabetes. Therefore, we propose that focal ablation of diseased photoreceptors is a potential mechanism for the action of macular photocoagulation in DRD.

RP and DR: A Negative Association

In early experiences using xenon-arc photocoagulator and the ruby laser, Amalric et al,[48] and Wessing and Myer-Schwickerwath[49] noted that PDR may be prevented or regressed by the development of disseminated choroiditis. Laser treatment of advanced-stage DR was therefore performed to mimic old choroiditis scars, which also resembled the lesions of RP. Years later, citing these initial observations, Sternberg et al[50] conducted a survey of retina specialists reporting that not a single case of PDR was known among people who had both DM and any form of RP. Moreover, he and his collaborating epidemiologists determined that approximately 4% of all known patients with RP in the United States had DM, a rate that was on par with the general population in 1984. Their calculations suggested that an ample number of patients with RP and

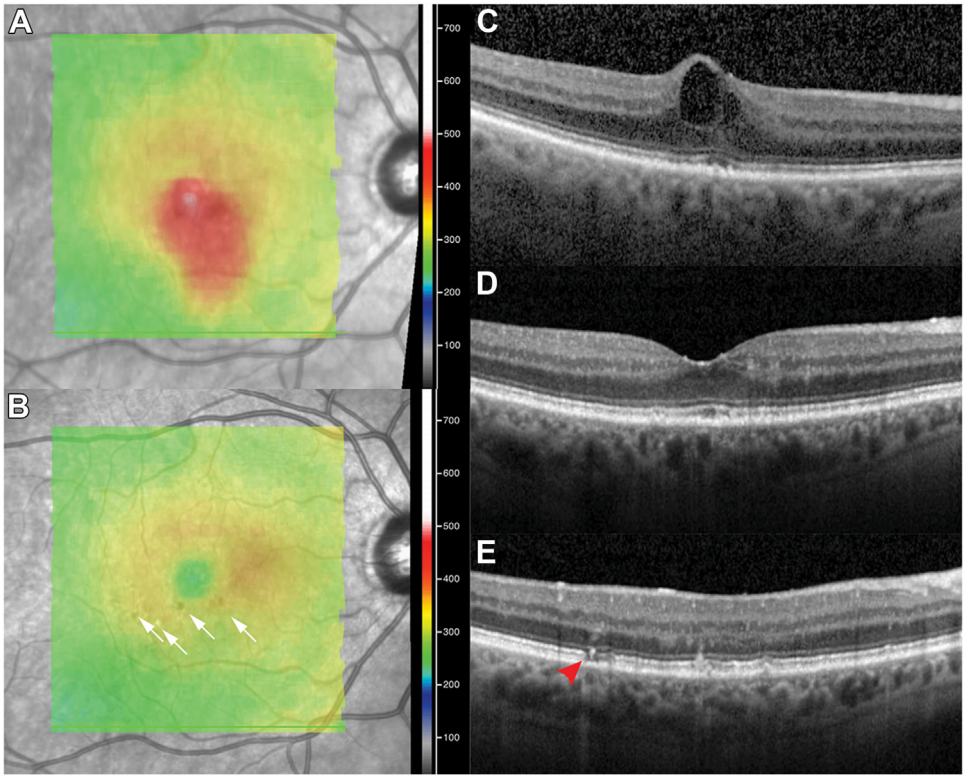

Figure 1. Outer retinal defects after focal macular laser therapy. A patient with type 2 diabetes suffering from diabetic macular edema was treated with focal laser photocoagulation. **A,** Near-infrared en face retinal map showing baseline macular thickness. **B,** Repeat thickness measurements show improvement in macular volume with focal laser scars visible (white arrows). Optical coherence tomogram through the foveal center at baseline (**C**) and at 3 months after laser (**D**). **E,** OCT cross-sectional scan through a paracentral location inferior to the fovea, within the field of laser treatment, shows defects in the ellipsoid zone and the interdigitation zone with sparing of the external limiting membrane, retinal pigment epithelium, and the entire inner retina (red arrowhead).

PDR should have been detected, and therefore there must be a negative coincidence between these entities.

After this, the late electrophysiologist Dr Geoffrey Arden posited that the high metabolic demand of photoreceptors creates a unique vulnerability of the retina to damage from diabetes.[51] In support of this hypothesis, he pointed to the early work of Kern and Engerman,[52] who demonstrated that in experimental models, vascular endothelial abnormalities such as microaneurysms and loss of pericyte coverage occur in retinal capillaries but not in brain capillaries of dogs with diabetes. These classic experiments led the authors of that study to conclude that "local influences" in the eye were permissive for the development of DR and called into question prevailing ideas that direct injury to capillaries from hyperglycemia was the primary driver of DR pathogenesis. Arden[53] hypothesized that the unique metabolic demands of rod photoreceptors, specifically their need to maintain ionic balance when depolarized in the absence of light, and their high rate of outer segment lipid bilayer turnover, made the retina exquisitely sensitive to even minor compromises in blood flow. Furthermore, he hypothesized that prolonged dark adaptation would exacerbate DR because it would impose increased energetic demands on the rods. As a corollary, he predicted that in the presence of peripheral retinal atrophy due to conditions such as RP, the energetic demands of the retina would be low. Indeed, like Wessing and Myer-Schwickerwath also surmised,[49] peripheral retinal laser ablation could mimic this condition (Fig 2) and reduce energetic demands on a vascular system compromised by diabetes.

Driven by this rationale and these observations, Arden[53] conducted a survey of patients who had coincident RP and DM. Confirmation of the presence of diabetes and RP was accomplished by contacting the primary eye care providers of each of the survey respondents. His final group included 25 patients with IDDM and 30 with NIDDM, who all had coincident RP. The mean ages were 20.8 and 65.5 years and the mean duration of diabetes was 19 and 14 years in the IDDM and NIDDM groups, respectively. In the IDDM group, 5 of 11 patients who had sufficient medical record data to assess systemic health conditions were confirmed to have nonocular complications of diabetes, such as nephropathy or peripheral neuropathy. In the NIDDM group, 8 of 18 patients had such complications. Strikingly, no patients in either group (total n = 55) had any DR. One limitation of Arden's[53] analysis was that DR was not assessed using

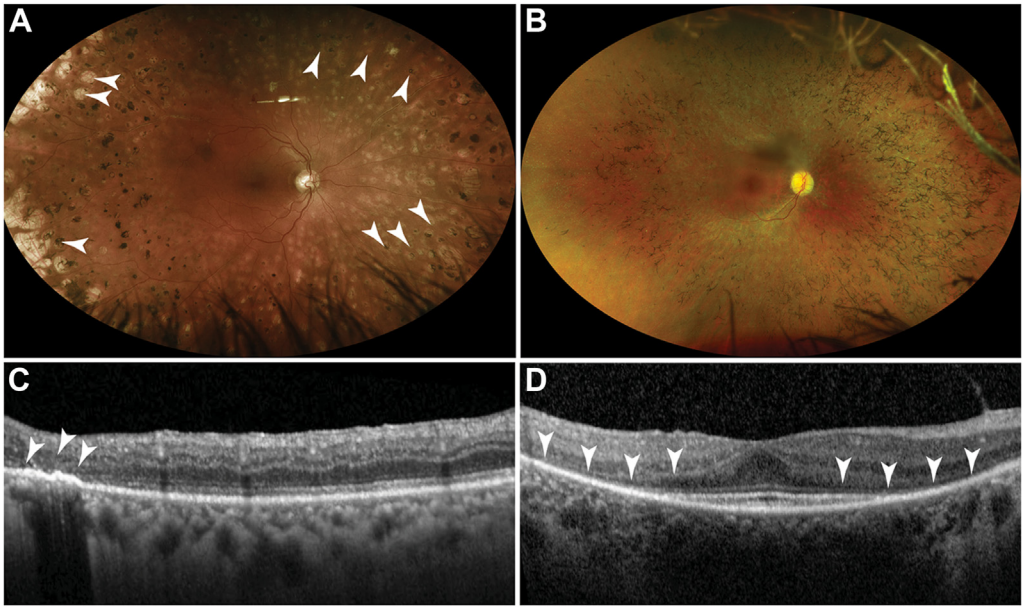

Figure 2. Phenotypic similarities between panretinal photocoagulation and retinitis pigmentosa. **A,** Wide-field scanning laser ophthalmoscopy of a patient with proliferative diabetic retinopathy treated by panretinal photocoagulation. Laser scars are present in the periphery of the retina (arrowheads). **B,** Wide-field scanning laser ophthalmoscopy of a patient with retinitis pigmentosa due to a *RHO* c.1040C>T heterozygous polymorphism and concomitant type 2 diabetes, showing peripheral atrophy, bone spicule pigmentation, and no vascular signs of diabetic retinopathy. **C,** Optical coherence tomogram showing an outer retinal scar from peripheral laser photocoagulation (arrowheads). **D,** Optical coherence tomogram from a patient with retinitis pigmentosa showing paracentral atrophy of the outer retina (arrowheads).

fundus photography but was instead assessed via medical record review of the treating ophthalmologist. Nonetheless, his data supported a negative coincidence of RP and DR.

To reduce the energetic demands of the retina in diabetes, Arden et al[51] hypothesized that preventing dark adaptation at nighttime, using a light-emitting mask worn during sleep, would be beneficial. The CLEOPATRA trial indeed tested this hypothesis but found no effects of the light mask on DR severity.[54] Several possible explanations could reconcile these negative results, including poor patient compliance, short follow-up, or insufficiently sensitive outcome measures. Another sobering result came from a clinical trial testing visual cycle inhibition on DR severity. In this study, a chemical inhibitor of RPE65, emixustat, was given to patients with PDR with the main outcome being a postulated reduction in neovascular burden. The drug showed no effect, beneficial or deleterious, over a period of almost 3 months.[55] This study was also limited by a small sample size (originally 12 patients in each arm), a short follow-up duration of only 3 months, and a high rate of attrition in the emixustat arm (nearly 50%).

The results of these interventional clinical trials call into question the mechanisms accounting for the negative relationship between DR and RP and suggest that this relationship may be more complex than initially described. However, the negative relationship may indeed be authentic, as a recent large database analysis also found that RP is associated with far less PDR than would be predicted in a Taiwanese cohort.[56]

Do Alterations in Molecular Processes Underlying Visual Function Underlie the Development of DR?

Transducin is localized to photoreceptor cells in the eye, and it plays a critical role in phototransduction. On the other hand, retinoid isomerohydrolase (RPE65) and lecithin retinol acetyltransferase are found in the RPE, and both are critical enzymes of the visual cycle. Diabetic mice made genetically deficient in transducin[11,14] or RPE65[14] or lecithin retinol acetyltransferase (submitted for publication) or treated with an RPE65 inhibitor (retinylamine[57]) have been shown to be protected from the diabetes-induced increase in permeability and degeneration of retinal capillaries, as well as impairments in visual function and molecular and functional abnormalities that contribute to the retinopathy. These preclinical data provide intriguing mechanistic hypotheses but would benefit from corroboration in a clinical setting. Unpublished observations by one of our groups (R.R.) using the IRIS® (Intelligent Research in Sight) database were inconclusive in determining an association between transducin1-related vision loss and DR development. A major limitation was the low prevalence of these coincident conditions in the Intelligent Research in

Sight database (only 56 unique patients with transducin1 disease within a total data set of 10 197 538 patients with DM).

Conclusions

To date, there are no large clinical studies with robust enough sample sizes to provide definitive proof of a specific cellular origin for DR, one of the most common blinding illnesses worldwide. However, we reviewed evidence from several case series that, in aggregate, provide a compelling argument for the central role of photoreceptor involvement in DR. Major mechanistic questions are still open, but the clinical data provide ample rationale to explore these mechanisms further, probing what specific cellular processes are affected in photoreceptors during the course of diabetes, understanding how these pathologic processes may affect visual function, and importantly, how they impact other cells in the retina, notably cells of the capillary vasculature, the most widely recognized target of diabetes in the retina. Ultimately, the understanding of these early processes could pave the way for novel therapeutics that are needed for this disease that continues to expand in prevalence, outpacing the progress made by the advent of vasogenic antagonists. Finally, the mechanistic understanding of early photoreceptor pathology in diabetes could facilitate the development of better screening techniques to identify individuals at risk at far earlier stages than current screening paradigms.

Footnotes and Disclosures

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Conception and design: Rajagopal, Kern

Data collection: Rajagopal, Kern

Analysis and interpretation: Rajagopal, Kern

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Abbreviations and Acronyms:
DM = diabetes mellitus; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRD** = diabetic retinal disease; **ERG** = electroretinography; **IDDM** = insulin-dependent diabetes; **NIDDM** = noninsulin-dependent diabetes; **NPDR** = nonproliferativediabetic retinopathy; **PDR** = proliferative diabetic retinopathy; **RBP3** = retinol binding protein 3; **RP** = retinitis pigmentosa; **RPE** = retinal pigment epithelium.

Keywords:
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