

Addressing Unmet Needs in Diabetic Retinopathy

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Introduction to Diabetic Retinopathy

Background and Epidemiology

Diabetic retinopathy (DR) is a common complication of chronic, poorly controlled diabetes mellitus.¹ In addition to chronic hyperglycemia, major modifiable risk factors for DR include hypertension, obesity, and dyslipidemia.²⁻⁴ Nonmodifiable risk factors include duration of diabetes, puberty, and pregnancy.^{1,5}

DR is a major cause of blindness among adults in the United States,⁶ accounting for about 80% of cases of legal blindness in persons aged 20 to 74 years.⁷ In 2005, the prevalence of DR among US adults 40 years and older was 5.5 million, and in 2010, it was estimated that approximately 7.7 million persons living in the United States had DR.^{6,8} This figure is expected to rise to an estimated 16 million by 2050.⁶

Patients with any type of diabetes (type 1 [T1D], type 2 [T2D], gestational) are at risk for DR, and an estimated 40% to 45% of all patients with diabetes in the United States have some form of DR, although they may not be aware of it.¹ Evidence indicates that after 20 years of living with diabetes, DR is present in almost all patients with T1D and in more than 60% of those with T2D.⁹ The risk of developing DR rises with increased duration of diabetes, and its rate of onset or progression can be especially rapid in women with gestational diabetes.¹

Pathogenesis and Disease Progression

Although the pathogenesis of DR is complex, it arises predominantly due to the metabolic effects of chronic hyperglycemia, which cause retinal microvascular damage leading to retinal damage and ischemia.¹ DR progresses through varying severities of nonproliferative diabetic retinopathy (NPDR) and ultimately advances to proliferative diabetic retinopathy (PDR).⁹ Initially, hyperglycemia damages retinal capillaries and results in formation of focal microaneurysms characteristic of mild NPDR. These may bleed or exude fluid onto the retina and thus distort vision.¹ As disease severity progresses to moderate NPDR, increasing numbers of microaneurysms and hemorrhages develop, as well as venous beading and retinal deposits called cotton wool spots. The increasing severity of

ABSTRACT

Diabetic retinopathy (DR), the primary retinal vascular complication of diabetes mellitus, is a progressive disease and a major cause of impaired vision and blindness, especially among individuals who are of working age. Early detection and treatment of DR can prevent 50% to 70% of its associated blindness. However, fewer than half of all US adults with diabetes adhere to guideline-recommended eye-screening schedules. Patients with DR typically have no symptoms in the early stage of the disease and may not seek medical evaluation until DR advances and results in vision impairment. These delays in diagnosis and treatment may result in visual impairment that is permanent and cannot be reversed. Although the direct medical costs of DR are substantial, the indirect costs of visual impairment with respect to loss of productivity, increased nursing home admissions, and decreased quality of life are far more copious. Greater adherence to eye screening guidelines among patients with diabetes is required to facilitate prompt diagnosis and early treatment of DR, and in doing so, reduce the resulting vision loss and economic burden associated with DR.

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microvascular lesions further disrupts retinal blood flow, stimulating the retina to produce growth factors that promote formation of new blood vessels that characterize the proliferative stage of the disease.¹ These abnormal proliferations of new retinal blood vessels may also bleed, ultimately leading to scarring and retinal detachment.¹

Studies have shown that 24% of patients with severe NPDR and 11% of those with moderate NPDR will go on to develop PDR within 3 years, with 22.2% of all patients with DR developing PDR within 1 year.^{10,11} Patients with DR may also develop diabetic macular edema (DME), which is characterized by severity according to the level of retinal thickening or hard exudates involving the center of the macula.¹²

Vision Loss

Several mechanisms contribute to vision loss in patients with DR. Even in mild NPDR, microaneurysms may bleed or exude fluid onto the retina and thus distort vision.¹ However, vision impairment increases with rising disease severity, and in PDR, it may result from vitreous hemorrhage due to bleeding of the proliferations of new blood vessels.⁴ It can also be a consequence of tractional retinal detachment that may occur secondary to distortion of the retina by these new proliferations of blood vessels and associated connective tissue. The disruption of retinal blood supply that accompanies the microvascular changes of DR results in death of retinal neurons, which is also a key component of the underlying pathophysiology of vision loss in DR.⁴ In approximately half of all patients with DR,¹ damage to blood vessels in the central retina (macula) contributes to the central vision loss that is characteristic of DME.⁴ Although DME can arise at any stage of the condition, the risk of its occurrence rises with increasing severity of DR.¹

Burden of Illness of Diabetic Retinopathy

Clinical Burden

Characteristic symptoms of DR vary; they may include fluctuating vision, blurred vision, double vision, distorted vision, floaters in the field of vision, or changes in refractive error.⁷ Because there are generally no initial symptoms of DR, the condition often remains undiagnosed until its more advanced stages when it begins to affect the patient's vision.¹ In one study, about 25% of hospitalized patients with diabetes had previously undiagnosed DR, varying from mild to vision-threatening.¹³ Even among patients with diabetes who receive ongoing eye care, many are unaware of their DR.¹⁴ Among 2795 patients with diabetes who underwent teleophthalmology evaluation, 82% of patients with DR and 78% with moderate NPDR or worse, or DME, were unaware that they had DR, despite reporting an eye exam within the past year.¹⁴

Although many patients with DR have only mild disease, their disease has the potential to progress to more advanced forms that can significantly impact their vision and health-related quality-of-life

(HRQOL) outcomes.¹⁵ In particular, the more advanced stages of DR may involve complications such as vitreous hemorrhage, macular ischemia, or tractional retinal detachment that can have severe consequences for vision.¹

A recent study of US adults with diabetes highlighted that vision-related functional burden is greater in patients with more severe DR. The results of this study indicated that 72.3% of the participants had no retinopathy and 27.7% had retinopathy (25.4%, mild or moderate NPDR; 2.3%, severe NPDR or PDR). Vision-related functional burden was experienced by 20.2% of those without retinopathy, 20.4% of those with mild or moderate NPDR, and 48.5% of those with severe NPDR or PDR. Approximately half the patients with either severe NPDR or PDR had difficulty performing at least 1 visual function task (such as reading or noticing objects off to the side) that might affect their daily activities.⁶

In particular, the vision functional burden was 4 times higher in those who had either severe NPDR or PDR than in patients without DR, even after adjusting the analysis to account for central visual acuity or DME. This increased burden in more advanced DR is likely due to peripheral retinal changes that result in loss of visual field, dyschromatopsia, nyctalopia, or reduced contrast sensitivity. Such peripheral changes may be associated with tractional retinal detachment, vitreous hemorrhage, or retinal destruction following panretinal photocoagulation (PRP).⁶

Health-Related Quality of Life

Visual impairment is associated with substantial patient morbidity, psychological impacts, and clinical treatment burden, including anxiety, depression, and financial strain.¹⁵ Patients who lose their vision often report feelings of social isolation and dependence, especially due to practical difficulties associated with no longer being able to drive.⁷ Visual impairment can also reduce patients' ability to work and thus earn money, frequently as a result of no longer being able to drive. Vision loss may also hasten admission to nursing homes, which results in a large economic cost, and can impact caregivers, including family members.¹⁶

The Los Angeles Latino Eye Study used National Eye Institute Vision Specific Questionnaire (NEI VFQ-25) and Short Form 12-Item Health Survey subscales as instruments to assess the HRQOL in Latino patients with DR. The results of this study showed that patients with more severe DR had worse HRQOL scores. Those with grade 2 DR (minimum) through grade 8 DR (unilateral moderate) had a mild, constant reduction in HRQOL. However, as DR further advanced to grades 9 through 15 (bilateral moderate NPDR to bilateral PDR), patients experienced significantly steeper drops in HRQOL. The greatest effects on patients' HRQOL occurred in the areas of vision-related daily activities, dependency, and mental health.¹⁵

The association of depression with visual function loss and visual acuity impairment was investigated using 2005 to 2008 National

Health and Nutrition Examination Survey (NHANES) data from 10,480 US adults 20 years and older. Patients self-reported their visual function loss using the NEI VFQ-25 and depressive symptoms using the 9-item Patient Health Questionnaire (PHQ-9). Among adults presenting with visual acuity impairment, the prevalence of depression (PHQ-9 score of >10) was 10.7%, compared with 6.8% among those without visual acuity impairment. Depression was more prevalent and more severe among those with greater vision loss. Approximately 20% of adults with visual function loss reported mild depressive symptoms compared with 12.1% of those without impaired visual function.¹⁷

Economic Burden

From 1990 to 2010, the prevalence of diabetes in the United States tripled, and its annual incidence doubled. Its US prevalence is expected to continue to climb, rising by 54% from 35.6 million in 2015 to an estimated 54.9 million in 2030.¹⁸ As a result, total annual diabetes-related costs in the United States are expected to make a similar increase, rising from \$407.6 billion in 2015 to \$622.3 billion in 2030,¹⁸ of which annual medical costs are expected to account for \$472 billion.¹⁸ The results of an analysis of MarketScan claims data from 2006 through 2009 for people with diabetes indicated that approximately 20% of commercial insurance and Medicare costs involved diabetes-related complications. These costs were trended to 2012.¹⁹

In 2013, the annual healthcare costs associated with retinal disorders in the United States totaled nearly \$8.7 billion, with \$4.1 billion of this attributed to diabetes-related retinal disorders.²⁰ In an earlier study, the total economic burden of DR and other visual disorders on the US healthcare system was estimated in an analysis of direct medical and nonmedical costs and productivity losses using large Medicare and commercial claims databases. The total direct medical costs of visual disorders (eg, age-related macular degeneration, cataracts, DR, refractive error, glaucoma) in the US population 40 years and older were estimated to exceed \$16 billion in 2004. In this same study, total productivity losses, measured by lost wages due to decreased workforce participation of those who become visually impaired and blind, were estimated to exceed \$8 billion.¹⁶ DR accounted for an estimated \$493 million of the total direct medical costs for visual disorders.¹⁶ Treatment in the outpatient setting was associated with the highest direct medical cost in the DR population aged 40 to 64 years, with an average treatment cost per patient of approximately \$629 per year.¹⁶ In addition, long-term care/nursing home costs due to visual disorders

totaled \$11 billion; other direct costs included \$94 million for government purchase programs and \$62 million for guide dogs.¹⁶

In a real-world analysis of administrative claims data gathered from 17 large employers, total annual direct and indirect healthcare costs were measured over a 12-month period following an initial diagnosis of DR. Employees with DR (n = 2098) had substantially higher total annual costs compared with the matched control population (1:1) of employees with diabetes without a DR diagnosis (**Table 1**).²¹ Of those employees with DR, 28.6% had PDR (n = 600), 15.2% had DME (n = 318), and 7.6% (n = 160) had both PDR and DME. Mean annual direct costs of medical services and prescriptions in employees with DR were \$5146 higher than in the control population (\$14,671 vs \$9525, respectively). Mean annual indirect costs were \$1174 higher in employees with DR than in the control population, including higher costs of healthcare-related absenteeism (\$1640 vs \$1218, respectively) and disability (\$1908 vs \$1156, respectively). Notably, this may be an underestimation of the total indirect costs of DR, as other potential cost drivers were not accounted for, such as lost productivity at work (presenteeism), changes in employment/wages related to DR medical burdens, or caregiver costs.²¹

Current Standards of Care for Diabetic Retinopathy Diagnosis of DR

Recent decades have brought significant medical advances that have improved the management of DR. Early detection of the condition facilitates prompt management that can prevent or delay its associated visual impairment. Overall, the ophthalmic examination for patients with diabetes mellitus should consist of a typical comprehensive eye evaluation, paying special attention to features that are particularly relevant to DR. These include lesions, such as preretinal or vitreous hemorrhage, and macular edema and neovascularization. Pupil dilation is necessary for optimal retinal evaluation, and ophthalmologists should also evaluate intraocular pressure.²²

TABLE 1. Comparison of Mean Annual Direct and Indirect Costs for Employees With DR^{21a}

	Total Cost	Direct Costs ^b	Indirect Costs
Employees with diabetes without DR	\$11,898	\$9530	\$2380
Employees with DR	\$18,218	\$14,665	\$3553
Employees with DME	\$28,606	\$23,514	\$5092
Employees without DME	\$16,363	\$13,090	\$3273
Employees with PDR	\$30,135	\$24,470	\$5696
Employees without PDR	\$13,445	\$10,756	\$2689

DME indicates diabetic macular edema; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy.

^aCosts are in 2005 dollars. The sum of direct and indirect costs may not add up to total costs due to rounding. Direct and indirect costs discussed in text may not match due to rounding.

^bIncludes prescription drug costs.

Adapted from Lee LJ, Yu AP, Cahill KE, et al. *Curr Med Opin.* 2008;24(5):1549-1559.

Screening for DR

For patients with T1D, ophthalmic screening examinations are recommended annually, starting 5 years after diagnosis. Because about one-third of patients with T2D have signs of DR at diagnosis, they should receive ophthalmic examination immediately upon diagnosis. Women with diabetes who plan to become pregnant should receive screening ophthalmic examinations before pregnancy. They should also receive another eye examination during the first trimester, and further follow-up examinations as necessary, based on previous examination findings.²²

In many areas of the United States, patients' compliance with the guideline recommendation for annual eye examinations is 50% or less,²³ even among insured patients with diabetes.²⁴ In a study of 113 patients with diabetes, just 40% had received a dilated eye examination within the previous 12 months.¹³ Among patients who did not receive a dilated fundus examination within the previous 12 months, the most commonly reported barriers to adhering to recommended ophthalmic screening for DR included physical disability, lack of transportation, illness, too many other medical appointments, lack of affordability, and the appointment not being a priority.¹³ Telemedicine approaches may be helpful if there is little opportunity for patient screening, such as in situations where the ratio of providers to patients is low or the distance to reach a provider is a barrier.⁴

Tests for DR

Further tests can enhance diagnosis and management of the patient with DR. For example, optical coherence tomography is a diagnostic imaging tool that provides high-resolution images of the retina. It is used to measure retinal thickness and monitor macular edema, and these findings may serve to guide management with regard to deciding whether to repeat anti-vascular endothelial growth factor (VEGF) injections, change treatments, initiate laser treatment, or consider vitrectomy surgery.²²

Fluorescein angiography (FA) is not typically included in the routine examination of patients with diabetes. However, it is a valuable ancillary test for use in patients with more advanced DR, such as in those with macular edema or PDR, or to evaluate for neovascularization and ischemia. In particular, FA can help investigate unexplained vision loss, or differentiate macular swelling as a result of diabetes from that associated with other forms of macular disease.²²

Treatment of DR

For patients with DR, clinicians can provide education and increase awareness of the importance of optimal glycemic control in delaying or preventing disease progression.²² Although patients with mild-to-moderate DR typically do not require DR-specific therapies unless they develop clinically significant macular edema,²² some may need

to make lifestyle changes or take medical therapies to help control hypertension, hyperglycemia, or hyperlipidemia.⁶ Indeed, findings from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study demonstrated that both intensive glycemic control and the drug fenofibrate reduced progression of DR in patients with T2D and additional cardiovascular risk factors.²⁵ In the subsequent ACCORD Follow-On (ACCORDION) Study, although the benefit of tight glycemic control extended throughout the 8 years of follow-up, the benefit of fenofibrate did not.²⁶

Patients with more severe forms of DR, however, may require more frequent treatment interventions.²² Although the specific treatment plan will be tailored to an individual patient's condition, PRP is considered standard care for patients with vision-threatening DR, with adjunct surgical vitrectomy when PRP alone is inadequate or not feasible due to vitreous hemorrhage.⁶ Vitrectomy may also be required in cases involving traction retinal detachment or combined traction-rhegmatogenous retinal detachment.²² Other therapies may include focal/grid macular laser surgery, intravitreal corticosteroid injections, or intravitreal anti-VEGF injections.²²

Intravitreal anti-VEGF injections represent a pharmacological alternative to PRP.⁶ The treatment regimen may not be cost-effective in the United States for patients with PDR but without vision-impairing DME.⁶ Management of DR and the role of anti-VEGF injections in NPDR and PDR are evolving.

The range of potential complications (**Table 2**) associated with each therapy should also be considered when developing a patient's treatment plan.^{6,22} This is a general list and not all-inclusive to respective treatments within each category.

Despite availability of guideline recommendations for screening and education of patients with diabetes, data from NHANES indicate that about one-third of US patients with diabetes are not receiving the appropriate ophthalmological care that could help avoid vision impairment and blindness.^{27,28}

Strategies are being developed to increase the availability and effectiveness of DR screening programs. Screening alternatives include telemedicine-based digital imaging strategies, which can significantly improve rates of DR screening.²⁹ Artificial intelligence-based deep learning algorithm technology offers the potential to increase the efficiency and accessibility of DR screening programs.³⁰ Additionally, home monitoring systems have been shown to be effective screening methods, such as for early detection of choroidal neovascularization in patients with age-related macular degeneration.³¹

Given the public health problem posed by the growing epidemic of diabetes, improved clinical management of this patient population is critical to address its debilitating and potentially devastating vision-related consequences. In particular, screening for diabetes-related eye problems would allow for timely diagnosis and treatment of DR.³² Studies have shown that use of standard-of-care screening

for DR, prompt diagnosis, and treatment of the condition can help prevent 50% to 70% of retinopathy-related blindness. Importantly, adherence to preventative screening can lead to a potential annual savings of \$600 million for the US healthcare system.¹³

According to the CDC, every percentage-point reduction in glycosylated hemoglobin (A1C) level generally reduces a patient's risk of developing microvascular complications, such as DR, by 40%.³³ Regarding the benefit of annual eye screening in patients with T2D, the reduction in risk of developing severe vision loss from DR varies according to a patient's age and level of glycemic control.³⁴ For example, a 45-year-old high-risk patient whose A1C level is 11% gains 21 days of sight over their lifetime from undergoing annual eye screening compared with every-third-year screening; a 65-year-old low-risk patient whose A1C level is 7% gains an average of 3 days of sight over their lifetime.³⁴ These data highlight the importance of especially targeting patients with poor glycemic control for eye screening.³⁴

Conclusions

Adherence to recommended eye screening schedules to facilitate early identification of DR among patients with diabetes remains a significant unmet need. It is important for policy makers to keep this in mind to reinforce best practices among clinicians who should stay up to date with screening recommendations for this high-risk population and should be aware of patient-level barriers to ophthalmic care. This will allow clinicians to use strategies to improve eye screening, diagnosis, and treatment, and ultimately patient outcomes. This is especially important for working-age patients: The disease burden in this population is particularly significant, not just for the patients themselves, but also for the US healthcare system and society. Given the low rate of eye screening not only for the uninsured but also among medically insured persons with diabetes, payer organizations should consider creating systematic strategies within their existing benefit structures to address the need. One strategy would be to emphasize eye screening through telemedicine and other novel technologies in primary care settings among persons with elevated A1C and/or diagnoses of diabetes. Ultimately, improving the uptake of eye screening will allow earlier detection and appropriate management, thus providing opportunity to enhance patients' clinical and HRQOL outcomes. ■

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TABLE 2. Potential Complications of Some Commonly Used Therapies for Diabetic Retinopathy^{6,22,a}

Therapy	Potential Complications
Focal laser surgery	<ul style="list-style-type: none"> Initial transient decrease in central vision Scotomas Expansion of scar area
Panretinal photocoagulation	<ul style="list-style-type: none"> Visual field loss Peripheral visual field constriction Nyctalopia Vitreous hemorrhage Reduced accommodation Loss of color vision Reduced contrast sensitivity Mydriasis
Intravitreal injections	<ul style="list-style-type: none"> Cataract Increased intraocular pressure Infectious endophthalmitis Noninfectious inflammatory reactions Systemic effects related to the injected agent Pain Conjunctival hemorrhage Retinal detachment
Vitrectomy	<ul style="list-style-type: none"> Vitreous hemorrhage Retinal tear or detachment Infectious endophthalmitis Vision loss Cataract

^aThis is a general list and not all-inclusive to respective treatments within each category.

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