

Overview of Diabetic Macular Edema

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Overview of Diabetes Mellitus, Diabetic Retinopathy, and Diabetic Macular Edema

Diabetes mellitus (DM) is a growing healthcare concern; in the United States, almost 30 million individuals have DM, and another 86 million have prediabetes. Medical costs for individuals with DM are twice as high as those for individuals without DM.¹ Between the medical costs and lost work/wages for patients with DM, the disease costs the US healthcare system \$245 billion annually.¹ Outside the United States, 382 million adults aged 20 to 79 years old, or 8.3% of the world population, were estimated to be living with DM in 2014.^{2,3} The number of individuals at risk of developing DM is also on the rise; projections estimate that 592 million individuals will have DM by 2035, an increase of 55% in 22 years.^{2,3} The CDC predicts that up to 33% of the US population will have DM by 2050.⁴

Individuals with DM are at risk for serious macrovascular and microvascular complications, including hypertension, heart disease and stroke, eye diseases, kidney disease, lower-limb amputations, peripheral nerve disease, periodontal disease, hearing loss, erectile dysfunction, depression, and complications of pregnancy.⁵⁻⁷ Additionally, DM is the seventh leading cause of death in the United States.⁶

Diabetic eye disease is a manifestation of the microvascular complications of DM, and about 33% of individuals with DM will develop some form of diabetic-related eye damage.³ Among the eye diseases associated with DM are diabetic retinopathy (DR), diabetic macular edema (DME), anterior ischemic optic neuropathy, and retinal vein occlusion.⁸ Placing an additional burden on healthcare systems and society in general, individuals with untreated DM are 25 times more likely to become blind than the general population.⁹

DR is the most common ocular complication of DM and the leading cause of blindness among working-age adults globally.¹⁰⁻¹² Individuals with DM have elevated

Abstract

Diabetes mellitus (DM) is a rapidly growing epidemic in the United States, and it is expected to affect 592 million individuals within the next 20 years. Diabetic retinopathy (DR) and diabetic macular edema (DME) are the 2 most common ophthalmic complications of DM. DR is the leading cause of blindness among working-age adults around the world, and development of DR is tied to DM disease duration. With the only identifier of early markers of DR being a complete ophthalmic exam, early signs of the disease are asymptomatic. Yearly, or at least every other year, ophthalmic exams are recommended for all patients with DM; but often, individuals with DM have not undergone screening exams and do not have regular eye exams until vision loss has occurred. With spending estimates of \$490 million to treat the vision complications of DM, it is clear that DR and DME impose a substantial burden for patients, caregivers, and healthcare systems.

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glucose levels in their blood, and it is those high levels of glucose that damage the blood vessels in the retina over time, causing DR. Nearly every patient who has any form of DM will develop DR to some degree.¹⁰

Multiple studies have confirmed that the key modifiable risk factor associated with the development of DR is hyperglycemia.¹³⁻¹⁸ The Diabetes Control and Complications Trial Research Group found that “intensive treatment” (defined as achieving blood glucose values as close to the normal range as possible after the administration of insulin 3 or more times daily either with an external insulin pump or by injection), in an effort to maintain blood glucose levels, delayed the onset and slowed the progression of DR,¹⁹ but it did not reverse the existing damage.

DR follows a natural course, progressing from mild nonproliferative DR (NPDR) to moderate and severe NPDR, eventually leading to proliferative DR (PDR), which is considered the most advanced stage. All stages of the disease are characterized by retinal vascular abnormalities, and, as the disease progresses, the retinal vessels eventually “close down,” leading to decreased retinal perfusion and even ischemia. Focal and panretinal photocoagulation laser therapy are potential treatments at these stages.¹⁰ To improve communication among ophthalmologists and general practitioners globally, an international clinical disease severity scale was developed for DR and DME, with validation studies under way (Table 1²⁰ and Table 2²⁰).¹⁰

Diabetic Macular Edema

The most common cause of vision loss from DR is DME,²¹ which can occur at any stage of DR and is characterized by edema and retinal thickening—the latter of which may also include hard exudates.

In both DR and DME, chronic hyperglycemia causes an upregulation of vascular endothelial growth factor (VEGF), thus increasing vascular permeability and increased angiogenesis.^{5,22-25} While the underlying pathophysiology of DME is VEGF mediated, there is a growing body of evidence suggesting that inflammatory mediators are also partly responsible and that those mediators contribute substantially to the vascular permeability and edema present in DME.²⁵⁻³³

The American Academy of Ophthalmology (AAO) and the American Diabetes Association (ADA) recommend eye examinations at regular intervals.^{10,34} For adults and children 10 years of age and older with type 1 diabetes mellitus (T1DM), an eye examination should

■ **Table 1.** International Clinical Diabetic Retinopathy Disease Severity Scale²⁰

Proposed Disease Severity Level	Findings Observable Upon Dilated Ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild NPDR	Microaneurysms
Moderate NPDR	More than just microaneurysms but less severe than severe NPDR
Severe NPDR	Any of the following and no signs of proliferative retinopathy <ul style="list-style-type: none"> • More than 20 intraretinal hemorrhages in each of 4 quadrants • Definite venous beading in 2 or more quadrants • Prominent IRMA in 1 or more quadrants
PDR	One or more of the following: <ul style="list-style-type: none"> • Neovascularization • Vitreous/preretinal hemorrhage

IRMA indicates intraretinal microvascular abnormalities; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.
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be performed within 5 years of the DM diagnosis. For patients with type 2 diabetes mellitus (T2DM), the examination should be performed at the time of diagnosis. The examination should be repeated at regular intervals, typically annually; however, less frequent checkups (eg, once every 2 years) may be acceptable after 1 or more normal examinations, particularly in patients with well-controlled DM.³⁴ Unfortunately, fewer patients are being referred to ophthalmologists for eye exams than anticipated, and often patients themselves do not follow vision care guidelines.¹⁰

Because the earliest stages of DR and DME are usually asymptomatic, individuals with DM are often unaware they have developed such complications. Symptoms are somewhat dependent on the location of the edema within the retina; non-center-involved macular edema is rarely symptomatic. As the edema spreads to encompass the central macula, however, patients generally experience progressive vision loss that occurs anywhere from weeks to months after the initial symptom.^{5,35,36}

Historically, DME was classified as focal or diffuse, with a wide range of definitions for both based on clinical exams, fundus photography, fluorescein angiography, optical coherence tomography (OCT), or any combination of these.^{37,38} Many patients often have mixed features

■ Table 2. International Clinical Diabetic Macular Edema Disease Severity Scale²⁰

Proposed Disease Severity Level	Findings Observable Upon Dilated Ophthalmoscopy
Diabetic macular edema apparently absent	No apparent retinal thickening or hard exudates in posterior pole
Diabetic macular edema apparently present	Some apparent retinal thickening or hard exudates in posterior pole

If diabetic macular edema is present, it can be categorized as follows:

Proposed Disease Severity Level	Findings Observable Upon Dilated Ophthalmoscopy ^a
Diabetic macular edema present	<ul style="list-style-type: none"> • Mild diabetic macular edema; some retinal thickening or hard exudates in posterior pole, but distant from the center of the macula • Moderate diabetic macular edema: retinal thickening or hard exudates approaching the center of the macula but not involving the center • Severe macular edema: retinal thickening or hard exudates involving the center of the macula

^aHard exudates are a sign of previous macular edema. Diabetic macular edema is defined as retinal thickening; this requires a 3-dimensional assessment that is best performed by a dilated examination using a slit-lamp and/or stereoscopic fundus photography. Reprinted from *Ophthalmology*, 110(9), Wilkinson CP, Ferris FL III, Klein RE, et al; Global Diabetic Retinopathy Project Group. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales, 1677-1682. Copyright (2013), with permission from Elsevier.

of both types of edema, and it remains unclear what clinical value these definitions have when predicting treatment response or visual acuity outcomes.³⁸ Currently, it is common to define DME based on its OCT appearance as “center involved” or “not center involved” (ie, referring to whether or not there is edema at the fovea, which is the center of the macula).

Prevalence of Diabetic Macular Edema and Retinopathy

The global prevalence of DME among individuals with T1DM or T2DM varies by geographic region, with rates as low as 11.4% in European countries to as high as 45.3% in North American countries.³ In the United States, the prevalence of DM is accelerating. In 1994, half of the states had a DM prevalence of less than 4.5%, and only 1 state had a prevalence greater than 6.0%. By 2013, the prevalence of DM was greater than 6% in all states, and 25 states had a prevalence greater than 9.0% (Figure³⁹).³⁹

The prevalence of DR is well reported. A pooled analysis of data from 35 different population-based stud-

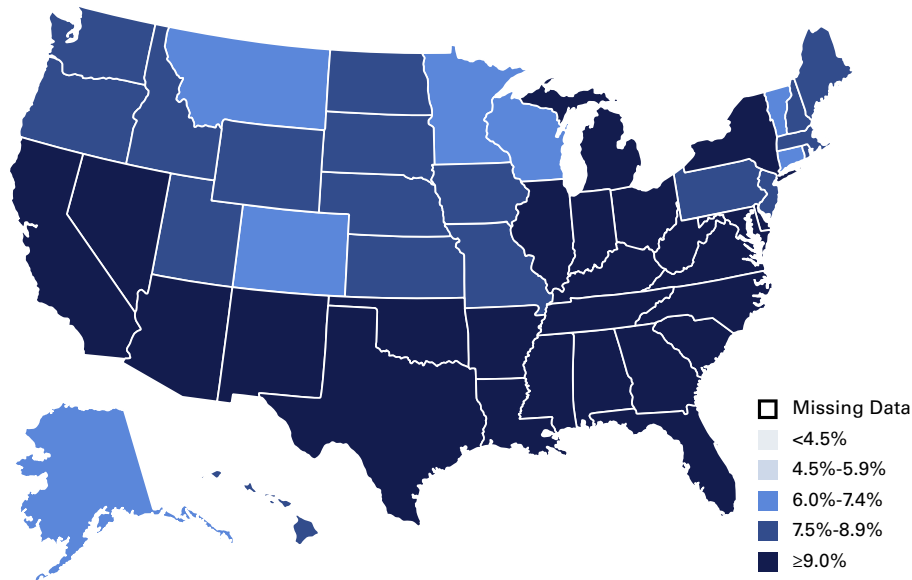
ies across the globe estimated that close to 93 million individuals have DR worldwide (17 million have PDR, 21 million have DME, and 28 million have vision-threatening DR),¹¹ making DR and DME significant public health burdens. This translates to a prevalence of 35.4% worldwide for DR, 7.2% for PDR, 7.4% for DME, and 11.7% for vision-threatening DR among those who have DM. Prevalence rates are similar in men and women, but ethnicity is an important risk factor. Prevalence estimates are highest in African Americans and lowest in Asians.¹¹ The 10-year incidence of DR in those with T1DM is almost 36%, and for development of DME, 11%.⁴⁰

About a decade ago, between the years 2005 and 2008, the estimated prevalence of DR was 28.5% among American adults with DM, with 4.4% having vision-threatening DR.⁴¹ The duration of disease plays a significant role in the onset of DR—the AAO notes that about 25% of individuals with T1DM will develop DR within 5 years, and 60% of those with T1DM will develop DR within 10 years. For individuals with T2DM, 84% of those taking insulin and 53% of those not taking insulin will develop DR within 19 years.¹⁰ The AAO notes, however, that because there is now increased emphasis on close monitoring and tighter glycemic control to manage DM compared with the time of data collection, these percentages may improve.

In the United States, the overall weighted prevalence of DME is 3.8%, or about 746,000 individuals over 40 years of age. Higher levels of glycated hemoglobin (A1C) (>7%) and disease duration are also associated with a greater risk of DME.⁴² Finally, the prevalence of DME is substantially higher among individuals with T1DM (14% in worldwide pooled data) than those with T2DM (6% in worldwide pooled data).^{11,42} The lower prevalence rates reported by Varma et al compared with those reported by Yau et al may be a result of the ethnicity of their respective diabetic populations. Varma concentrated on the United States alone (74% non-Hispanic whites), while Yau reported on global rates, where 44% of the population was Caucasian white.^{11,42}

Incidence rates of DME are not as well studied. The Wisconsin Epidemiologic Study of Diabetic Retinopathy found that approximately 20% of patients with T1DM and 14% to 25% of patients with T2DM developed DME over 10 years. Over 25 years, 29% of patients with T1DM in this study developed DME, and 17% developed clinically significant DME. In the latter follow-up periods, there was a lower risk of incident DME that may be the result of improvements in care.⁴³ The Los Angeles Latino Eye Study

■ **Figure.** Age-Adjusted Prevalence of Diagnosed Diabetes Mellitus Among US Adults, 2013³⁹



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compared primarily Mexican Americans (ie, Latinos) to non-Hispanic whites and found a much higher incidence and progression of DR in Latinos over a 4-year period.⁴⁴ The 4-year incidence of DR, DME, and clinically significant macular edema was 34%, 5.4%, and 7.2%, respectively. More than double the percentage of participants had worsening or progressing DR than improvement (38.9% vs 14%, respectively). An earlier study of US Latinos found a 4-year cumulative incidence of DR of 22.5%, and a cumulative rate of progression of 24.1%.⁴⁵

While the rates of DME may be decreasing in patients with DM, the increasing numbers of newly diagnosed individuals with DM increase the overall prevalence rates of diabetic complications.

Economic Impact of DM and Its Ophthalmic Complications

Of the \$245 billion total yearly medical cost associated with DM, \$176 billion is attributed to direct medical costs and \$69 billion is due to reduced productivity.^{1,46} Claims data support these figures—direct medical costs for driver employees with DME, DR, or DM were \$6470, \$8021, and \$5102, respectively, which were approximately 2.8 times higher compared with driver controls (ie, those without DM).⁴⁷ Also, absenteeism was much higher for those with DM as a result of sick leave, short-, and long-term disability.

There is an increasing number of therapeutic treatments for DME, but that raises questions about economics and the overall cost of treating and managing the disease. Claims data from 2000 to 2001 estimated that the direct medical cost of DR among US adults would be \$493 million in 2004.⁴⁸ More recently, Lee et al analyzed direct and indirect costs of DR by reviewing claims data from 17 large companies over a 5-year span (1999-2004).⁴⁹ Their analysis compared employees with DR and those without DR, and consisted of several subgroup analyses to determine what treatments employees received (if any). Employees with DR had significantly higher costs than controls, and indirect costs were almost 20% of the overall spending. Costs for patients with PDR were \$30,135, compared with \$13,445 for patients with DM but not PDR. Similarly, costs for patients with DME were \$28,606 compared with \$16,363 for patients with DM but not DME. The largest discrepancy was between patients who underwent vitrectomy (\$69,933) and those who did not (\$17,239), but the authors clarified that the cost was based on treating the individual patient and not the cost of the procedure. In a Medicare population, patients with new-onset DME had 31% higher 1-year costs and 29% higher 3-year costs compared with patients with DM but without DME.⁵⁰

It is important to note that the health economic data presented above predates our current management of DR

and DME. Whereas photocoagulation was the primary treatment for DR and DME for decades, intravitreal injections have rapidly become the standard of care⁵¹; this is due to the ability of anti-VEGF injections to improve both visual and anatomic outcomes.

While the newer pharmacologic interventions provide a greater clinical benefit to patients with DME and DR,⁵² they are substantially more costly than traditional laser treatments (focal/grid laser or panretinal photocoagulation).

Vision Loss and Impact on the Individual

Almost 20 years ago, the Melbourne Vision Impairment Project found that almost 60% of those with DM did not undergo an eye exam in the previous year⁵³; those numbers have improved slightly, but remain far from the recommended 100%. According to the AAO, upwards of 40% of individuals with DM forego annual screenings for DR.¹⁰ The ADA recommends initial screening within 5 years of diagnosis if T1DM is confirmed, and annually for both T1DM and T2DM.³⁴

Patients are often unaware of how DM will affect their vision. A Joslin Vision Network study (N = 2795) found that 83% of patients with DR and 78% with vision-threatening DR were unaware that they had the disease at their first visit, and 50% with vision-threatening DR had longer than recommended intervals for follow-up eye exams.⁵⁴ For patients with T2DM, signs of ocular complications are often present at the time of diagnosis of DM.^{54,55} Yet, as recent as 2010, less than 45% of US adults with DME reported that a physician explained that the disease had affected their eye or that they had retinopathy.⁵⁵

Numerous studies have correlated quality of life with improved vision. In one study of cost-effectiveness of treatment in patients with DME, combination therapy (laser treatment and an anti-VEGF treatment) achieved the largest quality-adjusted life-years, followed by monotherapy with an anti-VEGF agent.⁵⁶ A recent cross-sectional study assessing the impact of DR on quality of life and treatment satisfaction used the Audit of Diabetes-Dependent Quality of Life questionnaire and the Diabetes Treatment Satisfaction Questionnaire.⁵⁷ DR severity had a substantial influence on perceived quality of life, and treatment satisfaction was influenced by the severity of DME.

Factors Affecting the Increasing Incidence of Diabetes Mellitus and Its Complications

The exponential growth in the number of individuals with diagnosed DM, coupled with the estimates of those

with undiagnosed DM, were partially responsible for the CDC's National Diabetes Prevention Program, which launched in 2015.⁵⁸ There are several key risk factors for the progression of DR, including the duration of disease, poor glycemic control, hypertension, renal disease as evidenced by proteinuria, and sex (for gestational DM). Managing the risk factors for DM will, in turn, reduce the risk of DR.³⁴

Therapies and Treatment Plans

Patients can best help themselves by managing the systemic aspects of their disease.⁵⁹ In epidemiologic studies, the level of glycemic control has been associated with the risk of microvascular complications, including retinopathy.³⁴ Intensive treatment has been consistently shown to substantially reduce the risk and progression of retinopathy and microvascular complications.^{13,19,51,52,59}

The Action to Control Cardiovascular Risk in Diabetes and Fenofibrate Intervention and Event Lowering in Diabetes studies both suggest that therapies aimed at lipid control may reduce the risk of DR.^{59,60} Other systemic therapies, including glitazones (ie, thiazolidinediones), have produced inconsistent results in their ability to effect DME. Fong and colleagues conducted a retrospective analysis of pharmacy database records for more than 170,000 patients in the Kaiser Permanente Southern California healthcare system to look for potential associations between DME and other variables, and found a modest association between use of glitazones and DME.⁶¹ Similarly, a retrospective study in the United Kingdom by Idris and colleagues involving 103,368 patients with T2DM found that thiazolidinedione users were significantly more likely than nonusers to develop DME at both 1 and 10 years.⁶²

Two studies have suggested that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have beneficial effects on DR when being used to treat elevated blood pressure. The Diabetic Retinopathy Candesartan Trials found that DR developed in 25% of patients receiving candesartan versus 31% who received placebo ($P = .0508$), but that candesartan had no effect on DR progression.⁶³ The Renin Angiotensin System Study found that patients with DR and A1C levels higher than 7.5% at baseline were able to decrease the rate of DR progression with the use of enalapril or losartan (27% progressed on the drugs vs 46% who progressed without treatment).⁶⁴

This corresponds with the recommendation from the ADA to make an ACE inhibitor or ARB part of the antihypertensive regimen for patients with DM and hypertension.³⁴

Patients with DM average 25 physician visits yearly.⁶⁵ Even with improvements in care for DM over the course of a decade, however, large proportions of these patients will still have poor glycemic control (20%), elevated blood pressure (33%), and poor cholesterol control (40%).⁶⁶ Life with DM complications (and especially end-stage complications) has consistently been rated by patients as producing a significantly lower quality of life than undergoing treatments, but comprehensive DM care is also negatively associated with quality of life.⁶⁷ DME has a negative impact on patients' health-related quality of life, and these patients consume more healthcare resources and incur much higher costs than individuals with DM but without retinal complications.⁶⁸

Conclusion

It is clear that the number of individuals affected by DM is growing exponentially, as is the number of patients with complications from DM. Fortunately, the ocular manifestations of DM (DME and DR) can be identified and treated before significant vision loss occurs if patients with DM undergo regular eye exams and better manage their systemic disease.

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