ABSTRACT

Diabetes mellitus has become a worldwide concern, affecting an estimated 171 million adults. Patients with diabetes commonly develop eye problems, such as cataracts and glaucoma, but the effect of the disease on the retina, known as diabetic retinopathy (DR), is the main threat to vision. The prevalence of retinopathy is strongly linked to the duration of diabetes. Most patients with type 1 diabetes and more than 60% of patients with type 2 diabetes develop diabetic changes in the retina after approximately 20 years. Approximately 20% of newly diagnosed patients with diabetes have been found to have some degree of retinopathy. A person with diabetes is 25 times more likely to sustain severe loss of vision than a person in the general population. Diabetes affects the retinal vasculature. The earliest phase of DR (nonproliferative DR) is characterized by microaneurysms and retinal hemorrhages. The microaneurysms and affected microvasculature become incompetent, leaking fluid into the macula, to cause macular edema and associated loss of central vision. In addition, there can be capillary nonperfusion, and the circulatory system responds with a pathologic neovascularization (proliferative DR) that is mediated by angiogenic factors. These delicate new vessels are prone to hemorrhaging and, as abnormal vessel growth continues and scar tissue develops, vitreous hemorrhage, neovascular glaucoma, and tractional retinal detachment can result. The mechanisms that contribute to cellular damage in the retina include increased flux through the polyol pathway leading to sorbitol accumulation, production of advanced glycation end products, increased oxidative stress, and activation of the protein kinase C pathway. An increased understanding of the pathways involved in the pathogenesis of retinopathy is essential and has led to the development of treatment options that are under investigation.

Diabetic retinopathy (DR) and its associated pathology, including diabetic macular edema (DME), macular ischemia, vitreous hemorrhage, traction detachment, and neovascular glaucoma, are common microvascular complications in patients with diabetes and may have a sudden and debilitating impact on visual acuity (VA) that may eventually lead to blindness. In the United States, DR is recognized as the leading cause of blindness in the working-age population (20–74 years) and is responsible for 8% of new cases of blindness each year.1

Even before DR has progressed to blindness, loss in VA can be a major problem. A subset of patients with type 1 diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy manifested a significant loss of VA over time: VA 20/40 or worse in the better eye in 12.7% of patients, doubling of the visual angle in 14.2% (eg, from 20/20 to 20/40), and blindness in 2.4%. An analysis of the population of individuals with type 1 and type 2 diabetes showed that over a 10-year period, 10% developed clinically significant DME and an additional 14% of the individuals developed DME that was not clinically significant.3 Data show that approximately 50% of patients with DME will lose 2 or more lines of VA within 2 years.4 Clinically significant DME is defined as the presence of any of the 3 following features.

* Assistant Professor of Ophthalmology, Indiana University-Purdue University, Staff Surgeon, Retina Vitreous Macular Service, Midwest Eye Institute, Indianapolis, Indiana.

Address correspondence to: Thomas A. Ciulla, MD, Retina Service, Midwest Eye Institute, Methodist Medical Plaza North, 201 Pennsylvania Parkway, Indianapolis, IN 46280. E-mail: midwestmacula@yahoo.com.
retinal thickening at or within 500 µm of the center of the macula; hard exudates at or within 500 µm of the center of the macula, if associated with thickening of the adjacent retina; and a zone or zones of retinal thickening 1 disc area in size, at least part of which is within 1 disc diameter of the center.5

Diabetes-related blindness and visual impairment places a significant burden on society.6 In the United States, the annual cost of blindness secondary to diabetes has been estimated to be roughly $500 million.6 Healthcare and economic burdens of DR are further compounded by the resulting decline in quality of life; undeniably, monetary costs significantly underestimates total cost to society.6

**Epidemiology of Diabetic Retinopathy**

An estimated 171 million adults have diabetes worldwide.8 In the United States alone, as many as 29 million adults are thought to have diabetes or impaired glucose tolerance.9 Over time, most of these individuals will develop some degree of retinopathy.8,10

Among individuals with type 1 diabetes, DR is not often present at the time of diagnosis; however, as many as 21% of individuals with type 2 diabetes already have retinopathy by the time diabetes is diagnosed.11 This difference is the basis for the American Diabetes Association recommendation of initial screening 3 to 5 years after diagnosis for individuals with type 1 diabetes and shortly after diagnosis for those individuals with type 2 diabetes.12 The likelihood that retinopathy will develop increases with the duration of diabetes.9,10 In addition, because the incidence of type 2 diabetes increases with age, the prevalence of DR also increases with age, although the prevalence appears to diminish in one population (ie, ages >75 years compared to >65 years; Figures 1 and 2).13

Of the estimated 889 000 individuals with type 1 diabetes in the United States, the crude prevalence rate of any level of DR is 82.3% for white individuals and 74.9% for black individuals, with vision-threatening retinopathy estimated to be present in 32.2% and 30%, respectively.14 The prevalence of DR in individuals with type 2 diabetes appears to be greater in white and Hispanic individuals compared to black individuals; from the point of initial diagnosis, the percentage of patients affected increases over time.13

The incidence of retinopathy, its progression, and severity have been linked to adequacy of blood glucose control.15-18 However, there is evidence in type 1 and type 2 diabetes that hypertension and hyperlipidemia also play a role in retinopathy.19-22
PATHOGENESIS

Exactly how hyperglycemia initiates the vascular disruption that triggers retinopathy is not well established. Several pathways have been implicated that lead to abnormal blood flow and hemorrhages, changes in cell structure, pericyte loss, endothelial cell proliferation, and neovascularization.

Diabetic retinopathy/diabetic macular edema-related disruption in blood flow is characterized by abnormal vascular flow, disruptions in permeability, and closure or nonperfusion of capillaries. Early in DR, there are changes in the structure and cellular composition of the microvasculature. Damage to the endothelial cells that are responsible for maintaining the blood-retinal barrier leads to increased vascular permeability. Breakdown of the inner blood-retinal barrier allows accumulation of extracellular fluid in the macula. Damage to pericytes that are essential cellular components for regulating capillary perfusion in the retina leads to altered retinal hemodynamics, including abnormal autoregulation of retinal blood flow.

Retinal leukostasis also appears to play an important role in the pathogenesis of DR. Leukocytes possess large cell volume, high cytoplasmic rigidity, a natural tendency to adhere to the vascular endothelium, and a capacity to generate toxic superoxide radicals and proteolytic enzymes. In diabetes, increased leukostasis affects retinal endothelial function, retinal perfusion, angiogenesis, and vascular permeability. In patients with diabetes, leukocytes are also abnormal. These leukocytes are less deformable, a higher proportion than usual are activated, and they appear to be involved in capillary nonperfusion, endothelial cell damage, and vascular leakage in the retinal microcirculation.

Evidence from rats with streptozocin-induced diabetes shows that the timing and location of vascular leakage and loss of perfusion can be linked to retinal leukostasis. It appears that leukocytes occlude capillaries and cause capillary dropout or degeneration. Serial acridine orange leukocyte fluorography and fluorescein angiography show that areas of the retinal microcirculation lacking perfusion are directly downstream from trapped leukocytes.

Data obtained from animal studies suggest that within 2 weeks of onset of diabetes, which is coincident with leukocyte-mediated endothelial injury and cell death, platelet-containing microthrombi accumulate in the retinal vasculature. This accumulation is thought to be a protective mechanism that slows the breakdown of the blood-retinal barrier.

The retinal ischemia that results from occluded capillaries stimulates a pathologic neovascularization that is mediated by angiogenic factors, such as vascular endothelial growth factor (VEGF), and it leads to proliferative DR. Neovascularization is the predominant feature of proliferative DR, and it often leads to glaucoma, vitreous hemorrhage, and tractional retinal detachment.

NATURAL HISTORY

Diabetic retinopathy is a progressive disease. At onset there are minimal changes, but unless intervention occurs (eg, control of blood glucose level), it can advance into increasingly more severe pathology.

In its earliest stages, DR is characterized by retinal vascular abnormalities that include microaneurysms, intraretinal hemorrhages, and cotton-wool spots. Changes in vascular permeability occurring at this stage or later stages lead to retinal thickening (edema) and lipid deposits (hard exudates) that are associated with DME. When retinal thickening and adjacent hard exudates involve the center of the macula or encroach upon it, the pathology is termed “clinically significant DME.” DME can occur at any stage of DR, even when mild nonproliferating DR is present.

As nonproliferative DR progresses, the gradual closing of retinal vessels impairs perfusion, leading to retinal ischemia. As ischemia increases, venous abnormalities (eg, beading and loops) and intraretinal microvascular abnormalities develop. Leakage becomes increasingly severe and extensive, and retinal hemorrhages and exudation increase. Severity of symptoms escalates progressively, and the pathology can lead to severe nonproliferative DR.

Without therapeutic intervention, progression of retinal ischemia can lead to neovascularization on the inner surface of the retina, transforming nonprolifera-
tive DR into proliferative DR. When proliferative DR is present, the blood vessels at the optic disc and elsewhere in the retina are prone to bleeding into the vitreous humor. New blood vessels undergo fibrosis and contraction causing epiretinal membrane formation, vitreoretinal traction, retinal tears, and traction or rhegmatogenous retinal detachments.

Proliferative DR is considered to be at the high-risk stage when new vessels are accompanied by vitreous hemorrhage or when the new vessels in the optic disc extend to one fourth to one third of the disc area even in the absence of vitreous hemorrhage. New vessels growing on the iris and anterior chamber angle structures can cause neovascular glaucoma.

Clinical studies have shown that the progressive increase in VEGF correlates to progression from nonproliferative DR to proliferative DR. Studies of patients treated for ocular neovascularization lend further credence to this association as successful panretinal photocoagulation was associated with a 75% reduction in VEGF levels. Growth factors (eg, VEGF) are upregulated in microvascular disease (eg, DR and nephropathy), but growth factor expression and function may be abnormally low in macrovascular disease (eg, diabetic coronary disease and peripheral limb disease) in which collateral blood vessel supply is desired. Consequently, there may be a paradox between the need to limit growth factor expression and function in microvascular complications, while fostering growth factor expression and function in macrovascular complications.

ROLE OF HYPERGLYCEMIA AND PATHWAYS INVOLVED IN DIABETIC RETINOPATHY

The state of hyperglycemia funnels excessive glucose through pathways that have been linked to complications of diabetes. These pathways include the polyol pathway leading to sorbitol accumulation, production of advanced glycation end products (AGEs), increased oxidative stress, and activation of the protein kinase C (PKC) pathway (Figure 3).

ROLE OF THE POLYOL PATHWAY

Hyperglycemia that results from diabetes increases the flux through the polyol pathway.

Table 1. International Classification of Diabetic Retinopathy Disease Severity Scale

<table>
<thead>
<tr>
<th>Proposed Disease Severity Level</th>
<th>Findings Observable on Dilated Ophthalmoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No apparent retinopathy</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>Mild NPDR</td>
<td>Microaneurysms only</td>
</tr>
<tr>
<td>Moderate NPDR</td>
<td>More than just microaneurysms, but less than severe NPDR</td>
</tr>
<tr>
<td>Severe NPDR</td>
<td>Any of the following: more than 20 intraretinal hemorrhages in each of 4 quadrants; definite venous beading in 2+ quadrants; prominent IRMA in 1+ quadrant; and no signs of proliferative retinopathy</td>
</tr>
<tr>
<td>Proliferative diabetic retinopathy</td>
<td>One or more of the following: neovascularization and vitreous/preretinal hemorrhage</td>
</tr>
</tbody>
</table>

NPDR = nonproliferative diabetic retinopathy; IRMA = intraretinal microvascular abnormalities.

Table 2. International Classification of Diabetic Macular Edema Disease Severity Scale

<table>
<thead>
<tr>
<th>Proposed Disease Severity Level</th>
<th>Findings Observable on Dilated Ophthalmoscopy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic macular edema apparently absent</td>
<td>No apparent retinal thickening or hard exudates in posterior pole</td>
</tr>
<tr>
<td>Diabetic macular edema apparently present</td>
<td>Some apparent retinal thickening or hard exudates in posterior pole</td>
</tr>
<tr>
<td>Diabetic macular edema present</td>
<td>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 diabetic macular edema: retinal thickening or hard exudates involving the center of the macula</td>
</tr>
</tbody>
</table>

* Hard exudates are a sign of current or previous macular edema. Diabetic macular edema is defined as retinal thickening, which requires a 3-dimensional assessment that is best performed by a dilated examination using slit lamp biomicroscopy and stereo fundus photography.
The by-products of this pathway, such as sorbitol and fructose, accumulate excessively, causing cellular osmotic stress. Osmotic stress is thought to be responsible for cellular damage that is associated with the loss of integrity of the blood-retinal barrier. In the earliest stages of DR, retinal pericytes are lost, probably because of their sensitivity to the increasing concentrations of polyols.

Another explanation of how hyperglycemia impairs the retinal pigment epithelial cells and pericytes is the myoinositol depletion hypothesis. Increased glucose flux through the polyol pathway is accompanied by the depletion of myoinositol, a loss of Na/K adenosine triphosphatase activity, and the accumulation of sodium in several tissue types. Experiments using retinal pigment epithelial cells grown in a high glucose medium show these cells have marked increases in sorbitol and decreases in myoinositol content, in addition to reversible alterations in inositol phospholipid metabolism and DNA synthesis. Sorbinil, an aldose reductase inhibitor, can successfully prevent changes in sorbitol and myoinositol content. However, thus far the promise of aldose reductase inhibition has not been realized in DR. Although agents tested have demonstrated the ability to decrease microaneurysm count and fluorescein leakage, they have failed to stop DR progression.

ROLE OF ADVANCED GLYCATION END PRODUCTS

Intracellular hyperglycemia sets in motion the AGE pathway, causing glucose to combine with proteins (Schiff bases) that rearrange to become more stable Amadori-type early glycation products. These products undergo a slow complex series of chemical reactions, becoming AGEs. Because AGEs are irreversibly glycated, they do not normalize when hyperglycemia is corrected; they accumulate over the lifetimes of the vessel-wall proteins.

Excessive formation of AGEs is thought to be a cause of microvascular complications. AGEs affect functions, such as enzyme activity, binding of regulatory molecules, and susceptibility of proteins to proteolysis. AGEs also bind to several receptor proteins, including the receptor for advanced glycation end products (RAGE). RAGE has multiple downstream signaling targets that can perpetuate a proinflammatory signaling process and a proatherosclerotic state in vascular tissues. In vitro, the AGE–RAGE interaction has been linked to oxidative stress and the activation of nuclear factor-κB, which leads to excessive expression of proinflammatory cytokines, lymphocyte adhesion molecules (eg, vascular cell adhesion molecule-1), vasoactive mediators, and procoagulant factors. These processes may result in disruptions of retinal hemodynamics and damage to vascular endothelial cells.

Limited evidence from animal studies suggests blocking AGE formation may be beneficial in retinopathy by reducing the number of acellular capillaries, pericyte loss, and oxidative stress.

ROLE OF THE PROTEIN KINASE C PATHWAY

Animal evidence has shown that exposure of vascular tissues to elevated glucose concentrations leads to increased PKC activity and levels of diacylglycerol, an activator of PKCβ. PKC-β activity is also increased after exposure of vascular endothelial cells to oxidative stress, a mechanism that has been implicated in the development and progression of diabetic microvascular

Figure 3. Metabolic Pathways Implicated in the Development of Diabetic Microvascular Complications

PKC = protein kinase C.

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complications. PKC activation can lead to mitogen-activated protein kinase activation and phosphorylation of transcription factors that increase gene expression of multiple cellular stress-related genes (c-Jun kinases and heat shock proteins) that damage the cells. PKC-β has been shown to have an important role in regulating endothelial cell permeability and as a signaling component for VEGF. Preliminary studies suggest specific PKC-β inhibitors can prevent and reverse diabetic microvascular complications and it is hoped that longer-term prospective clinical trials will demonstrate important effectiveness.

ROLE OF OXIDATIVE STRESS

Three major cellular pathways (ie, polyol, PKC, and advanced glycation end products pathways) associated with the complications of diabetes are unified by a single mechanism: the overproduction of reactive oxygen species (ROS) by the mitochondrial electron transport chain. ROS is generated by increased flux through the polyol pathway, by protein glycation, and it also activates PKC.

Some support for the hypothesis that ROS production plays an integral role in the pathogenesis of diabetes complications comes from animal evidence that certain compounds that act as continuous scavengers normalize the diabetes-induced inhibition of aortic prostacyclin synthetase in animals and significantly improve diabetes-induced decreases in endoneurial blood flow and motor nerve conduction velocity. However, studies using antioxidant therapy to prevent/treat ROS have been equivocal. Animal evidence suggests that antioxidant therapies prevent microvascular complications, but trials involving individuals with diabetes have not shown consistent effects.

CONCLUSION

The prevalence of diabetes has reached epidemic proportions worldwide. Based on data from 2000, in the United States alone, 17.7 million individuals were thought to have had diabetes. With the aging of the population, this number will continue to increase. By 2030, the number of people in the United States with diabetes is projected to reach 30.3 million. Over time, most of these individuals will develop some degree of retinopathy. However, an increased understanding of the pathways involved in the pathogenesis of retinopathy offers potential new therapeutic targets that can be approached at an earlier stage in the disease before vision loss. Several drug therapies, targeting many of the pathways reviewed in this paper, are being tested.

REFERENCES

18. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complica-


