CHAPTER

5

Diabetic Retinopathy: An Overview

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INTRODUCTION

Diabetes mellitus (DM) is an important health problem affecting more than 350 million people worldwide, and its prevalence is still growing.[1] It has reached pandemic status and, as a serious chronic metabolic disease, it can bring about many types of complications that can severely impair people's quality of life.

DM is a group of metabolic diseases characterized by high blood sugar levels (hyperglycemia). There are two main classifications of this disease proposed by the American Diabetes Association (ADA) and the World Health Organization (WHO).

The ADA recognizes four DM forms: type 1, type 2, gestational diabetes, and other DM forms.

- Type 1 DM results from the body's failure to produce insulin due to autoimmune destruction of β cells of the islets of Langerhans. The diagnosis is often made around 25 years old but also affects older people. This form was previously referred to as '*insulin-dependent diabetes mellitus*' or '*juvenile diabetes*'.
- Type 2 DM is characterized by insulin resistance, a condition in which cells fail to use insulin properly. It is often observed in adults and is associated with obesity. This diabetes mellitus form was previously referred to as '*non-insulin-dependent diabetes mellitus*' or '*adult-onset diabetes*'.
- Gestational DM occurs when pregnant women develop a high blood glucose level without a previous diagnosis of diabetes. Rarely, it occurs after childbirth.
- Other specific types of DM include congenital diabetes, steroid diabetes induced by high doses of glucocorticoids, cystic fibrosis-related diabetes, and several forms of monogenic diabetes. Congenital diabetes is due to genetic defects of insulin secretion, and monogenic diabetes forms are caused by mutations in a single gene.

According to the WHO, DM is classified only into three groups: type 1, type 2, and gestational diabetes.

Diabetes without proper treatments may cause acute and chronic complications. Acute complications include hypoglycemia, diabetic ketoacidosis, and nonketotic hyperosmolar coma. Serious long-term complications include macroangiopathic complications (ischemic heart disease, cerebrovascular disease, and peripheral vascular disease) and microangiopathic complications (retinopathy, neuropathy, and nephropathy). DR affects small blood vessels in the retina and may lead to visual symptoms, reduced vision, and potentially blindness (Box 5.1).

EPIDEMIOLOGY

DR is one of the most serious diseases affecting the microvasculature of the retina.[2] DR accounts for about 2.4 million cases of blindness globally, and a proportion of 4.8% of the global population has DR.

In 2012, Yau *et al.*[3] estimated the prevalence of global DR and its severe stages (proliferative diabetic retinopathy (PDR) and DME) using individual-level data from population-based studies worldwide. Based on the data obtained from 35 studies on more than 20,000 participants, the overall prevalence of any DR was 34.6%, PDR was 7%, DME was 6.8%, and vision-threatening DR (VTDR) was 10.2%. The prevalence of DR and VTDR was similar in men and women.

The number of people with diabetes in the world is predicted to grow to 429 million by 2030, owing to the rising frequency of obesity, increasing life span, and improved detection of the disease.[4] The DR prevalence rate is substantially higher in people with type 1 diabetes than in type 2 diabetes[3] and increases with the duration of diabetes, glycosylated-hemoglobin (HbA1c) values, blood pressure, and cholesterol. Total serum

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BOX 5.1

Diabetes mellitus

Acute complications
- hypoglycemia
- diabetic ketoacidosis
- nonketotic hyperosmolar coma

Chronic complications
- macroangiopathic complications:
- ischemic heart disease
- cerebrovascular disease
- peripheral vascular disease

Microangiopathic complications
- diabetic retinopathy
- diabetic neuropathy
- diabetic nephropathy

BOX 5.2

The three major risk factors for diabetic retinopathy are:

1. diabetes duration
2. HbA1c
3. arterial blood pressure

cholesterol is also associated with a higher prevalence of DME.[3]

Epidemiologic studies have shown the effects of hyperglycemia, hypertension, and dyslipidemia on the incidence and progression of DR and clinically significant DME (CSME).

The three major risk factors for DR are diabetes duration,[3] HbA1c,[3,5] and high blood pressure.[3] Diabetes duration is the main risk for DR.[3] After 20 years of the disease, DR is present in more than 90% of type 1 diabetic patients and in nearly 60% of type 2 diabetic patients, although DR is higher in those patients taking insulin. Once retinopathy appears, duration of diabetes is less important than metabolic control for the further development and progression. The HbA1c level is the strongest risk factor for predicting the progression of DR, although it accounted for only 11% of the retinopathy risk in the DCCT.[6] Data from several studies suggest roles of other factors including sleep apnea[7]; nonalcoholic fatty liver disease[8]; and serum prolactin, adiponectin, and homocysteine levels,[9] as well as genetic factors including mutations in the erythropoietin gene promoter.[10] However, the relative contributions that these factors may have on the retinopathy risk in populations remains unknown.

DR is a diabetic complication that eventually develops to some degree in nearly all diabetic patients with long-standing disease. There are defects in the neurosensory retina before vascular damage is detected, but the earliest clinical manifestation is the presence of microaneurysms in the ocular fundus. Vascular permeability-related lesions (microaneurysms, hard exudates, hemorrhages) are first seen in diabetes, but with time retinal capillary nonperfusion appears (cotton wool spots, intraretinal microvascular abnormalities (IRMA), venous beading). In the advanced stages of the disease, closure of the retinal vessels and new vessels are the main changes.

Diabetic macular edema may be present in all stages of DR. Clinically significant macular edema is the term used to describe the presence of retinal thickening and hard exudates in the center of the macular area, and usually it is considered a vision-threatening complication (Box 5.2).

NATURAL HISTORY

DR may progress from minimal changes to more severe stages. It is very important to identify vision-threatening stages in order to prevent blindness. Several clinical trials have demonstrated that it is possible to prevent severe vision loss in more than 90% of the cases when patients are managed correctly.

These clinical trials are the Diabetes Control and Complications Trial (DCCT),[6] the United Kingdom Prospective Diabetic Retinopathy Study (UKPDS),[11] the Diabetic Retinopathy Study (DRS),[12] the Early Treatment Diabetic Retinopathy Study (ETDRS),[12] and the Diabetic Retinopathy Vitrectomy Study (DRVS).[13]

There are two main classifications of DR: the classification proposed by the ETDRS and the Global Diabetic Retinopathy Project Group (GDRPG). The ETDRS classification is considered the gold standard in clinical trials. However, it is not used in clinical practice due to its complexity.[14] In 2002, The GDRPG proposed the International Scale Severity of Retinopathy. This new classification of diabetic retinopathy is based on the results of the ETDRS but is easier to use in practice (Table 5.1; Fig. 5.1; Fig. 5.2). A detailed correlation between both classifications can be found in http://www.rcophth.ac.uk/page.asp?section=451.[1]

The overall prevalence of nonproliferative DR is higher in type 2 diabetic patients.[15]

There are also several classifications for DME. The ETDRS classification has been the most commonly used worldwide.

TABLE 5.1 Classification of Diabetic Retinopathy adapted from the ETDRS*

DR Severity Level	Ocular Fundus Findings
Mild nonproliferative retinopathy	At least one microaneurysm; and definition not met for moderate nonproliferative retinopathy
Moderate nonproliferative retinopathy (Fig. 5.1)	Hemorrhages and/or microaneurysms ≥ standard photograph 2A*; and/or soft exudates, venous beading, or intraretinal microvascular abnormalities definitely present
Severe nonproliferative retinopathy	Soft exudates, venous beading, and intraretinal microvascular abnormalities in at least two fields; or two of the preceding three lesions present in at least two of fields four through seven and hemorrhages and microaneurysms present in these four fields, equaling or exceeding standard photograph 2A in at least one of them; or intraretinal microvascular abnormalities present in each of fields four through seven and equaling or exceeding standard photograph 8A in at least two of them
Early proliferative retinopathy	New vessels; and definition not met for high-risk proliferative retinopathy
High-risk proliferative retinopathy (Fig. 5.2)	New vessels on or within one disc diameter of the optic disc (NVD) ≥ standard photograph 10A* (about one-quarter to one-third disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ one-quarter disc area

DR: diabetic retinopathy.
**Early Treatment Diabetic Retinopathy Study Research Group.*[35]

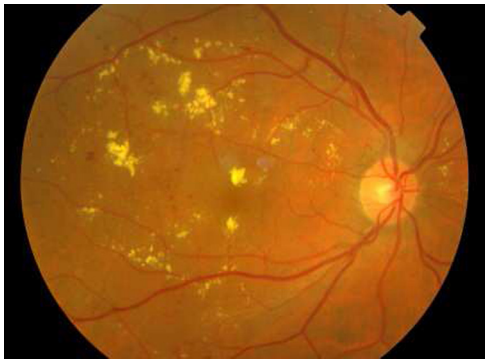

FIGURE 5.1 Nonproliferative diabetic retinopathy with diabetic macular edema. (See color plate section)

To diagnose CSME, one of the following characteristics must be present on clinical examination:

1. any retinal thickening within 500 μm of the center of the macula;
2. hard exudates within 500 μm of the center of the macula with adjacent retinal thickening;
3. retinal thickening at least one disc area in size, any part of which is within one disc diameter of the center of the macula.

Trying to improve communication, the GDRPG also proposed the use of the International Diabetic Macular Edema Severity Scale (Table 5.2).[14]

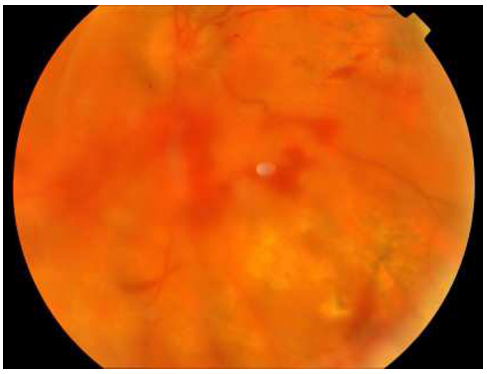

FIGURE 5.2 Proliferative diabetic retinopathy with vitreous hemorrhage. (See color plate section)

TABLE 5.2 Diabetic Macular Edema International Severity Scale.[14]

Diabetic Macular Edema (DME) Severity Level	Ocular Fundus Findings
DME NOT PRESENT	
Thickening apparently absent	Not thickening, no exudates in the posterior pole
DME PRESENT	
Thickening or hard exudates in the posterior pole	Thickening or hard exudates in the posterior pole *Mild*: some thickening or hard exudates distant from the center of the macula *Moderate*: some thickening or hard exudates approaching the center of the macula but no involvement *Severe*: some thickening or hard exudates involving the center of the macula

PATHOPHYSIOLOGY

The pathogenesis of DR is highly complex and involves multiple interlinked mechanisms leading to cellular damage and adaptive changes in the retina.[16]

Traditionally DR has been considered a microvascular disease, in which small retinal vessels are injured by chronic hyperglycemia and the induced endothelial

damage is primarily responsible for the development of microangiopathy.[17]

However, DR is a multifactorial progressive disease with a very complex pathophysiology. The underlying mechanism is still poorly understood. Both neural and vascular damage seem to occur in this disease. DR is indeed a neurovascular disease in which neural dysfunction can be initiated in early-stage diabetes.[18]

Hyperglycemia has been considered as the initiator of retinal damage in DR, but this is a simple way to understand the development of this complication. Several metabolic pathways are activated. There are many studies suggesting that excess plasma glucose may not account for all the cellular and functional changes involved in DR.[19] In addition, it is well known that an intensive metabolic control reduces the risk of progression of DR but is not enough for its prevention.

This disease induces deregulated levels of metabolites such as glucose, lipids, or hormones that induce changes in the production of a number of mediators resulting in increased vascular permeability, apoptosis, and angiogenesis.[20] Many of the diabetic complications are clearly associated with oxidative stress, inflammation, mitochondrial dysfunction, and apoptosis.[21]

DR is a disease that progresses chronologically into two different phases. The first phase represents the passive suffering of the affected structures (neurons and vessels), while the second phase is a compensatory but aberrant response. In the first phase, biochemical changes, especially hyperglycemia, will deteriorate the retinal neural and microvascular system, leading to a hypoxic situation. The hypoxic retinal tissue triggers compensatory vasodilation and neovascularization to increase blood flow and tissue oxygenation. The reactive dilation of retinal vessels causes increased vascular permeability and subsequently edema (DME).

Several pathogenic mechanisms seem to be involved in the natural history of DR, and they can be grouped into biochemical, physiologic, hematologic, endocrinologic, and anatomical changes.[17,19] Biochemical alterations are most important in the early stages of DR and anatomic changes are more relevant in later stages of the disease.[17]

The cellular damage in the retina has been speculated to be caused by biochemical alterations, but many of these hypotheses have not yet been validated in human studies or clinical trials (Box 5.3).[16]

BOX 5.3

Hyperglycemia has been considered as the initiator of retinal damage in diabetic retinopathy

BIOCHEMICAL CHANGES

The major biochemical changes induced by hyperglycemia, which are implicated in the pathogenesis of DR, include[16–20]:

- increase of polyol pathway flux;
- increase of intracellular advanced glycation end product (AGE) formation;
- protein kinase C (PKC) activation;
- hexosamine pathway;
- polyadenosine diphosphate ribose polymerase (PARP) activation;
- increase of oxidative stress and reactive oxygen species (ROS) production;
- nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) activation;
- Ras activation.

Other relevant biochemical changes are:

- high plasma homocysteine level;
- higher levels of branched chain amino acids in the diabetic retina;
- dysregulation of taurine level and its transporter;
- increase of adenosine level in the retina;
- dysregulation of nutrient levels such as α-lipoic acid, folic acid, vitamin C, vitamin E, and minerals.

Polyol or Sorbitol Pathway

In normal conditions, glucose is metabolized enzymatically by the glycolytic pathway and the pentose pathway. In chronic hyperglycemia, an alternative pathway, the sorbitol pathway, is activated.[17,22,23]

In this situation, glucose is metabolized by two enzymes: aldose reductase (AR) and sorbitol dehydrogenase (SDH). AR is an enzyme found in the endothelial cells, the ganglion cells, and the nerve fibers of the retina. It has an important role in the genesis of cataract, DR, and diabetic neuropathy.[17] This enzyme reduces aldehydes produced by oxygen free radicals to inactive alcohols and catalyze glucose to sorbitol using nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor (Fig. 5.3). Thus, the NADPH level is reduced, resulting in increased oxidative stress, a major factor in retinal damage.[22] NADPH is a cofactor required for glutathione reductase, a necessary enzyme that maintains the intracellular pool of reduced glutathione (GSH). GSH is an important scavenger protecting the endothelial cells against oxygen free radicals.

Sorbitol does not readily cross cell membranes. Then its intracellular concentration becomes higher and produces an increase of the osmotic pressure leading to water diffusion into the cell with the subsequent intracellular edema. The edema produces osmotic stress, which

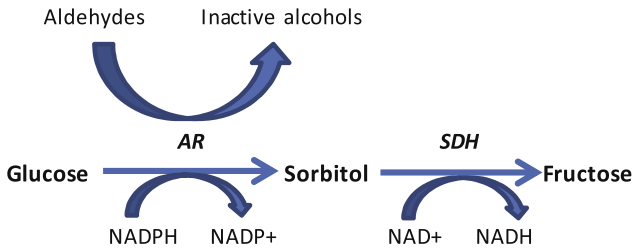

FIGURE 5.3 Polyol pathway. AR catalyzes the reduction of glucose to sorbitol and aldehydes to inactive alcohols. In this reaction NADPH is used, so its intracellular level decreases. SDH oxidizes sorbitol to fructose slowly. AR: aldose reductase. NAD: Nicotinamide adenine dinucleotide; NADH: reduced nicotinamide adenine dinucleotide; NADP+: oxidized form of nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate; SDH: sorbitol dehydrogenase.[17,20]

TABLE 5.3 Actions Induced by Advanced Glycation End Product Overproduction

- Endothelial dysfunction
- Powerful free-radical generators
- Coagulation disorder that predisposes to the microthrombi formation
- PKC activation
- Blood–retinal barrier dysfunction
- Increase of nitrative stress in the retinal vascular cells
- Increase of VEGF, MCP-1, and ICAM-1 expressed in microvascular endothelial cells through intracellular ROS generation
- Retinal capillary cell apoptosis via activation of NF-κB and caspase-3
- Activation of NF-κB and NADPH oxidase with increase in ROS and apoptosis of pericytes and other retinal cells

ICAM-1: intercellular adhesion molecule-1; MCP-1: monocyte chemoattractant protein-1; NADPH: nicotinamide adenine dinucleotide phosphate; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PKC: protein kinase C; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor.[17,20,21]

alters the electrolytes' balance and the cell membrane's permeability, causing tissue hypoxia.[23]

Increased nitrotyrosine, increased lipid peroxidation products, and depletion of antioxidant enzymes are other biochemical consequences of polyol pathway activation.[23,24]

Intracellular Advanced Glycation End Product Formation

Biochemical changes observed in DR have also been associated with nonenzymatic glycosylation of proteins and the Maillard reaction between reducing sugars such as glucose and amino residues of proteins, lipids, or nucleic acids. The increase of nonenzymatic glycation leads to a high level of AGEs. This biochemical reaction is irreversible and depends on the glycemic level present in the body.[17,24]

Overproduction of AGEs is followed by intracellular and extracellular actions and by a breakdown of the blood-retinal barrier (Table 5.3).

TABLE 5.4 Actions Induced by Protein Kinase C Activation

- Increase of vascular permeability
- Decrease of nitric oxide production
- Increase of endothelin-1 activity
- Change in vascular smooth muscle contractility
- Increase of basement membrane protein synthesis and basal membrane thickening
- Stimulation of neovascularization, endothelial proliferation, and apoptosis
- Activation of cytokines and vasoactive factors such as VEGF, IGF-1, and TGF-β
- Increase of blood flow, extracellular matrix expansion, and leukocyte adhesion

IGF-1: insulin-like growth factor 1; TGF: transforming growth factor; VEGF: vascular endothelial growth factor.[16,17]

AGEs alter microvascular homeostasis and play a central role in inflammation, neurodegeneration, and microvascular dysfunction in DR.[24] The receptor for AGEs (RAGE) is ubiquitously expressed in various retinal cells and is upregulated in the retinas of diabetic patients, resulting in activation of pro-oxidant and proinflammatory signaling pathways.[24]

Protein Kinase C Activation

PKCs are a family of enzymes with at least 11 isoforms. Nine of them are activated by the second messenger diacylglycerol (DAG), which is the physiologic activator of PKC.[25]

In very early DR stages, hyperglycemia increases *de novo* synthesis of DAG from glucose via triose phosphate, which activates PKC. Hyperglycemia primarily activates the β and δ isoforms of PKC in vascular cells. The activation of β isoforms of PKC (PKC-β) has been implicated in the pathogenesis of early and late manifestations of RD (Table 5.4).[17,25]

PKC activation, hypoxia, and hyperglycemia collaborate in the stimulation of vascular endothelial growth factor (VEGF) expression.[17] The PKC-β activation is also essential for facilitating VEGF activity on vascular permeability and neovascularization.[25]

Hexosamine Pathway

Hexosamine content is increased in retinal tissues of humans and rats with diabetes and may mediate some of the toxic effects of high glucose and ROS concentrations into the cell.[26] In contrast, ROS may increase the hexosamine biosynthesis pathway by inhibition of glyceraldehyde 3-phosphate dehydrogenase (GAPDH), a multifunctional protein with diverse cytoplasmic membrane and nuclear activities.[17]

The GAPDH inhibition causes an increase in the production of uridine diphosphate N-acetylglucosamine

(UDP-GlcNAc) and may result in increased levels of the glycolytic metabolite glyceraldehyde 3-phosphate that can activate the AGE pathway by activating methylglyoxal, an intracellular AGE precursor.[27]

Polyadenosine Diphosphate Ribose Polymerase Activation

PARP is a family of enzymes found in the cell's nucleus and implicated in a number of cellular processes involving mainly deoxyribonucleic acid (DNA) repair and programmed cell death (apoptosis). It can also inhibit GAPDH activity and control the progression of DR. Zheng *et al.*[21] demonstrated that the activity of PARP is increased in the retina, endothelial cells, and pericites of diabetic rats and contributes to the induced cellular death of vascular cells in this disease.

Oxidative Stress

Retinal cellular homeostasis is maintained by a tight balance between the formation and elimination of ROS.[17] In diabetes, retinal blood flow is reduced, even at the early stages of the disease,[5] and, in more established stages, retinal oxygen supply will be reduced not only because of a reduced retinal blood flow but also because there is a decrease in choroidal oxygen partial pressure (PO_2).[28] Both decreased blood flow and choroidal PO_2 are responsible for the hypoxic state of the retina, the breakdown of the blood-retinal barrier, and the alteration in cellular homeostasis.[29] The formation of reactive nitrogen oxide species (RNOS) also stimulates the expression of growth factors in DR.[17]

The main biochemical pathways involved in the pathogenesis of DR (polyol pathway, intracellular AGE formation, PKC activation, and hexosamine pathway) seem to be interconnected (Fig. 5.4; Box 5.4).

Nuclear Factor-κB Activation

Nuclear Factor-κB (NF-κB) is a protein complex that controls the transcription of DNA. It is an inducible transcription factor and an important regulator of many genes involved in inflammatory (including adhesion molecules) and immune responses, proliferation, and apoptosis.[17] Activation of NF-κB leads to endothelial

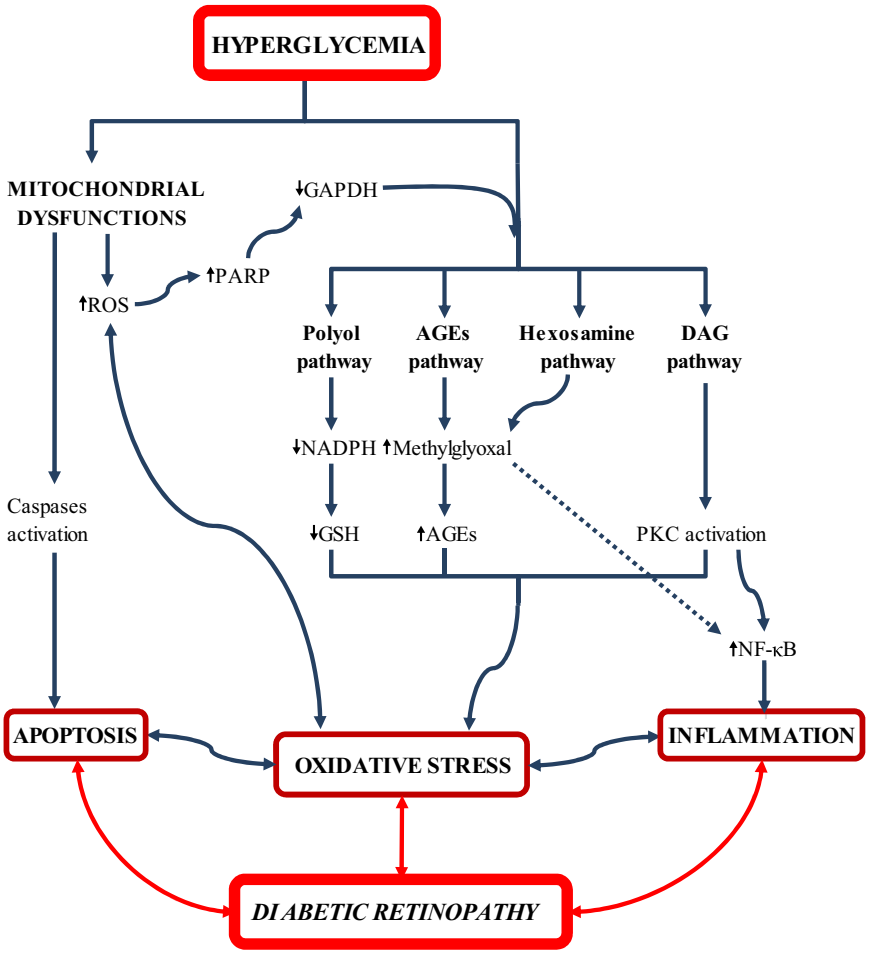

FIGURE 5.4 Possible pathogenesis of diabetic retinopathy. Hyperglycemia ends in a common final pathway that involves the interaction between apoptosis, inflammation, and oxidative stress, leading to the diabetic retinopathy production. AGE: advanced glycation end product; DAG: diacylglycerol; GAPDH: glyceraldehyde 3-phosphate dehydrogenase; GSH: glutathione; NADPH: nicotinamide adenine dinucleotide phosphate; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; PARP: polyadenosine diphosphate ribose polymerase; PKC: protein kinase C; ROS: reactive oxygen species.[16,17,20,21,23,24,26,27,30,31]

BOX 5.4

Oxidative stress plays a central role in the development of diabetic retinopathy

BOX 5.5

Main biochemical changes involved in the pathogenesis of DR include:

1. increase of oxidative stress;
2. increase of polyol pathway flux;
3. increase of intracellular AGE formation;
4. PKC activation;
5. hexosamine pathway.

apoptosis via Bcl-2, caspase-3, and caspase-9 pathways.[30] NF-κB is also a critical regulator of antioxidant enzymes.

Oxidative stress can trigger a redox-sensitive NF-κB, and thus it activates a new pathway for the development of DR.

Several studies suggest that NF-κB plays an important role in the pathogenesis of early-stage DR. It has been found that inhibiting NF-κB or proteins whose expression is regulated by NF-κB (such as inducible nitric oxide synthase (iNOS) and intracellular adhesion molecule (ICAM)-1) may inhibit the development of the retinopathy (Box 5.5).

MITOCHONDRIAL DYSFUNCTION

Mitochondria are organelles involved in cell metabolism, energy production, and apoptosis. They are considered to be the main source of superoxide radicals.[17]

Hyperglycemia is followed by an increase in glucose oxidation at the mitochondrial level and an increase in the voltage gradient across the mitochondrial membrane. This leads to superoxide production and cell damage.[31]

All of the molecular mechanisms mentioned above ultimately may produce neuronal dysfunction, inflammation, and neovascularization in the late stages of the disease.

NEURONAL DYSFUNCTION AND INFLAMMATION

The neurosensory retina is also altered in diabetes. There is an impairment in the metabolism of glutamate (main neurotransmitter) and a loss in the synaptic activity and apoptosis in the ganglion cells and nuclear layers.[18]

The neuroprotective effect of the platelet-derived growth factor (PDGF) is also reduced in these eyes, and it contributes to the pericyte loss and to the impairment of the blood-retinal barrier. Nowadays most authors recognize the concept of the neurovascular unit. This neurovascular unit is altered as result of diabetes.[32]

Inflammation is also present in DR and plays an important role in its development. Inflammatory mediators such as interleukin-1β, tumor necrosis factor (TNF)-α, ICAM-1, and angiotensin II have been found elevated in DR. Microglial cells are also activated, and all these changes are implicated in the progressive retinal impairment.[32]

VASCULAR DAMAGE

As a result of all molecular changes there is an important increase in expression of intraocular VEGF levels and other cytokines. VEGF probably plays an important role in mediating the structural and functional changes in the retina.[33]

VEGF is a glycoprotein secreted by vascular endothelial cells, smooth muscle cells, and other cell types. There is an increase in the expression of VEGF and its receptors in DR and DME.[34]

VEFG belongs to a dimeric glycoprotein family that includes the placental growth factor (PIG) and several VEGF isoforms: VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and VEGF-F. The isoform involved in DR and the most investigated is VEGF-A. It can act through the specific receptors VEGFR-1 and VEGFR-2.[33]

VEGF-165 is the main VEGF-A isoform. It is a 45-kDa homodimeric glycoprotein and it causes increased vascular permeability and neovascularization stimulation in both physiologic and pathologic processes.[34]

The expression of VEGFR-1 is upregulated by hypoxia and it binds VEGF with higher affinity than VEGFR-2. The latter is the main mediator of the mitogenic and angiogenic effects of VEGF and is responsible for the increased vascular permeability.[34]

Endothelial cells and pericytes are damaged in the early stages of the disease and microaneurysms appear in the ocular fundus. The blood-retinal barrier is broken and blood and hard exudates appear in the retina. In the advanced stages of the disease, hypoxia and vascular occlusion are present.

DIAGNOSIS AND PREVENTION

The appropriate care process for DR includes a medical history, an ophthalmic examination, and close follow-up.

TABLE 5.5 Actual Follow-Up Recommendations According to Diabetic Retinopathy Severity

Severity Level	Follow-Up Recommendation
No apparent DR	Annually*
Mild nonproliferative DR	Annually
Moderate nonproliferative DR	Every 6 months
Severe nonproliferative DR	Every 4–6 months
Low-risk proliferative DR	Consider treatment
High-risk proliferative DR	Treatment
CSME	Treatment

CSME: clinically significant diabetic macular edema; DR: diabetic retinopathy.
**Some authors consider every 2 years in type 2 diabetic patients who are well controlled due to the low risk.*

The features of DR are detected by direct examination of the eye fundus (ophthalmoscopy). DR is asymptomatic in the early stages, and there is no visual dysfunction until the disease is well established. Patients with nonproliferative diabetic retinopathy (NPDR) may suffer some disturbances in their activities, but visual acuity only decreases when the macula is affected.

A comprehensive exam must be done in all diabetic patients. Dilated fundoscopy and biomicroscopy of the posterior are the best way to detect DR. Before inducing mydriasis, it is necessary to examine the iris to exclude the presence of iris neovascularization.

Undilated ophthalmoscopy has poor sensitivity and specificity.

Annual exams of the ocular fundus are recommended by the American Academy of Ophthalmology (AAO) in all diabetic patients, starting at the moment of diagnosis in type 2 diabetic patients and 3–5 years after diagnosis in type 1 diabetes. After DR has been diagnosed, the follow-up schedule depends on the stage of the disease. The actual recommendations are summarized in Table 5.5.

In type 2 diabetic patients without risk factors, annual exams can be replaced by biannual exams due to the slow progression of the disease.

The gold standard for detection and classification of DR is stereoscopic color fundus photographs in seven standard fields, as defined by the ETDRS group.[35] This procedure is time consuming and requires trained personnel. It is only used for clinical trials. In clinical practice, dilated ophthalmoscopy, biomicroscopy, and manual grading are considered the best methods.

However, in clinical practice, manual screening of all the diabetic population by trained ophthalmologists seems impossible due to the high prevalence of the disease. Even in the most developed countries, less than 50% of the diabetic patients are being followed correctly.

BOX 5.6

Laser photocoagulation remains the standard technique for the treatment of diabetic retinopathy

Several types of screening programs have been designed throughout the world to meet this problem. Screening exams or tests should aim for a sensitivity of at least 60%, though higher levels are usually achievable.[36] Specificity levels of 90–95% and technical failure rates of 5–10% are considered appropriate for both measures.[37]

The AAO recognizes that screening for DR using appropriately validated digital image technology is effective and sensitive for this purpose. These screening programs have great value in circumstances in which access to ophthalmic care is limited,[37] although they do not replace a comprehensive ophthalmic exam.

Patients must be aware of the importance of blood glucose and blood pressure control in both type 1 and type 2 diabetes. The benefits of metabolic control on the retinopathy progression have been well established in randomized clinical trials (DCCT, UKPDS).

The DCCT showed that the development and progression of DR in type 1 diabetic patients can be delayed if glucose concentrations are maintained in the near-normal range. This study showed how the risk of retinopathy was decreased by 53% in children aged 13–17 years without retinopathy at study entry, and the risk of retinopathy progression was decreased by 70% in those who had retinopathy at the beginning of the study. The benefits of intensive therapy continued to be evident 7 years after the end of the DCCT, as demonstrated in the Epidemiology of Diabetes Interventions and Complications study.[38] Evidence about the effects of controlling hyperglycemia in type 2 diabetic patients comes from observational data as well as the UKPDS (Box 5.6).

TREATMENT OF DIABETIC RETINOPATHY AND DIABETIC MACULAR EDEMA

DR is defined by progressive development of microvascular and neurovascular damage in the retina that leads to vision-threatening complications such as PDR and DME.

Retinal laser photocoagulation has been considered the standard technique for treating DR since the publication of the ETDRS results in the early 1980s. Laser photocoagulation techniques can be classified as panretinal, focal, or grid. Panretinal photocoagulation (PRP) should be performed whenever PDR is reached. Focal or grid

BOX 5.7

Intravitreal corticosteroids

Triamcinolone
Dexamethasone
Fluocinolone acetonide

Intravitreal antiangiogenics

Bevacizumab
Ranibizumab
Aflibercept

macular laser treatment should be considered for all eyes with CSME.

According to the ETDRS, scatter PRP significantly reduced the risk of severe vision loss (severe blindness) from PDR, and focal or grid laser photocoagulation can reduce the risk of moderate vision loss (doubling of the visual angle) from CSME. ETDRS results were achieved by rigorously applying laser recommendations and through close follow-up, with retreatment as needed. The regression of new vessels occurs often at three months, but in nearly 4.5% of patients the disease progresses to advanced disease even in the presence of adequate PRP.[39]

Recommendations for the type and pattern of laser treatment for DR have not changed since the 1980s.[40,41]

In patients with advanced DR and vitreous hemorrhages or tractional retinal detachment, laser is not useful and patients must undergo surgery (vitrectomy) (Box 5.7).

Since the 1990s, significant developments in pharmacotherapy have emerged, but they are still an adjunct to panretinal photocoagulation.

Corticosteroids and antiangiogenic drugs have shown promising results in preventing neovascularization and in the management of DME.

Intravitreal triamcinolone acetonide (IVTA) has been studied for its potent effects in DME. The Diabetic Retinopathy Clinical Research (DRCR) Network investigated the efficacy and safety of two doses (1 and 4 mg) of IVTA compared with the standard of care (focal/grid laser) in patients with DME. After 3 years of treatment, laser was associated with better visual acuity and fewer side effects (see http://drcrnet.jaeb.org).

Sustained drug delivery systems of corticosteroids are being tested in clinical trials in patients with DME. Ozurdex® (Allergan) is a biodegradable dexamethasone intravitreal implant approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment of macular edema secondary to retinal vein occlusion. Its efficacy in DME is now being investigated in randomized clinical trials.

Iluvien® (Alimera Sciences, Inc.) is a nonbiodegradable implant designed to release the drug fluocinolone acetonide for up to 3 years. It has been approved in Europe, but the FDA considers that this device cannot be approved in the USA in its present form because of the high prevalence of side effects, mainly cataracts and increased intraocular pressure.[42]

There are other sustained drug delivery systems under investigation such as the Cortiject® implant (NOVA63035, Novagali Pharma) and the Versiome® drug delivery system (Icon Bioscience, Inc.) but only in phase I and II clinical trials.[43]

In addition, antiangiogenic drugs have been found to be effective for treatment of PDR and DME. As has been mentioned, there is an overexpression of VEGF in DR. The standard average point for evaluating effectiveness of anti-VEGF drugs is 6 months, but only a few studies include this 6-month follow-up period after intravitreal injection.

Avastin® (bevacizumab, Genentech, Inc.) is a full-length humanized antibody that binds to all subtypes of VEGF and has shown promising results in DR. Avery *et al.*[44] reported transient iris and retinal neovascularization regression after intravitreal use of this drug. Shin *et al.*[45] have demonstrated that intravitreal bevacizumab reduced the VEGF expression to some degree in a limited number of PDR patients. It is used off label as a clinical adjunct to laser treatment in patients with PDR and in advanced disease 3–5 days previous to vitrectomy to reduce intraoperative and postoperative complications, mostly hemorrhages. In most studies, bevacizumab is administered 1 week preoperatively to avoid the occurrence of tractional retinal detachment.[46] The same authors have also suggested its use in cases of vitreous hemorrhage after vitrectomy.

Lucentis® (ranibizumab, Genentech Inc. and Novartis Pharma) is a recombinant humanized antibody fragment against VEGF approved by the FDA and the EMA for DME treatment. There are no final reports on the effect of ranibizumab in the treatment of PDR. The results of the clinical trial evaluating this drug by the DRCR Network in this stage of the disease are awaited by the scientific community.

Other anti-VEGF drugs are under investigation for this purpose, such as VEGF Trap-Eye® (aflibercept, Eylea, Bayer HealthCare and Regeneron Pharmaceuticals, Inc.).

A major limitation of anti-VEGF therapy is the recurrence of new vessels after 2 weeks of intravitreal injection. Some authors have suggested a period of reinjection of 3 months.[47] There is lack of information about long-term side effects of this therapy in PDR. Caution is warranted.

There is some evidence that the hyaloid and the posterior vitreous may influence the progression of DR and DME. It is accepted that the course of the disease seems more favorable in patients with posterior vitreous detachment.[43] Then, the posterior vitreous detachment induction may be beneficial in the treatment of DME and PDR. Intravitreal microsplamine (Ocriplasmin) has been recently approved by the FDA for this purpose. It is useful in resolving vitreomacular adhesion and it is safe and well-tolerated.[48]

Several attempts have been made with systemic therapy to prevent DR or its progression to PDR. Fenofibrate is a lipid-lowering drug used to treat dyslipidemia. Its main clinical effect is due to the inhibition of the actions of peroxisome proliferator-activated receptor alpha (PPAR-α). Some benefits in the prevention of DR and slowing the progression to advanced disease have been demonstrated with this drug in type 2 diabetic patients in the Fenofibrate Intervention and Event Lowering in Diabetes (the FIELD study), although the mechanism of this effect is unknown.[49]

In addition, some benefits have been shown with renin-angiotensin system inhibition in the DIabetic Retinopathy Candesartan Trial (DIRECT) study with candesartan[50] and with PKC inhibition that seemed to ameliorate vision loss without definitive conclusions.

There is still a long way to go in this field and a lot of work to do. New insights in the pathogenesis of this disease may open new possibilities for treatment. Many new compounds are currently in or entering clinical trials. The role of these new compounds in diabetic retinopathy must be defined.

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