Overview of Age-Related Ocular Conditions

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Abstract

The United States is an aging society. The number of Americans 65 years or older is expected to more than double over the next 40 years, from 40.2 million in 2010 to 88.5 million in 2050, with aging baby boomers accounting for most of the increase. As the society ages, the prevalence of age-related diseases, including diseases of the eye, will continue to increase. By 2020, age-related macular degeneration, one of the leading causes of vision loss, is expected to affect 2.95 million individuals in the United States. Likewise, the prevalence of open-angle glaucoma, estimated at 2.2 million in 2000, is projected to increase by 50%, to 3.36 million by 2020. As the eye ages, it undergoes a number of physiologic changes that may increase susceptibility to disease. Environmental and genetic factors are also major contributors to the development of age-related ocular diseases. This article reviews the physiology of the aging eye and the epidemiology and pathophysiology of 4 major age-related ocular diseases: age-related macular degeneration, glaucoma, diabetic retinopathy, and dry eye.

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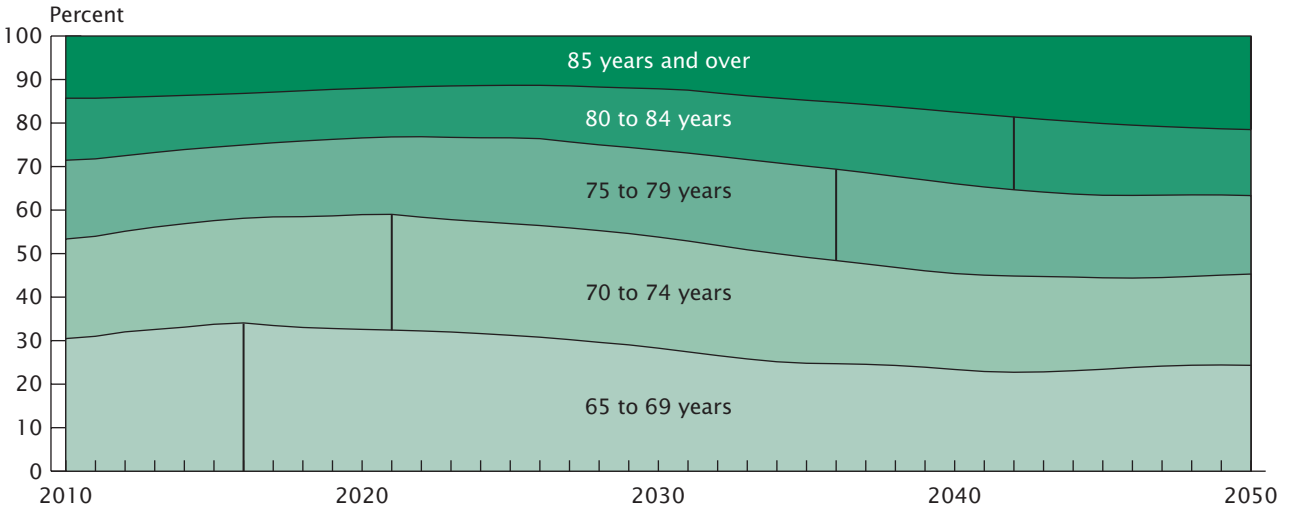
For author information and disclosures, see end of text.

The population of the United States continues to age, a trend consistent with many western industrialized nations and some Asian societies. According to the US Census Bureau, the number of Americans 65 years or older is expected to increase from 40.2 million in 2010 to 88.5 million in 2050, with most of the increase attributable to aging baby boomers.[1] Nearly 1 in 5 US residents will be above age 65 years by 2030, the time at which all of the baby boomers will represent the country's older population.[1] The number of oldest Americans (≥85 years of age) is projected to increase from 5.8 million in 2010 to 8.7 million in 2030, and to approximately 19 million in 2050, when they will account for 4.3% of the population.[1] **Figure 1** shows the projected changes in the age distribution of older Americans in the coming decades.

Consistent with this trend, the prevalence of age-related conditions is also rapidly increasing. As the body ages, changes in the structural and functional characteristics of the vasculature combined with behavioral, genetic, and environmental risk factors contribute to the development of age-related vascular diseases, such as atherosclerosis, renal insufficiency, and cerebrovascular disease.[2] Advancing age remains the strongest independent risk factor for developing atherosclerotic cardiovascular disease.[2] Advanced age is a major risk factor for many eye diseases. The incidence and prevalence of age-related macular degeneration (AMD), glaucoma, and vascular occlusive diseases increase significantly with age.[2] Among US adults, the prevalence of glaucoma is 0.7% among those aged 40 to 49 years and 1.8% among those aged 60 to 69 years, and increases to 7.7% for those 80 years and older.[3] Similarly, the prevalence of AMD increases from 2.1% in the 40 to 49 year age group to 35.4% among individuals aged 80 years and above.[3]

The frequency of visual impairment associated with ocular diseases of aging is increasing rapidly. According to the Eye Disease Prevalence Research Group (EDPRG), in 2000, an estimated 937,000 Americans (0.78%) over age 40 years were blind, as defined by a best-corrected visual acuity of 20/200 or worse in the better-seeing eye, and an additional 2.4 million individuals (1.98%) had low vision, defined as best-corrected visual acuity less than 20/40, which is the level of vision required for driving.[4]

Figure 1. Distribution of the Projected Older Population by Age for the United States: 2010 to 2050[11]



Note: Line indicates the year that each age group is the largest proportion of the older population.

The EDPRG projected that the number of blind persons living in the United States will increase to 1.6 million (1.1%) by 2020, and the number living with low vision to 3.9 million (2.5%), for a total of 5.5 million visually impaired Americans (3.6% of the total population). Much of this increase is attributable to the demographics of an aging population—while persons aged 80 years and older comprised only 7.7% of the population in 2000, they accounted for almost 70% of observed blindness.

Predictably, the dramatic increase in the prevalence of vision impairment among older Americans will have enormous societal and economic implications. The estimated total financial costs of major vision disorders in the United States in 2004 was $35.4 billion—$16.2 billion in direct medical costs, $11.1 billion in other direct costs, and $8 billion in lost productivity.[5] A 2010 study by the AMD Alliance International put the worldwide cost of vision loss at an estimated $3 trillion; of that amount, visual impairment due to AMD alone accounted for $343 billion, including $255 billion in direct healthcare costs.[6]

The past decade has seen significant advances in the treatment of several of the most common ocular diseases associated with advancing age. For example, the introduction of anti-vascular endothelial growth factor (anti-VEGF) agents has revolutionized treatment of the neovascular, or wet, form of AMD.[7] These drugs are now being applied to other exudative ocular conditions, including diabetic macular edema (DME) and branch and central retinal vein occlusions.[7] The success of these new therapies comes at a high price, however—a single intravitreal injection of the VEGF inhibitor ranibizumab costs approximately $2000.[8]

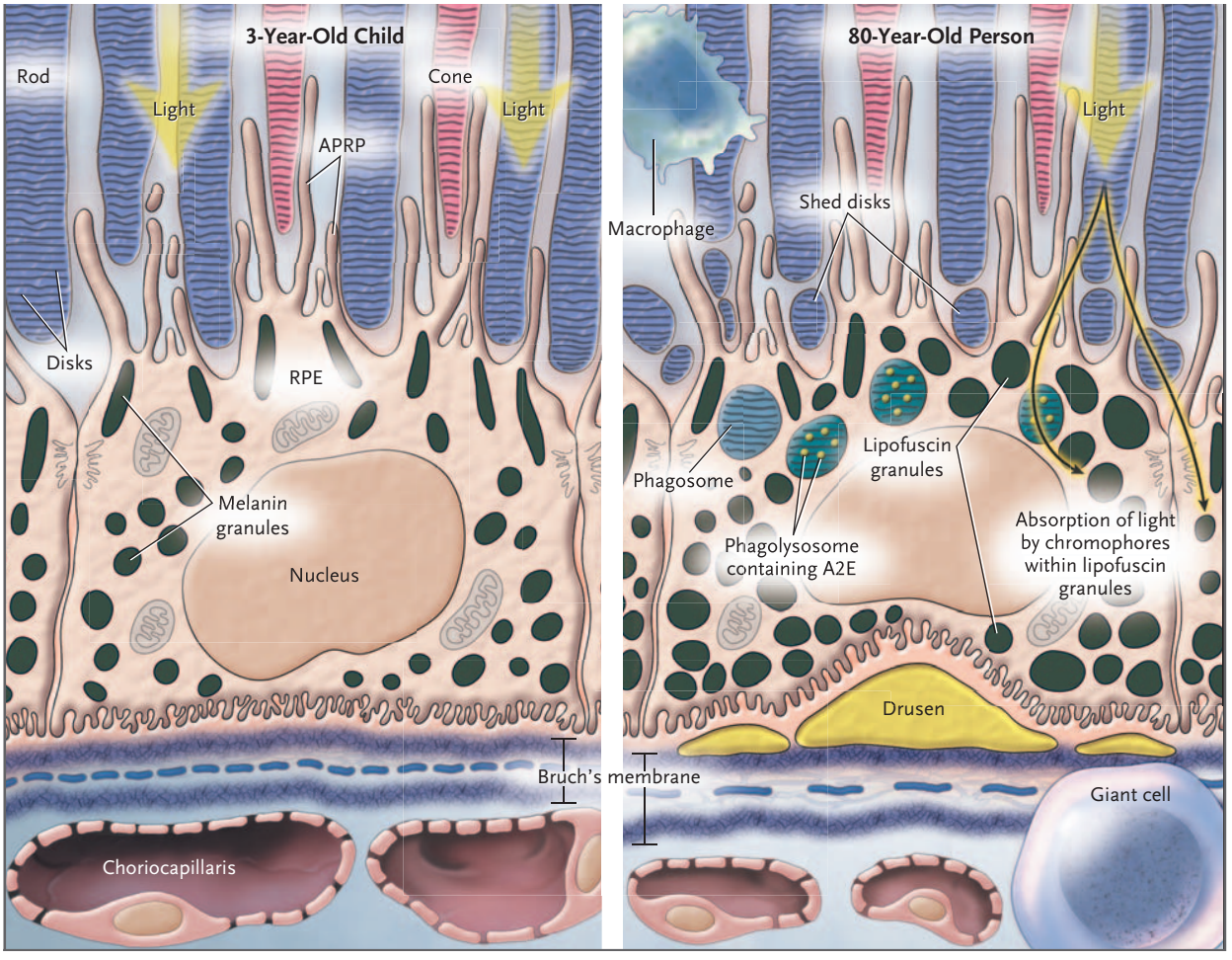
This article reviews the basic physiological changes in the aging eye that set the stage for development of ocular disease and provides an overview of the epidemiology and pathophysiology of 4 major age-related eye conditions: AMD, glaucoma, diabetic retinopathy (DR), and dry eye disease.

Physiological Changes in the Aging Eye

As the eye ages, it undergoes a number of structural and functional changes that increase susceptibility to ocular diseases. These changes include loss of cells in the ganglion layer, loss of retinal pigment epithelial cells and photoreceptors, changes to the optic nerve, reduced blood flow, condensation of the vitreous gel, loss of endothelial cells, and meibomian gland dysfunction.[2,9,10]

Thickness of the retinal nerve fiber layer decreases by an average of 3 μm per decade, corresponding to a loss of approximately 60,000 retinal ganglion cells.[11] On average, the retina of a 95-year-old contains approximately half as many retinal ganglion cells as that of a 25-year-old.[11] Changes that occur with age to the retinal pigment epithelium (RPE) are central to the development of AMD. One of the essential functions of the RPE is renewal of photoreceptors through phagocytosis of metabolic byproducts and cellular debris.[12] As the number of retinal pigment epithelial cells declines with age, phototoxic waste products and debris, such as lipofuscin, A2E, and chromophores, accumulate in the RPE.[12] It is estimated that these debris can occupy one-fifth of the total volume in an RPE cell in the eyes of an 80-year-old individual.[12] These substances damage cell membranes and deoxyribonucleic acid, and induce chronic inflammation, which can lead to AMD (**Figure 2**).[12]

■ **Figure 2.** Retinal Pigment Epithelium Cell in a 3-Year-Old Child (Left-Hand Panel) and an 80-Year-Old Person (Right-Hand Panel)[12]



The outer segments of the rods and cones are embedded in the interphotoreceptor matrix (blue-gray areas) and partially surrounded by apical pseudopodial retinal pigment epithelium (RPE) processes (APRP). The shed disks (right-hand panel) become encapsulated in the phagosomes and are digested in phagolysosomes in the cell cytoplasm of the RPE. Macrophages and fused macrophages (giant cells) remove cellular debris around the cell. Light-induced toxicity occurs as light is absorbed by the various chromophores in the lipofuscin granules. This damages deoxyribonucleic acid and cell membranes and causes inflammation and apoptosis. The right-hand panel shows enlarged lipofuscin granules, the thickened Bruch's membrane, and the attenuation of the choriocapillaris. The central elastic lamina in Bruch's membrane becomes more porous in old age.
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Age-related vascular changes that occur systemically also affect ocular vascular beds. Studies show that ocular blood flow generally diminishes with age, which may result from an atherosclerotic process and narrowing of the retinal vessels.[2] There is a progressive thinning of the choroid, the vascular membrane that lies between the retina and the sclera, from 193 μm in the first decade of life to 84 μm in the tenth decade.[13] Choriocapillary density decreases by 45%—from 0.75 in the first decade to 0.41 in the tenth decade—and lumen diameter of the choriocapillaris decreases by 34%.[14] Vascular changes in the eye are thought to impede regulation of blood pressure and flow, limiting the exchange of nutrients and removal of metabolic waste and creating conditions of ischemia.[2]

Dysfunction of the vascular endothelium, a monolayer of cells covering the inner surface of blood vessels, is a common pathological feature of a number of age-related diseases and is thought to be a factor in some ocular diseases, such as glaucoma.[2] The vascular endothelium regulates the microcirculation through the release of vasoactive factors, including the vasodilator nitric oxide (NO) and the vasoconstrictor endothelin-1.[2] In the aging eye, endothelial dysfunction leads to decreased production of NO, thereby increasing vascular tone and vasoconstriction, and restricting blood flow.[2] Reduced NO levels have been reported in the aqueous humor of patients with glaucoma, suggesting that vascular endothelial dysfunction plays a role in the pathophysiology of this condition.[2]

With advanced age, changes also affect the ocular surface. Structural and functional changes to the cornea that occur with age can affect its ability to refract light and repair itself, and can leave it more vulnerable to infection.[9] As the cornea ages, there is an increase in epithelial permeability, which may represent a breakdown of epithelial barrier function.[9] Moreover, there is a gradual decrease in the number of corneal endothelial cells with age that may adversely affect endothelial function and leave the cornea more vulnerable to hypoxic stress.[9] Aging is also a major risk factor for dysfunction of the meibomian gland, a specialized sebaceous gland located in the eyelid that releases a mixture of lipids that lubricate the surface of the eye and prevents tear evaporation.[10] Consequences of meibomian gland dysfunction (MGD) include increased tear evaporation, tear film instability, increased shear stress, and inflammation of the ocular surface—all of which are major clinical features of dry eye disease.[10]

Age-Related Macular Degeneration

AMD is the leading cause of blindness among people of European descent who are over 65 years of age.[15] Advanced AMD can be non-neovascular (dry, atrophic, or nonexudative) or neovascular (wet or exudative). Based on a meta-analysis of population-based studies and US census data, the EDPRG estimated that in the year 2000, 1.2 million Americans had the wet form of AMD in at least 1 eye, 973,000 had geographic atrophy of the RPE (advanced dry AMD), and an additional 7.3 million individuals had large drusen (≥125 μm in diameter) in their macula (a strong AMD risk factor) in 1 or both eyes.[15] The group projected that the prevalence of AMD would increase by 50%, to 2.95 million, by 2020 due to the rapidly aging population. In addition to advanced age, studies have shown that genetic predisposition, Caucasian race, and a history of smoking are also significant risk factors. A complex association of genetic, environmental, and age-related factors most likely contribute to the development of AMD.[16]

The presence of drusen, focal deposits of acellular debris, between the RPE and Bruch's membrane, is the defining clinical feature of AMD.[16] Drusen are categorized by their size (small, medium, or large) and the appearance of their margins (hard or soft).[12,13,16] As shown in **Figure 3**, the stage and progression of AMD is classified by the size, number, and appearance of drusen on funduscopic examination, and the presence and extent of geographic atrophy and choroidal neovascularizion.[16]

While small drusen are commonly found in the eyes of older adults, large drusen or excessive numbers of them damage the RPE and trigger an inflammatory response.[12,16] Inflammation is accompanied by increased production of angiogenic factors that stimulate choroidal neovascularization, which is characteristic of wet AMD. VEGF, the primary angiogenic cytokine in wet AMD, is also a highly potent vascular permeability factor. Proliferating choroidal capillaries are therefore excessively leaky and fragile, which leads to subretinal hemorrhage and fluid exudation, leading to RPE detachment from the choroid and eventually macular scarring in advanced wet AMD.[13,16]

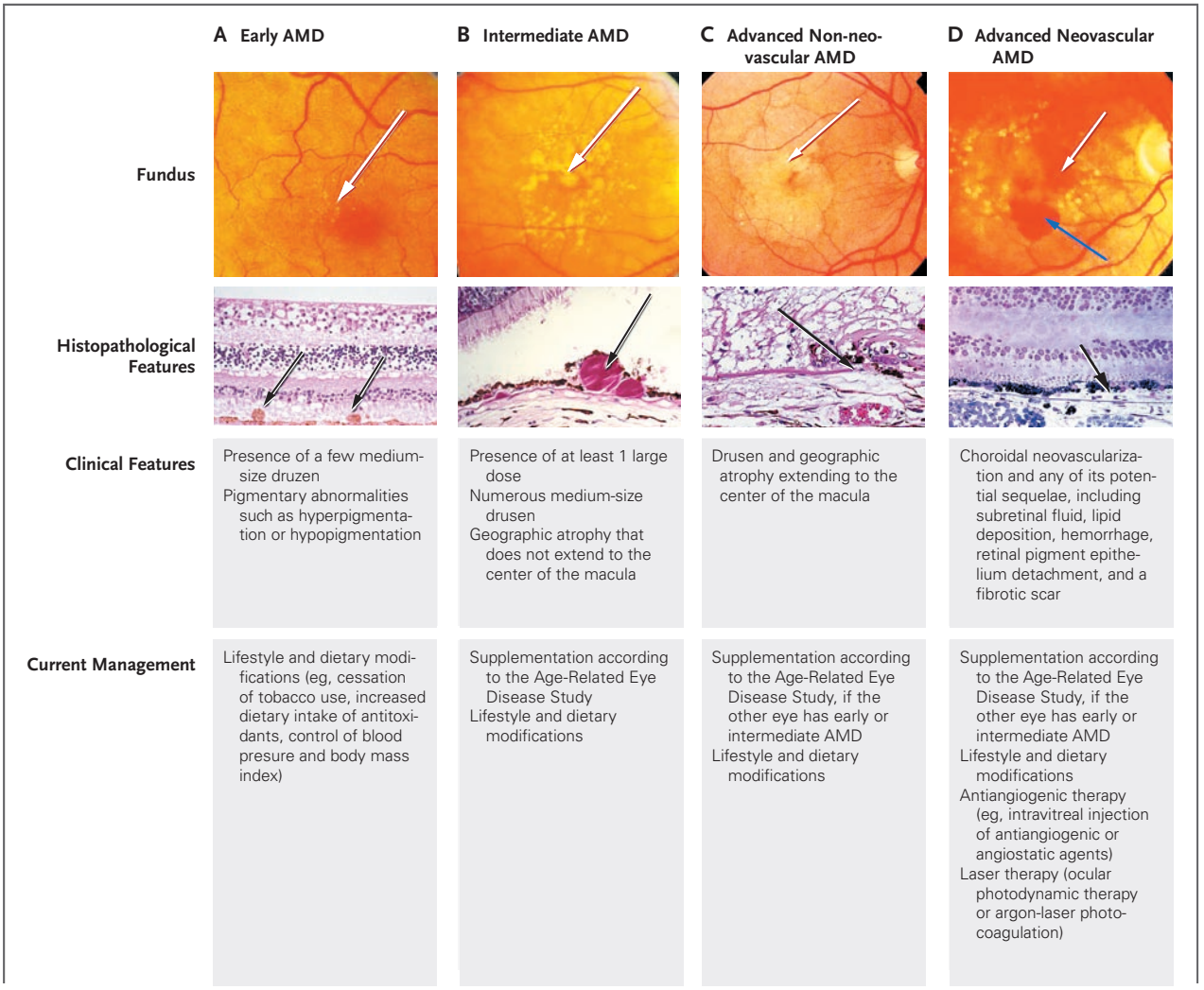
Age-related changes to Bruch's membrane also play a key role in the development of AMD. Bruch's membrane regulates the transport of oxygen, nutrients, and metabolic waste products between the RPE and choriocapillaries.[12] As the eye ages, Bruch's membrane becomes thicker, more calcified, and less elastic, which allows for the accumulation of cellular debris and lipids that may precede drusen formation and AMD.[12,13] Basal laminar deposits—deposits of basement membrane proteins and collagen, and a key early marker for AMD development—can appear in Bruch's membrane as early as the third decade of life.[12,13] Degeneration of Bruch's membrane also facilitates the growth of fragile, leaky capillaries from the choroid into the subretinal space.[12,16]

Symptoms that may accompany early-stage AMD include blurred vision and visual scotomas (blind spots in the central vision leading to difficulty with recognizing faces and reading small print).[16] Importantly, once advanced AMD develops in 1 eye, there is at least a 40% chance it will develop in the other eye within 5 years.[16] Although wet AMD comprises only 10% to 15% of all AMD cases, this form accounts for greater than 80% of severe vision loss or legal blindness from the disease.[16] Whereas vision loss associated with advanced dry AMD typically progresses over months to years, vision loss with wet AMD may be sudden and profound in the event of acute subretinal hemorrhage or fluid accumulation.[16]

Glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide, and the second-leading cause of blindness in the United States.[17,18] Of the various identified forms of glaucoma (eg, neovascular, pigmentary, mixed mechanism), the 2 major ones are open-angle, the most common form, and closed-angle (a much less common form in the United States). The terminology is derived from the appearance of the anterior chamber angle (open or closed), which is critical to the diagnosis.[17,18] Glaucoma is further distinguished between primary (not having an identifiable cause) and secondary forms, and also by intraocular pressure (IOP), which may be elevated or normal (normal tension glaucoma) in patients with primary open-angle glaucoma (OAG).[17,18]

Figure 3. Classification of Age-Related Macular Degeneration[16]



Column A shows medium-size drusen (arrows) in early age-related macular degeneration (AMD), and Column B shows a large druse (arrows) in intermediate AMD. In Column C, a photograph of the fundus shows geographic atrophy (white arrow), and a histopathological photograph shows geographic atrophy with loss of Bruch's membrane (black arrow). In Column D, the photograph of the fundus with neovascular AMD shows subretinal hemorrhage (blue arrow) and choroidal neovascularization (white arrow), and the histopathological photograph shows choroidal neovascularization (black arrow). (Images courtesy of Mort Smith, MD, and Deepak Edward, MD).
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OAG was estimated to affect 2.2 million Americans in 2000, and the prevalence was projected to increase by 50% to 3.36 million by 2020.[19] African Americans are almost 3 times more likely to have OAG than Caucasians, and are 15 times more likely to suffer visual impairment from the disease.[20,21] The prevalence of glaucoma increases steadily with age. According to the EDPRG, the prevalence of OAG among Caucasian women aged 40 to 49 years was 0.83%, compared with 2.16% in those aged 70 to 74 years, and 6.94% in those at least 80 years of age (based on year 2000 census data).[19] Glaucoma also has a strong genetic component: a person with a first-degree relative with OAG is 10 times more likely to develop the disease than someone without the family history.[21] Myopia and low diastolic perfusion pressure are also risk factors for primary OAG.[18]

Pathophysiologically, OAG is distinguished from other acquired optic neuropathies by the appearance of the optic nerve head, which becomes progressively thinner due to the loss of retinal ganglion cell axons and their supporting glia and vasculature.[18] During examination, clinicians look for a deepening and widening of the central depression (optic nerve cupping) in the optic disc where the retinal nerves pass out of the eye.[18,21] As more retinal ganglion cells become

affected, the ratio of the size of the central cup increases in relation to the overall size of the optic disc.[2,21]

Increased IOP is no longer a defining clinical feature of OAG, as many patients with glaucoma have IOP that falls within the normal range.[18,21] Elevated IOP is now considered an associative rather than causative disease factor.[21] However, IOP is the only modifiable factor that has been shown to decrease both the risk of developing glaucoma and its progression.[17,18] Very high IOP and ocular pain can occur in angle closure glaucoma (acute angle closure crisis), but chronic angle closure can be asymptomatic in many patients.[21]

OAG is distinguished from other optical neuropathies by its slow progression over months to years, and by the abnormal deepening of the central part of the optic disc.[21] The condition is typically painless and does not cause a dramatic change in visual acuity until it is fairly advanced, decreasing the visual field significantly. Studies have consistently shown that about half of all individuals with glaucoma are unaware they have the condition.[20,21] Vision loss associated with OAG is generally progressive and irreversible, affecting the peripheral visual field in the early disease stage, and central visual acuity in the late disease stage.[21]

Diabetic Retinopathy

DR is the leading cause of new cases of legal blindness among adults aged 20 to 74 years in the United States.[22] An estimated 10.2 million American adults are known to have diabetes.[23] A 2005 to 2008 National Health and Nutrition Examination Survey of adults greater than 40 years of age with diabetes reported a 28.5% prevalence of DR, with 4.4% experiencing vision loss from DR.[22] Non-Hispanic blacks had a higher estimated prevalence (38.8%) than non-Hispanic whites (26.4%). Extrapolating to the overall US population, the prevalence of DR and vision-threatening DR was 3.8% and 0.6%, respectively.[22]

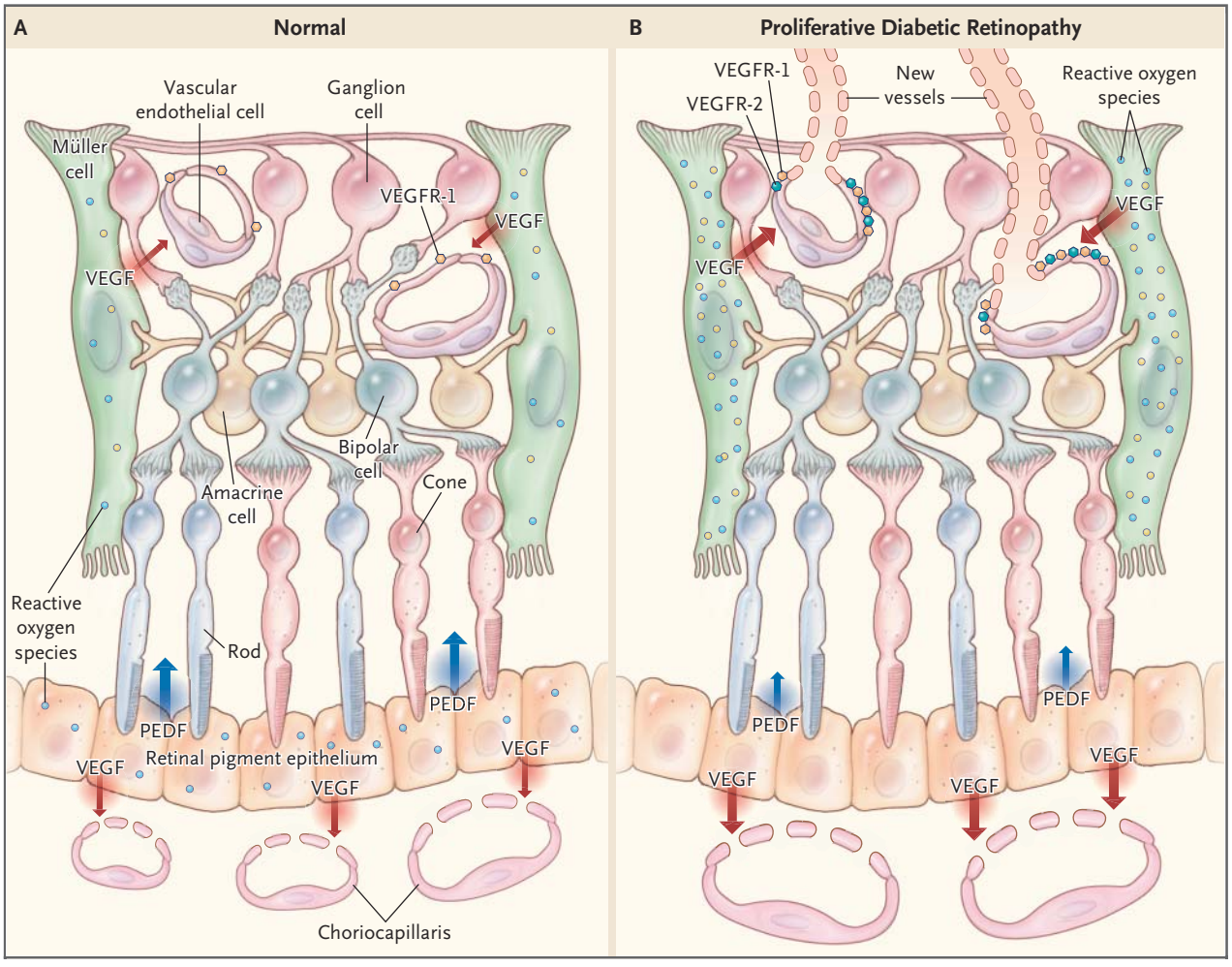
There is some evidence that the prevalence of DR and the proportion of individuals with diabetes who progress to severe DR have declined significantly over the past several decades.[23] These trends are likely attributable to better overall diabetes management, including strict blood glucose monitoring, more intensive control of glycemia and blood pressure, new medications, and screening and educational programs.[23] In a population-based study involving 955 individuals with type 1 diabetes mellitus, the estimated annual incidence of any visual impairment and severe visual impairment associated with DR declined by 57% and 77%, respectively, from 1980 to 2007.[23,24] However, these gains have been offset by a 33% increase in the frequency of hypoglycemia and a 100% increase in the prevalence of adults with diabetes who are overweight or obese.[23] Further, only a small fraction (7.3%; 95% confidence interval, 2.8%-11.9%) of adults with diabetes in the United States achieve the recommended targets for glycemic control (glycated hemoglobin level <7%, blood pressure <130/80 mm Hg, and total cholesterol levels <200 mg/dL) that have been shown in randomized controlled studies to substantially delay or prevent the occurrence of DR and other microvascular complications of diabetes.[25]

Clinically, DR is classified as 2 distinct forms: nonproliferative or proliferative.[26,27] The earliest clinical features of non-proliferative DR are microaneurysms—small dilations of the retinal capillaries—followed by small intraretinal hemorrhages.[26,27] These abnormalities are found in virtually all individuals with type 1 diabetes after 20 years, and in nearly 80 percent of those with type 2 disease.[27] With progression, intraretinal hemorrhages become larger and more numerous and may be accompanied by cotton wool spots (areas of necrosis in the nerve-fiber layer) and vascular abnormalities (dilated, tortuous, irregular appearance of the retinal veins).[26,27] While non-proliferative DR is often asymptomatic, the risk of transformation to proliferative DR increases with disease progression.[27]

Proliferative DR is marked by proliferation of new retinal blood vessels that can extend into the vitreous space.[26] These vessels are abnormally fragile and porous and may therefore hemorrhage into the vitreous cavity; they may also contract, causing tractional retinal detachment.[26,27] Macular edema, a vision-stealing complication of DR, occurs when hyperpermeable retinal capillaries leak fluid into the macula, the central portion of the retina that provides sharp, detailed central vision.[26] Thickening of the fovea, the central portion of the macula, as observed by optical coherence tomography, and vascular leakage as measured by fluorescein angiography, are apparent in DME.[23] The duration of central foveal thickening and the degree of plasma leakage are thought to be closely related to the severity and irreversibility of vision impairment.[23]

Increased VEGF expression in response to hypoxia in conjunction with decreased levels of the endogenous angiogenesis inhibitor pigment epithelium-derived growth factor is central to the initiation of neovascularization and breakdown of the blood-retinal barrier in DME.[26,27] VEGF has been detected in a number of non-vascular cell types in the eyes of patients with diabetes even before the development of retinopathy, including glial cells and retinal neurons, suggesting that DR is a disease of the entire neurovascular unit of the retina (**Figure 4**).[23,26] Injury to retinal neurons provokes an inflammatory response marked by activation of microglial cells and the

Figure 4. Retinal Anatomy and Mechanism of Diabetic Retinopathy[26]



A normal retina is shown in Panel A, and a retina from a patient with proliferative diabetic retinopathy is shown in Panel B.
PEDF indicates pigment-epithelium–derived factor; VEGF, vascular endothelial growth factor.
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release of various inflammatory cytokines.[23,27] Inflammation and neovascularization are interrelated processes—there is compelling evidence that inflammation contributes to both the development and the progression of DR and DME.[26,27]

Dry Eye

Dry eye is a common condition that leads to significant ocular discomfort and visual dysfunction. An estimated 40 million Americans have dry eye.[10] The prevalence of dry eye increases significantly with age, from approximately 8.4% of individuals under age 60 years to 19% in those greater than 80 years of age.[28] Women are affected more than men (16.7% vs 11.4%).[28] Dry eye is broadly defined as a multifactorial disease of the tears and ocular surface accompanied by increased osmolarity of the tear film and inflammation of the ocular surface, resulting in discomfort, visual disturbance, and tear film instability.[29] As shown in the **Table**, the severity of dry eye disease can be rated on a scale from 1 to 4 based on the severity of symptoms and the degree of physiologic abnormalities on the ocular surface.[29,30] In its most severe form (grade 4), there is pronounced corneal staining and erosions, conjunctival scarring, and constant and/or debilitating discomfort and visual symptoms.

The 2 primary forms of dry eye disease are aqueous-deficient, which results from decreased tear secretion from the lacrimal gland, and evaporative, in which there is excess water loss from the exposed ocular surface in the context of normal lacrimal tear production.[10,29] Aqueous-deficient dry eye is further divided between 2 subtypes: Sjögren's syndrome, an autoimmune disease of the lacrimal and salivary

Table. Dry Eye Severity Grading Scheme[29]

Dry Eye Severity Level	1	2	3	4[a]
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, stress or no stress	Severe frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/-	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
TFBUT (sec)	Variable	≤10	≤5	Immediate
Schirmer score (mm/5 min)	Variable	≤10	≤5	≤2

[a]Must have signs AND symptoms.
TBUT indicates fluorescein tear break-up time; MGD, meibomian gland disease.
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glands, and non-Sjögren dry eye.[29] Sjögren's syndrome affects up to 4 million Americans, the vast majority of whom are women.[31] About 10% of patients with clinically significant dry eye have an underlying Sjögren's syndrome.[32,33]

Dysfunction of the meibomian glands is the major cause of evaporative dry eye, the form most commonly associated with advanced age.[10,29] According to some estimates, MGD accounts for more than 75% of all dry eye cases worldwide.[10] While MGD is associated with a number of different diseases, age is considered to be a major risk factor.[10] Studies have shown that as the eye ages, meibomian glands develop significant structural abnormalities that affect lipid secretion. Further, the number of active glands decreases by half between the ages of 20 and 80 years.[10] Proposed mechanisms of MGD in the aging eye may include decreased androgen and growth hormone production, increased insulin resistance, loss of stem cell function, and progressive gland obstruction with subsequent downregulation.[10] MGD is also found in patients with Sjögren's syndrome.[10,29]

Pathologies of the lacrimal glands observed in older people can also lead to dry eye.[29] In addition, many common medications used by the elderly can promote or exacerbate dry eye; medication use as a contributing factor to dry eye is likely underreported. A 2007 to 2008 National Center for Health Statistics survey on prescription drug usage found that more than one-third (36.7%) of people at least 60 years of age used at least 5 prescription drugs daily, and more than 75% used at least 2 daily.[34] Many drugs commonly used by the elderly are known to be associated with symptoms of both dry eye and dry mouth.[35] These include various medications (eg, anticholinergics, diuretics, opioids, sedative/hypnotics, antiandrogens) for depression, prostate symptoms, anxiety, pain, hypertension, cardiac arrhythmias, and many other medical conditions.

Conclusion

The aging eye undergoes numerous physiologic changes that make it more susceptible to disease. The prevalence of these conditions and the vision loss they cause will continue to increase in the United States as baby boomers age. Current treatment options for glaucoma, AMD, DR, and dry eye disease are discussed in the second article of this supplement.

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revision of the manuscript for important intellectual content (EKA, RAS); and supervision (EKA).

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