SLOW AMD PROGRESSION

Early detection continues to be essential in preserving patients' vision.

BY SHERROL A. REYNOLDS, OD, FAAO

Age-related macular degeneration (AMD) is a complex and progressive retinal disease. An estimated 11 to 15 million people have some form of AMD in the United States, and that number is expected to increase to 22 million by the year 2050.[1,2] AMD is the most common cause of irreversible vision loss in the elderly; advanced forms of the disease account for more than 90% of the cases of legal blindness in this country.[3]

The aging population has rendered AMD a major public health concern. The accurate and timely identification of affected and at-risk patients is critical to preserving vision, but underdiagnosis remains a problem. The disease can go undetected in a large percentage of patients in the primary eye care setting.[4]

CURRENT UNDERSTANDING OF AMD DEVELOPMENT AND PROGRESSION

AMD is classified into three separate stages: early, intermediate, and late, based on the severity of symptoms, the number and size of drusen, hyper-or hypopigmentary changes, and the presence or absence of choroidal neovascularization (Figure 1 and Table).[5]

Several factors contribute to a person's risk of developing AMD and experiencing disease progression. Nonmodifiable risk factors include age, ethnicity, sex, family history, the presence of AMD in the fellow eye, and genetics. Modifiable risk factors include obesity (body mass index ≥ 30); smoking and vaping; chronic exposure to UV and blue light; poor nutrition; and cardiovascular conditions such as diabetes, hypercholesterolemia, and hypertension (see *Risk Factors for AMD*).[6]

Genetics

Several genetic variants contribute to the pathogenesis of AMD. Complement factor H and age-related maculopathy

AT A GLANCE

- Home monitoring devices can detect a transition from dry to wet AMD.
- Macular pigment optical density testing can help identify individuals at risk of AMD and its progression and gauge the effects of dietary changes and nutritional supplementation.
- Fundus photography, fundus autofluorescence, OCT, and OCT angiography have become essential for documentation and for managing and educating patients.

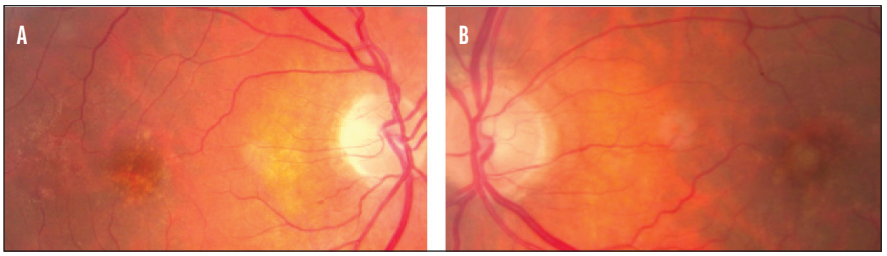


Figure 1. Based on the AREDS classification system, the right eye has early AMD (A), and the left eye has intermediate AMD (B).

susceptibility 2 genotypes significantly influence an individual's risk of developing AMD.[7,8] Genetics play a role in inflammation, lipid metabolism, extracellular matrix remodeling, and angiogenesis, and it contributes to disease progression and treatment response.[9]

The Age-Related Eye Disease Study (AREDS) 1 and 2 explored the roles of diet and nutritional supplementation in AMD pathogenesis. The intake of antioxidant vitamins (ie, vitamins C and E), lutein, zeaxanthin, and zinc slowed the progression of intermediate AMD by approximately 25% in an otherwise well-nourished population.[10-12] A 10-year follow-on study affirmed that AREDS2 eye vitamins with lutein were safe and effective.[13] Macular pigment optical density testing can help identify individuals at risk of AMD and its progression and gauge the effects of dietary changes and nutritional supplementation.

EARLY DETECTION

Subclinical AMD has structural and functional consequences before drusen, a hallmark of the disease, become evident on clinical images.[14] Functional testing, including dark adaptation with devices such as AdaptDx (MacuLogix), can detect early impairment. Dark adaptation measures the number of minutes it takes the eye to adapt after conditions change from bright light to darkness, referred to as the *rod intercept time*. Less than 6.5 minutes indicates impaired function.[15]

Evidence also suggests that lipid or cholesterol from retinal pigment epithelium (RPE) cells accumulates beneath the RPE cell layer and in Bruch membrane before drusen form.[16,17] As the disease progresses, cholesterol continues to build up, resulting in focal areas that are thick enough to be identified as drusen.[16,17] The accumulation causes inflammation and oxidative stress and disrupts the supply of oxygen and nutrition to the outer retina.[16,17]

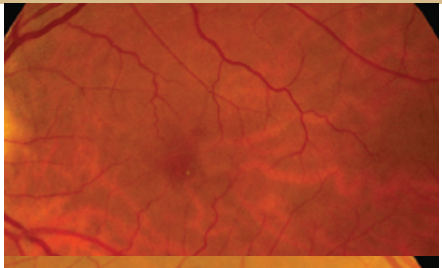
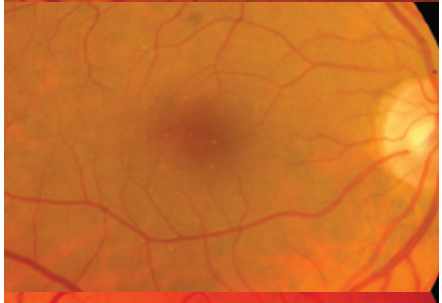
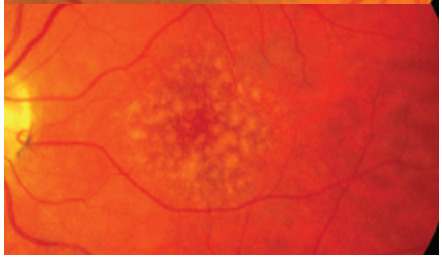
Drusen are dynamic over time. Examining the size and number of deposits guides the management of patients with early disease. Drusen formation signals RPE dysfunction, which can lead to RPE and photoreceptor death, geographic atrophy, and release of vascular endothelial growth factor (VEGF).[18] Drusen progression and regression are considered precursors to late-stage AMD. Specifically intermediate and large drusen are a risk factor for progression to advanced AMD, and drusen loss is a strong predictor of progression to geographic atrophy.[18,19]

Home monitoring devices can detect a transition from dry to wet AMD. ForeseeHome (Notal Vision) uses hyperacuity perimetry to identify changes in macular metamorphopsia that suggest a conversion to neovascular AMD.[20]

THE ROLE OF ADVANCED IMAGING

Multimodal imaging technology has improved the diagnosis and management of patients with AMD. Fundus

TABLE. The Stages of AMD

CATEGORY	CLINICAL FINDINGS	FEATURES
1 (no AMD)		No or few (five to 15) small (< 63 µm) drusen; no pigment abnormalities
2 (early AMD)		Multiple small drusen or a few intermediate-sized (63 µm - 124 µm) drusen, or macular pigmentary changes
3 (intermediate AMD)		Extensive intermediate drusen or at least one large (≥ 125 µm) drusen, or GA not involving the foveal center

Abbreviation: AMD, age-related macular degeneration; GA, geographic atrophy

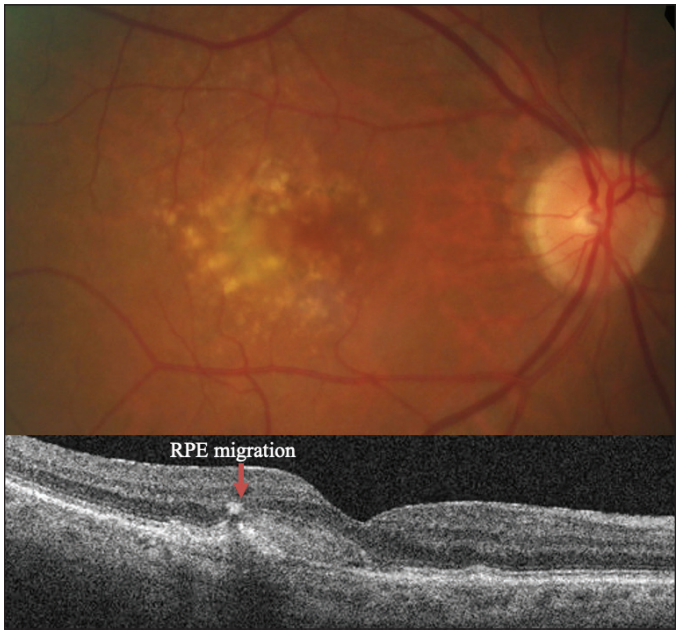


Figure 2. Intermediate AMD based on the AREDS classification system. RPE migration indicates a high risk of disease progression.

RISK FACTORS FOR AMD

- Older age (≥ 55 years)
- Sex (women are at 1.3 x greater risk than men)
- Iris color (light iris > darker iris)
- Caucasian
- Family history of AMD
- AMD in the fellow eye
- Genetics
- Smoking and vaping (the strongest environmental risk factor increases risk by 2 to 5 times)
- Prior cataract surgery
- History of cerebrovascular or cardiovascular disease
- Exposure to UV and blue light
- Obesity (body mass index ≥ 30)
- Hypertension
- Triglyceride levels
- Hypercholesterolemia
- Diabetes
- Poor nutrition

photography, fundus autofluorescence, OCT, and OCT angiography systems have become essential for documentation as well as for managing and educating patients. Early OCT findings may signify disease progression. These findings include compromised RPE integrity, disrupted photoreceptors, drusen associated with intraretinal hyperreflective foci (pigment migration; Figure 2), and the presence of hyporeflective foci within drusen (softening of the drusen).

Groundbreaking advances in AMD treatment have improved diagnosis as well. For example, the introduction of injectable anti-VEGF agents shed light on the pathogenesis of vascular leakage and neovascular growth in AMD.

STILL MUCH TO BE LEARNED

Eye care providers' general understanding of AMD has improved greatly, but how the disease develops is not yet fully understood. Treatment has also advanced significantly. Intravitreal injections of anti-VEGF agents have become the standard of care. Newer options include a bispecific antibody that inhibits both the angiopoietin-2 and VEGF-A pathways and a reusable drug reservoir that allows patients with wet AMD to forego monthly eye injections.

There is no cure for AMD. Millions of Americans with the disease continue to lose vision. Moreover, there is no effective treatment for early- or late-stage dry AMD. Educating patients about AMD and the importance of yearly comprehensive eye examinations therefore remains critical. ■

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- Financial disclosures: Speaker (Allergan, American Diabetes Association, VSP Vision Care)