HOW DO I ANSWER DIFFICULT PATIENT QUESTIONS ABOUT AMD?*

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ABSTRACT

Patients who receive a diagnosis of the early or intermediate stage of age-related macular degeneration (AMD) invariably raise a multitude of questions, ranging from why it developed to the risk of blindness. These patients want and deserve informative answers, in addition to reassurance that something can be done to preserve vision. Most questions tend to cluster around causes and risk factors, the use of nutritional supplements, the risk of vision loss, the effect of general surgery or surgery for other eye conditions on risk of AMD progression, and treatment. This article addresses questions that patients frequently ask and reviews available data to ensure that the questions are answered as adequately and completely as possible. The article also provides practical advice for the comprehensive ophthalmologist and the patient to encourage lifestyle changes, reduce risk, and preserve vision. (Adv Stud Ophthalmol. 2007;42[2]:43-48)

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Very important aspect of clinical practice, regardless of medical specialty, is to answer questions posed by patients. Whether a question is directly related to the patient’s clinical condition or deals with an ancillary issue, such as the cost of treatment, or whether it is simple or complex, it should be addressed, with the answer based on the best data available.

When an ophthalmologist tells a patient that he or she has the early or intermediate stage of age-related macular degeneration (AMD), the patient invariably has questions, often a series of difficult questions (Sidebar). In this scenario, it is important for the ophthalmologist to bear in mind that the questions are not only requests for informative answers, but also an opportunity to counsel patients about reducing risk, slowing or preventing progression to advanced AMD, and preserving vision.

Most questions often fall into 1 of 5 categories: causes of and risk factors for AMD; use of nutritional supplements; risk of vision loss; impact of surgery, particularly cataract surgery, on AMD; and current and investigational therapies. This article addresses the most frequently asked questions within each category, reviews available data, and provides valuable practical advice that comprehensive ophthalmologists can use when counseling patients with AMD.

CAUSES AND RISK FACTORS

Although the wording varies from patient to patient, virtually all patients with a diagnosis of AMD ask about its causes and whether anything can be done to prevent its progression.

As shown in the Table, there are numerous risk factors for AMD. Some, such as age, gender, family history, and smoking, consistently have had a positive
association, suggesting a role in the pathogenesis of AMD. Others, such as excessive exposure to sunlight, have had inconsistent or weak association with AMD in epidemiologic studies. Similarly, some risk factors, such as cigarette smoking and consumption of a high-fat diet, are amenable to modification that might decrease the risk in some individuals, whereas others, such as age and family history, are not. Given this roster of risk factors, ophthalmologists should encourage their patients with the early or intermediate stage of AMD to focus on modifiable risk factors to optimize outcomes coupled with an explanation of how associations are not necessarily “cause and effect.”

**GENETICS AND AMD**

Because many chromosomes in the human genome have been implicated in AMD, many genes could be involved in its development. However, the expression of these genes may be affected by their exposure and response to environmental influences, such as diet. Because siblings and other relatives of individuals with AMD share a common gene pool and similar environmental influences, they too are at increased risk for the condition.

However, an important point is that some genes are positively associated with AMD, whereas others, including those responsible for other conditions affecting the macula or choroid, are negatively associated with AMD (ie, conferring lower risk) or not associated with AMD at all. Specifically, the gene for Doynes’ familial honey-combed choroiditis is negatively associated with AMD, whereas the autosomal dominant gene for Best’s disease (which occurs during the first few years of life and is also known as heredodamacular degeneration, vitelliform degeneration of the macula, and cystic heredodamacular degeneration) is not associated with AMD. Similarly, the apolipoprotein E (apoE) epsilon4 allele is associated with a lower risk for AMD\(^1\) and could play a protective role in the pathogenesis of the disease,\(^1\) but the apoE epsilon2 allele is associated with a slightly increased risk.\(^2\)

For the patient with the intermediate stage of AMD who asks about developing “wet” AMD “just like my mother did,” the answer is a simple “probably.” However, the intermediate stage of AMD is a spectrum disease, with a higher point score on the clinical severity scale developed by the Age-Related Eye Disease Study (AREDS) investigators carrying a higher risk of pro-

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<th>Table. Risk Factors for AMD</th>
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<tr>
<td>Female gender</td>
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<td>Light iris color</td>
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<td>Family history</td>
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<td>Hypertension*</td>
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<td>High-fat diet; obesity*</td>
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<td>Low carotenoids*</td>
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<td>Elevated cholesterol*</td>
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\(^*\) = modifiable; (?) = questionable, or conflicting data; AMD = age-related macular degeneration.
gressing to advanced AMD than a lower point score. Therefore, the ophthalmologist might want to frame the answer in terms of percentage risk for that particular patient and avoid using terms such as “dry AMD,” a “mild form of AMD,” or “wet AMD.” At this time, the ophthalmologist also encourage the patient to quit smoking, adopt a low-fat diet, and make other lifestyle changes to reduce the risk of progression.

**Environmental and Other Risk Factors**

In addition to questions about smoking and diet, which are addressed later in this article in the section on nutritional supplements, patients frequently ask about risk factors, such as exposure to sunlight, iris color, and skin pigmentation.

Prompted by earlier reports that sun exposure might be a risk factor for AMD, the investigators involved in a recent study of 445 patients with end-stage AMD found no association between AMD and sun exposure or related factors, such as iris color, change in iris color, or hair color at age 20 years. However, the investigators did find an association that reached borderline significance between skin prone to sunburn and geographic atrophy.

In contrast, the Beaver Dam Eye Study found associations between both sun exposure and iris color and the 10-year incidence of AMD. In examining the effects of sunlight exposure and skin sensitivity to sunburn on the macula, the study investigators found a significant association between extended exposure to the summer sun (ie, >5 hours a day when study participants were in their teens, their 30s, and at baseline vs <2 hours a day during the same time interval) and the 10-year incidence of early AMD and increased retinal pigment. The use of a hat and sunglasses when study participants were in their teens and 30s protected against the 10-year incidence of soft indistinct drusen and retinal pigment epithelial depigmentation, but only in participants who reported the highest amount of sun exposure during their teens and 30s.

Although the latter findings do not demonstrate that sunglasses protect all patients against AMD, they do support a recommendation to wear sunglasses—and a hat, primarily to protect the skin against sun damage—when outdoors, particularly if they live in an area with plenty of sunshine. The only caveat to patients who ask about wearing sunglasses is that they avoid sunglasses with blue lenses. Blue wavelength light is strongly absorbed by the yellow xanthophyll pigment in the central macula. Thus, blue light energy is concentrated in the central macula and could damage the retinal pigment epithelium and foveal photoreceptors. However, this caveat should be tempered with a discussion that indicates there is no definitive proof that blue lenses lead to damage of the macula.

As for iris color, the Beaver Dam investigators found that people with brown eyes were significantly more likely to develop soft indistinct drusen after 10 years than people with blue eyes, but significantly less likely to develop retinal pigment epithelial depigmentation. This contrasts with other studies, which have generally found that light iris color is a risk factor for AMD. The Beaver Dam investigators also found that persons with brown hair (at 15 years of age) were at higher risk of developing pigmentary epithelial abnormalities than those with blond hair. However, neither iris color, hair color, or skin sensitivity were associated with progression to late AMD.

Patients frequently ask whether very fair skin is a risk factor for AMD. Findings from the Blue Mountains Eye Study of more than 3600 Australians suggest that it could be. Compared to study participants with fair skin, those with very fair skin were more likely to develop geographic atrophy. However, those with sun-related skin damage were less likely than those without such damage to develop soft indistinct drusen.

Another frequently asked question is whether there is an association between AMD and mortality. As noted in a report from the AREDS Research Group, 7.3% of AREDS participants with early AMD, 9.3% of those with the intermediate stage of AMD, and 14.7% of those with advanced AMD died during a median follow-up period of 6.5 years. The study clearly demonstrated that more advanced AMD was associated with a higher mortality rate, and the investigators pointed out that deaths in patients with advanced AMD were associated with cardiovascular disease. This is not a surprising finding, given that some risk factors for AMD (eg, hypertension, elevated cholesterol levels, and elevated levels of markers of inflammation, such as C-reactive protein) also play a role in atherosclerosis and coronary heart disease. This association suggests that the reduced survival of patients with AMD may reflect the systemic, in addition to the local, processes that underlie the disease. The finding of reduced mortality in study participants randomly assigned to receive zinc requires further study that might confirm or refute this finding.
NUTRITIONAL SUPPLEMENTS AND DIETARY CHANGES

RISK REDUCTION

AREDS has shown that a formulation of high-dose vitamins C and E, beta carotene, and zinc, given as 2 tablets or 1 capsule twice a day, reduces both the 5-year risk of progression to advanced AMD and the risk of losing 3 or more lines of visual acuity by nearly 25%. Patients who are skeptical about the benefit of taking a vitamin and mineral supplement to protect their eyes could be told to think of the supplement as a pill that slows the aging process in the eye. When the recommendation to take the AREDS formulation is expressed in these terms, even skeptical patients may be more likely to comply.

Similarly, patients who are uncomfortable about taking the AREDS formulation because they are already taking a number of other nutritional supplements and/or medications should at least be encouraged to take zinc. AREDS investigators found that zinc alone reduced the risk of progression by approximately 17%, with vitamins C and E and beta carotene reducing the risk by an additional 3% to 6%.

Studies of docosahexaenoic acid (DHA), an omega-3 fatty acid, have found that it reduces the risk of AMD and the development of a choroidal neovascular membrane (CNVM) by as much as 30%. More recent investigations suggest that even 1 serving a week of foods high in DHA, particularly oily fish, will reduce the risk of developing a CNVM by 30% (Unpublished observations; Emily Chew, MD). Other studies have shown that low levels of 2 carotenoids, lutein and zeaxanthin, increase the risk of AMD, but that supplementation with these micronutrients may be protective.

Given the positive findings with DHA, in addition to reports that lutein and/or zeaxanthin may protect against the intermediate and advanced stages of AMD, the AREDS Research Group has incorporated lutein, zeaxanthin, and omega-3 fatty acids into some of the study arms of AREDS-2.

With regard to nutritional supplements, such as bilberry and gingko biloba, it is not yet known whether they protect against AMD progression.

QUESTIONS REGARDING DOSING AND FORMULATION

Many patients taking the AREDS formulation complain of gastrointestinal upset, which is usually attributable to the high dose of zinc (80 mg). Although it is unknown to what extent (if any) a reduction of the zinc dosage would lead to a reduced benefit in patients with AMD, some experts feel that 30 mg or 40 mg of zinc may be sufficient (Personal communication; David Newsome, MD, November 2000). Therefore, it may be appropriate to consider a lower zinc dose in those patients who cannot tolerate 80 mg a day because of gastrointestinal upset, although there is no strong evidence to support this recommendation.

Beta carotene, which is ultimately converted to vitamin A, presents a special problem for patients with the intermediate stage of AMD who smoke cigarettes. Studies have shown that smokers who took vitamin A or beta carotene had a higher incidence of lung cancer than smokers who did not take vitamin A or beta carotene. Some people advise smokers that they should substitute lutein for beta carotene in the AREDS formulation, in addition to quit smoking; however, there is little evidence regarding the safety or efficacy of this recommendation.

Patients often ask whether they can take 1 small gel cap (containing the same vitamins and minerals as the AREDS formulation) twice a day with meals instead of the standard AREDS formulation (2 large tablets twice a day with meals). This can be a particularly important issue for patients who have difficulty swallowing or who experience indigestion after taking the large tablets. Switching to gel caps is possible, although there is no published evidence to indicate whether the absorption is similar to the tablets, such that the efficacy would be similar. However, it should increase the chance for better compliance. Patients who want to continue with tablets should be advised to use Ocuvite PreserVision (Bausch & Lomb; Rochester, NY), which was the product evaluated in AREDS, rather than plain Ocuvite (Bausch & Lomb; Rochester, NY), which is of unproven benefit.

In summary, it is unknown at this time whether taking half the recommended dose of the standard AREDS formulation is better than taking nothing, gel caps, or lutein. Neither is it known whether taking half the dose, gel caps, or lutein provides the full benefit, half the benefit, or no benefit at all. What is known is that the AREDS formulation, in addition to the doses of its components, is effective.

Patients also ask about various non-AREDS vitamin formulations and dietary modifications. Patients taking vitamins or other formulations costing approximately $400 a month should be told that there is no
Evidence that they are any more effective than the AREDS formulation. With respect to diet, patients could be advised to reduce their intake of saturated fat and eat more fruit and vegetables to improve their cardiovascular and overall health, but there is no proof this would protect their eyes.

**Risk of Vision Loss**

Patients with the intermediate stage of AMD frequently ask about their risk for vision loss and blindness. They should be reassured that their chances of going blind are extremely low as long as they take high-dose antioxidants and zinc, stop smoking, modify other risk factors to reduce the risk of progression to advanced AMD, and monitor their vision to allow detection and prompt treatment of CNV, in addition to having regular eye examinations with an ophthalmologist. In this regard, it is often helpful to quantitate each patient’s 5-year risk for progression according to the AREDS clinical severity scale for AMD. For many patients, knowing their percentage risk for progression is sufficient motivation to take the necessary steps to preserve their vision.

Even if patients with the intermediate stage of AMD do progress, treatment with agents that directly target vascular endothelial growth factor (VEGF) can usually reduce the risk of vision loss. Treatment with anti-VEGF therapy when indicated, at good levels of acuity, usually prevents the formation of large disciform scars, thereby avoiding blindness in most patients. However, on occasion, patients with advanced AMD will have massive macular hemorrhages, for which there is no proven treatment at this time.

**Impact of Surgery**

Patients with AMD and cataracts often ask if cataract surgery will accelerate the progression of AMD. This is a difficult question to answer because studies have provided conflicting results. Whereas AREDS demonstrated no association between cataract surgery and the progression of AMD, the Blue Mountains Eye Study found that patients who had cataract surgery had a higher long-term risk of developing late AMD than patients who did not have cataract surgery. Because the difference in AMD rates between the surgery and no-surgery groups was so modest, the findings can be considered equivocal. At best, they yield an answer of “maybe” to the question.

Interestingly, bariatric surgery to promote weight loss in obese patients may have an indirect adverse effect on AMD. The dramatically reduced intake of food, in addition to the impaired absorption of nutrients after bariatric surgery, may lead to inadvertent vitamin and mineral deficiencies. Therefore, all patients with AMD who have undergone bariatric surgery, or are thinking about having it, should be reminded of the importance of considering AREDS supplements, and their potential benefit for AMD.

**Current and Investigational Therapies**

At present, treatment of the intermediate stage of AMD consists of nutritional supplements formulated by AREDS, considering smoking cessation, and modification of other risk factors such as obesity, hypercholesterolemia, and hypertension to prevent progression to advanced AMD. Neovascular AMD is currently treated with intravitreal injections of anti-VEGF agents, such as pegaptanib, ranibizumab, and bevacizumab.

However, for patients with neovascular AMD that has progressed to large disciform scars with marked decreased vision, there are no effective therapies at this time. When these patients ask about current or investigational treatment options, the answer is uniformly negative. Vitamin/mineral supplements and ranibizumab provide little help, and macular translocation is associated with poor results except in the most expert hands. Retina transplants, which are actually implants of preserved photoreceptors, are not yet available.

The “retina chip” has generated considerable excitement among ophthalmologists and many inquiries from patients. Thus far, it has been used only in patients with retinitis pigmentosa, but technical advances are being made. However, use of the retina chip in AMD is not imminent, and to imply that it is would be giving patients hope that is simply not present at this time.

**Aspirin and Warfarin**

Many patients with AMD ask about therapy with aspirin or warfarin for other conditions, and whether either drug will increase the risk for retinal hemorrhage. With respect to aspirin, the ophthalmologist should first ascertain why the patient is taking it and what dose is being taken. Patients who take 1 or 2 high-dose (325 mg) tablets a day on the advice of a
friend or relative, who typically declares that “it’s a good idea” or “it’s good for your heart,” should be told to cut back to 1 baby aspirin a day; 81 mg/day does not pose a problem for patients with AMD.

As for warfarin, it should be continued as long as the international normalized ratio is monitored and within the appropriate range for the condition for which it was prescribed (eg, pulmonary embolism, thrombophlebitis, and atrial fibrillation).

**CONCLUSIONS**

When patients ask questions about AMD, ophthalmologists should provide direct and realistic answers that are based on the most current and complete data available. If no data or only equivocal data are available, the ophthalmologist should say so, and then use his or her best judgment in advising the patient.

It is particularly important for the ophthalmologist to counsel the patient about risk factors that can be modified (Table) and to assure the patient that the situation is not hopeless. Even if 1 eye is severely affected, scrupulous attention to risk factor modification, vigilant monitoring of the other eye, and appropriate treatment might preserve vision.

Early detection, frequent monitoring of changes in visual acuity, and the availability of anti-VEGF therapies can stabilize or even improve vision and minimize the loss of visual acuity. These strategies represent major progress over the past 3 or 4 years and foreshadow additional progress yet to come.

**REFERENCES**


