Published in final edited form as:
Acta Hortic. 2009 August 31; 841: 103–112.

Nutritional Interventions against Age-Related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible visual loss in the developed world. This disease of the elderly robs them of central vision in one or both eyes leading to a devastating loss of the ability to drive, read, and recognize faces. In recent years, a number of novel treatments for the neovascular form of AMD (also known as “wet” or exudative AMD) have been introduced, and for the first time, the relentless downhill course of vision loss experienced by the majority of patients with this particularly malignant variant of AMD has been transformed to the stabilization and even improvement of vision in at least two-thirds of patients. Likewise, the slower, more insidious form of AMD known as dry AMD which leads to geographic atrophy of the macula has become the focus of pharmaceutical firms’ efforts for intervention. Unfortunately, all of these novel treatments have limitations, and they tend to be very expensive. Thus, prevention of AMD is of paramount importance to reduce the healthcare burden of this blinding disorder. Accumulating evidence suggests that encouragement of increased consumption of fruits and vegetables rich in the xanthophyll carotenoids lutein and zeaxanthin is a simple, cost effective public health intervention that might help to decrease the incidence of AMD. In this review article, the scientific underpinnings for these nutritional recommendations will be surveyed.

Keywords

retina; macula; carotenoid; lutein; zeaxanthin; nutrition

EYE ANATOMY

The human eye is the primary sensory organ for collection of visual information from our environment. Light rays initially pass through the cornea, the clear avascular tissue at the front of the eye where the first stage of refraction required for focused light perception occurs. The light then passes though the anterior chamber which is filled with clear aqueous fluid continuously made by the ciliary body. This fluid eventually exits the eye through the trabecular meshwork in the angle of the anterior chamber where the peripheral cornea meets the iris root. Light proceeds through the variably sized pupil of the eye formed by the iris, a muscular diaphragm that can dilate and constrict in response to varied levels of ambient light. Next, light is further refracted by the eye’s crystalline lens which is suspended by threadlike zonules attached to the ciliary body whose circularly arranged sphincter muscle fibers vary the shape of the lens allowing for fine focusing and accommodation. Focused light then passes through the clear vitreous gel until it finally reaches the retina, the thin but exquisitely organized neural tissue lining the back of the eye. Here, the photons of light are absorbed by light-capturing proteins in the photoreceptor cell outer segments known as opsins which bear a vitamin A-based chromophore in their active sites that isomerizes from a high energy 11-*cis* configuration to a lower energy all-*trans* form. This initiates a transduction cascade that amplifies the signal and eventually leads to hyperpolarization of the photoreceptor rod and cone cells. Hyperpolarization alters neurotransmitter output from the cells which is detected and processed

within the retina by intermediary cells such as the bipolar, amacrine, and horizontal cells and eventually communicated to the retina's ganglion cells whose axons exit the eye via the optic nerve to the brain. More distal to the photoreceptors is the retinal pigment epithelium (RPE), a monolayer of supportive cells resting on a basement membrane known is Bruch's membrane. The RPE phagocytoses and digests the shed tips of photoreceptor outer segments, isomerizes vitamin A to the active 11-*cis* configuration, and maintains the health of the outer retina.

The macula is the central area of the retina responsible for high acuity vision required for reading, driving, and recognizing faces. It encompasses only 4% of the retina's area, but loss of macular function will lead to 20/200 vision or worse. On the other hand, as long as peripheral vision is preserved, individuals can still easily navigate around a room without the aid of a cane or dog. The macula is about 5.5 mm in diameter and is defined as the region in which the ganglion cell layer is only one cell thick. Its center, the fovea, is especially rich in cone photoreceptors responsible for color vision.

CLINICAL CHARACTERISTICS OF AGE-RELATED MACULAR DEGENERATION (AMD)

Age-related macular degeneration is the leading cause of irreversible visual loss in the developed world. Depending on the definition of the disease, up to 20 million Americans have at least the early stages of AMD. The earliest signs of AMD are known as age-related maculopathy (ARM) and are characterized by the appearance of drusen, subretinal deposits of oxidized lipids and proteins beneath the retinal pigment epithelium as well as variable amounts of visible clumps of pigment in the macula. At this point, the patients are generally asymptomatic with 20/20 vision. In the intermediate stages of AMD, drusen become larger, and pigmentary changes are more severe. In the advanced stages of AMD, patients either develop subretinal neovascularization in which blood vessels from the choriocapillaris break through Bruch's membrane and invade the subretinal or sub-RPE space where they bleed and leak fluid (the exudative or "wet" form of AMD) and ultimately cause permanent loss of macular vision, or else patients develop the advanced "dry" form of AMD in which RPE and photoreceptor cells slowly die leaving behind sharply demarcated regions of dysfunctional macula known as geographic atrophy (GA). Wet AMD accounts for 10–15% of AMD, yet it is responsible for 90% of AMD-related blindness. A recent estimate by the National Eye Institute indicates that 1.75 million Americans have advanced AMD in at least one eye, and about 7.3 million have intermediate AMD and are therefore at high risk for progression to advanced AMD (National Eye Institute, 2004).

One of the first symptoms that patients may notice with AMD progression is distortion of straight lines which can be readily perceived on an Amsler grid, a checkerboard-like chart given to patients for home-testing. Patients are instructed to contact their eye-care provider if new distortion is noted in order to arrange to have a prompt dilated eye examination to look for declines in visual acuity and to assess whether or not there are signs of progression to advanced AMD such as the presence of blood and fluid in the macula or if geographic atrophy is beginning to affect the fovea. If progression is suspected, then imaging tests are generally performed including intravenous angiography with fluorescein or indocyanine green dyes to define the extent of choroidal neovascularization, optical coherence tomography (OCT) to look for macular thickening and pockets of intraretinal, subretinal, and sub-RPE fluid, and autofluorescence imaging to better define the borders of GA and to look for hyperfluorescent borders where GA is likely to progress next.

TREATMENT OF ADVANCED AMD

The treatment of advanced AMD has undergone dramatic improvements in the past two decades, especially for the exudative form. Initial approaches included argon laser photocoagulation of the choroidal neovascular membranes, but recurrences were common, and collateral damage to normal macular structures was unacceptably high. Thus, newer, less damaging laser-based treatments such as photodynamic therapy (PDT) were introduced in the past ten years in which photosensitizing dyes designed to concentrate in neovascular tissue were administered intravenously and then irradiated with low-power red laser light to close down the abnormal vessels. PDT was definitely an improvement over the natural history of AMD, but few patients exhibited visual improvement. Various surgical and radiotherapy approaches to wet AMD were also investigated at this time, including external beam radiation, subretinal surgery to extract choroidal neovascular membranes, and macular translocation to move the fovea to a less damaged area of the RPE. In the end, however, these other treatments never became popular because of poor efficacy or unacceptably high rates of complications.

More recently, treatment of wet AMD has entered the anti-angiogenic era in which biological molecules designed to block signals to grow new blood vessels are injected into the eye. The most successful of these angiogenesis inhibitors is ranibizumab (Lucentis), an antibody fragment genetically engineered by Genentech to block vascular endothelial growth factor (VEGF), the prime biological mediator of pathological angiogenesis in the eye. For the first time, the majority of wet AMD had visual stabilization, and about one-third had significant and sustained improvement of vision (Rosenfeld et al., 2006), but the cost was high. The drug costs over $2000 per dose and has to be administered by monthly injections directly into the vitreous cavity of the eye. Additional competing anti-angiogenic drugs are currently in clinical trials and will undoubtedly be comparably priced, but it is hoped that dosing could be much less frequent.

Treatments for advanced dry AMD have not progressed nearly as quickly as those for wet AMD. Plasmapheresis, a blood filtration technique to remove toxic metabolites systemically, has not been proven to be successful. Small molecule inhibitors of formation of lipofuscin, a highly fluorescent combination of oxidized lipids and retinoids, are in pre-clinical and early human trials, and a porous intravitreal implant that houses RPE cells transformed to secrete high levels of beneficial growth factors is in phase 2 trials. Thus, optical methods to augment residual visual acuity through magnification and use of eccentric fixation, external low vision aids, and experimental implantable intraocular telescopes still play an important role in these dry AMD patients as well as wet AMD patients who have failed current treatments.

RISK FACTORS FOR AMD

Since advanced AMD is a challenging and expensive disorder to treat successfully, it is clear that prevention or delay of its onset could have important public health implications. Much has been learned in the past few decades of risk factors for AMD. AMD is a quintessential disease of aging. While only 2% of 50–60 year-old have AMD, the disease prevalence rises exponentially with increasing age such that over 30% of individuals over age 75 exhibit some form of AMD (Eye Disease Prevalence Research Group, 2004). Heredity is known to play an important role as an AMD risk factor, with major risk loci on chromosome 1 in the complement regulatory genes (Hageman et al., 2005) and on chromosome 10 in the promoter region of the *HTRA1* gene (Yang et al., 2006). Knowledge of these genetic loci should permit development of targeted drugs to treat and possibly even prevent AMD. Other less important demographic AMD risk factors include female sex, light skin pigmentation, and light iris pigmentation.

All of the risk factors listed above are essentially unmodifiable, so current pubic health preventative strategies have focused on modifiable lifestyle risk factors. Foremost among these

is smoking prevention, as epidemiological studies have consistently demonstrated elevated risk of AMD in smokers, presumably as a result of excessive oxidative load and microvascular damage associated with smoking. Risk of cardiovascular disease and AMD are strongly correlated, so proven strategies to reduce cardiovascular disease such as control of hypertension, consumption of moderate amounts of red wine, and modification of blood lipid status, are likely to be beneficial for reducing AMD risk as well. Excessive visible light exposure at the levels encountered by fishers and others who have chronic daily exposure to high light intensities has been shown to be associated with risk of AMD (Taylor et al., 1992), but less intense exposures of everyday life for the general population are less certain to be a risk factor, yet the simple act of donning sunglasses is still prudent advice to those who wish to lessen the possibility of visual loss due to AMD. Finally, a variety of nutrients have been linked to risk of AMD, and these will be the focus of the remainder of this review.

NUTRITION AND AMD

It has long been suspected that antioxidant nutrients may play a role in ameliorating risk for AMD because the retina and the RPE have very high percentages of very unsaturated lipids that are susceptible to oxidative damage in a region of the body that has elevated exposure to light and oxygen. The protective role of antioxidants has been difficult to prove definitively, however, because AMD is a slowly progressing, complex disorder mediated by many interacting factors. Multiple investigational methods have been employed to approach this problem. Epidemiology can assess the association of nutrient intake and risk of AMD in large populations through case-control and cohort studies, providing a mechanism to focus further investigations and interventions. Animal studies of nutrients, likewise could be useful, but there are few, if any, generally accepted animal models that sufficiently mimic the human condition. Basic physiology and biochemistry studies can be used to demonstrate that the nutrient in question is found in appropriate quantities in the macula, that its physiological mechanisms are plausible, and that deficiency states are in some cases associated with higher risk of AMD. Ultimately, well designed randomized, placebo-controlled clinical trials may be required to provide definitive recommendations that are widely accepted by the clinical community.

A variety of nutrients have been epidemiologically linked with decreased risk of AMD. These include the antioxidant vitamins such as vitamins C, E, and A, and the minerals zinc and selenium that can act as co-factors for a number of endogenous antioxidant enzymes. The omega-3 fatty acids which are obtained from fish and certain vegetable oils are essential building blocks for the photoreceptor membranes, and several epidemiological studies have indicated that diets rich in these particular lipids are associated with decreased risk of AMD. Polyphenols and related compounds are powerful antioxidants found in berries such as bilberry and in red wine that have been promoted by the health food industry as healthy for the eyes. Unfortunately, the current epidemiological evidence for these claims is not very strong, and they are usually found in only trace amounts in the retina. The xanthophyll carotenoids lutein and zeaxanthin are of particular interest because not only are they specifically concentrated in the human macula, but also several large independent epidemiological studies have indicated a protective role against AMD. These studies will be discussed in more detail below.

XANTHOPHYLL CAROTENOIDS AND AMD

Carotenoids are members of a very large family of polyene compounds produced exclusively by plants and microorganisms. They generally share a common $C_{40}H_{56}$ core structure, and if they have one or more oxygen atoms, they are referred to as xanthophylls. Well over 600 carotenoids are found in nature, and humans consume on the order of 50–75 in the normal diet. Only about fifteen of these dietary carotenoids are detectable in the bloodstream, however, and just two carotenoids, the xanthophylls lutein and zeaxanthin and their metabolites, are present

in the human macula. These yellow colored compounds derived exclusively from the diet are found in such high concentrations (~1 mM) in the Henle fiber (cone axon) layer of the foveal region that the formal anatomical name of the macula is the *macula lutea* or "yellow spot." The selective uptake of lutein and zeaxanthin is driven by specific binding proteins expressed at high levels in the macula (Bhosale et al., 2004). Levels of the macular pigment are determined in part by dietary intake, but the relationship is complex, probably due to saturation of the specific macular binding sites at high levels of intake. Lutein is found in especially high levels in dark green leafy vegetables such as spinach, kale, and broccoli, while zeaxanthin is less common in the human diet, mainly in certain orange-yellow fruits and vegetables such as corn, mandarin oranges, and orange peppers (United States Department of Agriculture, 1998). The typical American diet provides 1–2 mg per day of lutein and zeaxanthin, usually in a 5:1 to 10:1 ratio, but high consumers of fruits and vegetables can easily ingest 6–10 mg or more of these two carotenoids per day.

The macular carotenoids are thought to protect against AMD by two different mechanisms - light screening and antioxidant. The macular carotenoids absorb blue light, the most phototoxic light to which the retina is routinely exposed, and their anatomical localization and deep yellow color are ideal for them to act as an optical filter for blue light. An animal study reported in abstract form indicates that primates raised on carotenoid-free diets are more susceptible to blue light induced damage (Barker et al., 2005). Lutein and zeaxanthin are also efficient quenchers of singlet oxygen and related reactive oxygen species, but it is debatable whether or not they are located close enough to the photoreceptor membranes most at risk for oxidative damage from the high levels of light and oxygen in the macula. A study of human autopsy eyes reported that AMD eyes have ~30% lower levels of macular pigment than age-matched normal controls (Bone et al., 2001), and monkeys made severely deficient in carotenoids exhibit pigmentary changes reminiscent of human age-related maculopathy (Malinow et al., 1980).

The first strong epidemiological evidence that lutein and zeaxanthin may be protective against AMD was published in the early 1990s by the Eye Disease Case-Control (EDCC) Study Group. They initially found in 421 cases and 615 controls that there was an inverse correlation between serum carotenoid levels and risk of exudative AMD (Eye Disease Case-Control Study Group, 2003). In a follow-up study of a subset of these same patients, they found that dietary consumption of fruits and vegetables rich in lutein and zeaxanthin was associated with a 43% decrease in risk of AMD, while diets rich in beta-carotene which is not found in the retina and which cannot be converted to xanthophylls were not protective (Seddon et al., 1994). As commonly encountered in epidemiology, subsequent studies have not always reached these same conclusions, in part due to different methodologies and population characteristics, but it is notable that a recently published very large study of 4519 Age-Related Eye Disease Study (AREDS) patients, well characterized clinically and by extensive dietary surveys, came to the same significant conclusions for all types of intermediate and advanced AMD (Age-Related Eye Disease Research Group, 2007).

All of the clinical studies discussed above measured either dietary intakes or serum levels of lutein and zeaxanthin, but these are, at best, indirect measures of macular carotenoid levels. Therefore, we and others have developed a variety of methods to measure macular carotenoid levels non-invasively in clinic populations. Using resonance Raman spectroscopy, we measured macular carotenoid levels in 93 eyes from 68 AMD patients and compared them to 73 normal eyes from 52 age-matched control subjects. We found that macular carotenoid levels were significantly lower (32%) in AMD subjects relative to controls as long they were not regularly consuming high-dose (4–40 mg per day) lutein supplements (Bernstein et al., 2002). AMD patients who had begun to take lutein supplements regularly after having been diagnosed with AMD had macular pigment levels that were back in the normal range. These results are compatible with the previously mentioned autopsy study and consistent with the

hypothesis that AMD is in part a manifestation of a dietary deficiency of lutein and/or zeaxanthin.

More recently, we have addressed the question of whether or not carotenoid supplements and diets unusually rich in carotenoids actually increase levels in the eye. This is particularly important because most studies have shown only relatively weak correlations between blood levels and noninvasive measurements of macular pigment, and supplementation studies have generally demonstrated rather modest and variable macular responses to high-dose lutein and/or zeaxanthin supplementation. Some of the difficulties arise from the methods used to measure macular pigment in clinical studies, most of which measure foveal macular pigment levels relative to a peripheral reference point several millimeters or more away from the fovea where carotenoid optical density is assumed to be zero. There is abundant evidence from autopsy eye studies of unsupplemented humans and monkeys that this assumption is indeed correct as long as the reference point is chosen to be sufficiently distant from the fovea, but this assumption may not be valid in the face of high-dose, long-term supplementation. In fact, if peripheral levels rise sufficiently, then true foveal rises of macular pigment in response to supplementation measured by these methods may be missed or even fall artifactually. To investigate this problem, we undertook a new autopsy eye study now that lutein supplementation has become popular in the Utah population. We examined 228 eyes from 147 Utah cornea donors free of any history of eye disease and performed HPLC analysis of lutein and zeaxanthin in the macula, peripheral retina, and lens (Bhosale et al., 2007). We noted that approximately 20% of the older half of the population age 48 or older had extraordinarily high levels of macular carotenoids, more than double the rest of the population's average level. No similar outliers were observed in the younger half of the population. When we contacted the outliers' families, we found that 14 of the 17 outliers regularly consumed a daily lutein supplement (2.5–10 mg/day). The rest of the outliers' families reported that they regularly consumed a diet unusually rich in carotenoids. Zero of 20 age-matched non-outliers' families reported regular lutein supplementation or a carotenoid-rich diet prior to death ($P < 0.001$). Lutein levels were also elevated up to 10-fold in the peripheral retina and lens of the outliers' eyes, sufficient to cause artifactual underestimates of macular pigment levels by most of the currently employed methods to measure macular carotenoid levels in living humans. Not only did this study demonstrate conclusively that carotenoid supplementation or diets rich in fruit and vegetable carotenoids can increase macular pigment levels, but it also provided insight into why many clinical studies have had difficulty demonstrating this phenomenon.

THE AGE-RELATED EYE DISEASE STUDIES (AREDS)

Ophthalmologists generally require a rigorous level of scientific evidence before recommendations for treatment and prevention of AMD become standard of care. Either the epidemiological evidence must be compelling and nearly unanimous across multiple epidemiological studies as it is for smoking and risk of AMD, or else large, long-term, prospective, randomized clinical trials must be conducted. Such interventional randomized trials are nearly impossible to perform with regard to fruit and vegetable consumption due to variability in diets, difficulty in enforcing long-term compliance with assigned diets, and the inability to use placebo controls or to mask subjects as to their assigned intervention. Thus, defined supplements are usually required, and then dietary recommendations can be inferred from the results.

Current clinical practice among AMD specialists is guided by the original AREDS study whose key results were published in 2001 (Age-Related Eye Disease Research Group, 2001). This multi-center study followed 4757 subjects 55–80 years old for at least five years. They were divided into four categories. Categories 1 and 2 were considered to be low risk for progression to severe visual loss (~1% risk in five years) and were not the primary focus of the supplement

intervention. Category 1 subjects had no drusen or a few small drusen and good visual acuity (better than or equal to 20/32), and Category 2 subjects had pigment abnormalities and non-extensive small or intermediate drusen with good visual acuity. Categories 3 and 4 were considered high risk for progression to advanced AMD (~30% risk in five years) and were prime candidates for the study of a nutritional intervention. Category 3 subjects had extensive intermediate-sized drusen, at least one large druse, or non-central geographic atrophy with preserved central acuity of 20/32 or better in both eyes. Category 4 subjects had good acuity and no advanced AMD in the study eye and advanced AMD in the fellow eye (choroidal neovascularization or central geographic atrophy) or visual acuity worse than 20/32 due to AMD in the fellow eye. The primary outcome measures were progression to severe visual loss (three or more lines of visual loss) in at least one eye due to advanced AMD or cataracts.

All AREDS patients were allowed to take a basic multi-vitamin (Centrum Silver) and they were then randomized to one of four intervention arms. One arm was randomized to high dose zinc oxide and cupric oxide (80 mg/day and 2 mg/day, respectively) along with an antioxidant mixture consisting of 500 mg/day of vitamin C, 400 international units (IU) of vitamin E per day, and 15 mg/day (25,000 IU/day) of beta-carotene. The second arm was randomized to high-dose zinc and copper but no antioxidants, and the third arm received high-dose antioxidants but no minerals. The fourth arm was assigned to placebo pills only. The results released in 2001 demonstrated a significant reduction in AMD progression in Category 3 and 4 subjects assigned to high-dose minerals and/or antioxidant vitamins (~25 decreased risk of progression at five years). There was no difference in cataract progression for any of the treatment groups. Although the reduction of AMD progression risk was modest, the public health implications were enormous since millions of people in the United States met the criteria for high risk of AMD progression, and recommendation of AREDS compliant formulas to at risk patients rapidly became the standard of care in ophthalmology.

The original AREDS formulation was based on the best nutritional knowledge of the late 1980s when the study was conceived, but it was clear at the conclusion of the study that additional optimization could be achieved. The emerging importance of lutein and zeaxanthin from both epidemiological and basic science studies suggested that they should be added to the AREDS formula perhaps in conjunction with a reduction of beta-carotene which had been linked with an elevated risk of lung cancer in smokers, and fish oil rich in the omega-3 fatty acids EPA and DHA likewise was a promising potential addition to the AREDS recommendations. The AREDS 2 study was initiated in 2006 to study the effects of high-dose xanthophylls (10 mg/day of lutein and 2 mg/day of zeaxanthin) and/or 1000 mg/day of fish oil in subjects age 50–85 at high risk for AMD progression (large drusen in both eyes or advanced AMD in one eye and large drusen or non-central geographic atrophy in the fellow eye). AREDS 2 is similar in scale to the original AREDS study with 4000 subjects who will be followed for five years at 100 sites. All subjects are encouraged to take the original AREDS formulation although some will have zinc and/or beta-carotene at reduced levels. Obviously, results will not be released until sometime in the next decade, but it is hoped that they will have an impact on AMD clinical practice similar to that of the first AREDS study.

GENERAL RECOMMENDATIONS FOR INDIVIDUALS AT RISK FOR AMD

In my clinical practice, I am commonly asked for nutritional recommendations by patients with high-risk AMD and by patients with low risk of imminent visual loss but who are worried nonetheless because of family history, advancing age, affected friends, or media attention. My first recommendation is always to encourage consumption of a healthy diet rich in multiple daily servings of colorful fruits and vegetables rich in lutein and zeaxanthin along with several weekly servings of fish. Not only is this sort of diet associated with decreased risk of AMD, but it is also likely to have many other health benefits such as decreased risk of cancer and

cardiovascular disease. For those patients who meet AREDS criteria for high risk of AMD progression, I always recommend an AREDS type supplement (without beta-carotene if they smoke), and I encourage them to consider supplementation with lutein and/or zeaxanthin at 6–10 mg/day and fish oil at 1000 mg/day because I think the basic science and epidemiological studies are strong enough and their safety is sufficiently proven to use in advance of the release of any AREDS 2 results. For those patients who do not meet AREDS criteria for high risk of AMD progression, I inform them that supplements are optional because their benefits are still unproven for them, and I reinforce the importance of maintaining a healthy diet. I offer similar cautionary advice to patients who wish to consume herbal supplements whose eye heath benefits are unproven, such as bilberry, eyebright, and gingko biloba, telling them that no rigorous scientific studies have been performed yet. I counsel all of my patients not to smoke, to use alcohol in moderation, to avoid excessive fat intake, and to use sunglasses on bright sunny days. Finally, for those patients who meet AREDS 2 eligibility, I encourage enrollment in the research study even if it may mean assignment to a low carotenoid or omega-3 fatty acid treatment arm because it is the only way we can bring definitive nutritional recommendations for AMD into widespread clinical practice.

Acknowledgments

This work was funded in part by an unrestricted departmental grant from Research to Prevent Blindness (New York, NY) and by NIH grant EY-11600.

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