

UPDATED EDITION

**Diagnostic & Treatment
Algorithms for
Retinal Health & Function**

Nutrition

The final part of an ongoing series

New paradigms in the understanding and
management of ocular nutrition.

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Presented by
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Dear Colleagues:

We all know the importance of eating right for our overall health, but when it comes to the role of nutrition in maintaining retinal function and preventing the progression of age-related macular degeneration (AMD), our knowledge is perhaps not so clear. To complicate matters, eye care practitioners are constantly faced with the task of sorting through the available literature in an effort to better their understanding of the ocular benefits of specific nutrients.

As the final installment of this algorithms series, this monograph breaks from the previous running topic of ocular surface disease states and focuses on ocular

nutrition, with a specific look at how diet and nutritional supplementation can improve visual function, particularly in the intervention of AMD.

Each of us has an interest in ocular nutrition and we are all honored to have been invited to contribute to this project. Our discussion, summarized here, is heavily evidence-based and full of tips, resources and frequently asked questions. We sincerely hope you find the end result to be of benefit to you and your patients. Special thanks to Bausch + Lomb for making this informative series possible.

— The Authors

About the Authors



Jeffrey R. Anshel, O.D., F.A.A.O., is the Founder of Corporate Vision Consulting as well as President and Founding Director of the Ocular Nutrition Society.



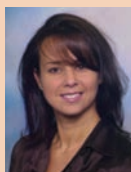
Laurie Capogna, O.D., is an active partner in Peninsula Eye Associates and is the co-author of “Eyefoods: A Food Plan for Healthy Eyes.”



Jeffrey D. Gerson, O.D., F.A.A.O., is a partner at WestGlen Eyecare in Shawnee, Kans., where he provides full-scope care. He is a well-known speaker and author in several fields within optometry.



Stuart P. Richer, O.D., Ph.D., F.A.A.O., is Director, Ocular Preventive Medicine, James A. Lovell Federal Health Care Facility, Department of Veterans Affairs in North Chicago.



Diana L. Shechtman, O.D., F.A.A.O., is Associate Professor of Optometry at Nova Southeastern University College of Optometry, where she serves as an attending optometric physician at the eye institute and diabetic/macula clinic.

PART I: Key Nutrients for Ocular Health

It is well established that a balanced, nutrient-rich diet and regular exercise are beneficial for overall human health as well as for ocular health. There is a growing interest in preven-

tive nutrition and in identifying the best dietary approaches for disease modification and for achieving optimal health. But the large quantity—and in some cases, low quality—of

information makes it difficult for clinicians to know what to recommend for their patients. Eat more carrots? Take supplements? And if so, which ones?

A committee of the National

Academy of Sciences publishes a recommended dietary allowance (RDA) for vitamins and minerals that is included on food labeling. The RDA, which originated in post-World War II efforts to prevent significant deficiency-related disease, incorrectly assumes a fairly balanced diet that is not overly high in sugar, simple carbohydrates, saturated fats, trans fats and other destructive elements. The RDA is likely far from adequate for basic health, let alone optimal performance.

In this monograph, we hope to clarify the research on the ocular benefits of specific nutrients and the state of the published literature on nutritional supplementation for ocular health. Specifically, we will address disease modification in age-related macular degeneration (AMD), for which supplementation is now standard of care for certain groups.

Some of the key nutrients for ocular health include the antioxidant vitamins A, C and E, as well as the carotenoids lutein and zeaxanthin; the minerals zinc and selenium; and omega-3 fatty acids.

Antioxidant Vitamins

Vitamin C. Vitamin C, or ascorbic acid, is the major extracellular water-soluble antioxidant. It functions within a complex antioxidant network, regenerating vitamin E and glutathione. It is critical to systemic health. While most other mammals can convert sugar to ascorbic acid, humans must obtain direct sources of ascorbic acid from the food supply.

The leading source of vitamin C in the American diet is orange juice, which—like many other foods in our society—is high in glucose. Glucose shares the same cellular transport with vitamin C and competes with it for absorption. Therefore, the more glucose in the diet, the higher the need for vitamin

retina. In fact, ocular tissue concentrations of vitamin C are 10–20 times higher than serum concentrations.

Most people recognize vitamin C as beneficial; supplementation is relatively common.

This water soluble substance is best taken throughout the day as it only has a half life of

FAQ

Q: If patients are taking an ocular-specific vitamin, is there still a role for a general multi-vitamin?

A: Probably yes. About 70% of the AREDS subjects were also taking Centrum multi-vitamins during the study, and these subjects appeared to have a decrease in overall mortality. The study demonstrated a benefit from the high-dose antioxidants and zinc regardless of whether a multi-vitamin was taken. It is important for patients to realize that quantity matters. A multi-vitamin, on its own, does not provide sufficient amounts of key ocular nutrients, but it may be a useful adjunct for general systemic health.

C. Better sources of vitamin C include whole citrus fruits, leafy greens, peppers, and broccoli.

Many experts recommend a daily vitamin C intake of at least 250-500 mg, which would require 9 to 13 fruit and vegetable servings daily. The upper end of this range is nearly impossible to obtain and even the lower end of the range requires a concerted effort. The more typical 3-serving consumption leaves most Americans mildly deficient in vitamin C.

Vitamin C is actively transported into the eye and is highly concentrated in all ocular tissues, including the cornea, aqueous, vitreous, and

30 minutes. It appears to be safe, even at high doses.

Vitamin E. The major cell membrane antioxidant is vitamin E, of which there are eight different forms. The isomer alpha-tocopherol is the most studied by the National Institutes of Health (NIH). In addition to limiting free-radical damage, these fat-soluble antioxidants play a role in immune function and metabolic processes. They are found primarily in nuts, seeds, and vegetable oils. Other food sources of vitamin E are sardines, avocados and eggs.

Vitamin E builds up in high concentrations in the retinal

pigment epithelium (RPE) of the parafovea. Along with the mineral selenium, it helps to cleanse the RPE cells. People with higher dietary intake of vitamin E have a lower risk of developing AMD.^{1,2} Supplementation with high levels of antioxidants, including vitamin E, has been shown to slow progression of AMD,³ but there are fewer reports of the benefits of vitamin E supplementation alone. In one large-scale randomized trial of female health professionals, long-term alternate-day use of 600 IU of vitamin E had no significant effect on AMD risk.⁴

Taking large doses of vitamin E with anticoagulant medications such as warfarin (Coumadin) has the remote potential to increase the risk of bleeding, especially in conjunction with low vitamin K intake. Vitamin E has also been associated with an increased risk of heart failure in people with established, severe vascular disease or diabetes.⁵

Vitamin A. Vitamin A is essential for many systemic processes, including bone growth, cell division and differentiation, and immune function. In the retina, it is converted to rhodopsin for rod vision or photopsin for cone vision; hence the adage that eating carrots (a source of one form of vitamin A) is good for the eyes.

Dietary vitamin A is available from both animal and plant sources. It is absorbed in the form of retinol from liver, whole milk, and some fortified food products. Beta-carotene and a few other carotenoids

from colorful fruits and vegetables can also be made into retinol in the body. With age, beta-carotene is less readily converted to vitamin A. In addition, if the liver stores of vitamin A are sufficient, there is no impetus for the body to convert additional beta-carotene to vitamin A, and it is instead stored under the skin.

Diets high in beta-carotene reduce the risk of AMD^{1,6} and supplementation with high-dose antioxidants including beta-carotene has been shown to reduce the risk of progression to advanced AMD.³ However, supplementation with beta-carotene alone can

with other fat-soluble nutrients such as vitamin D and the xanthophyll carotenoids (lutein and zeaxanthin) for cell transport.

Xanthophyll Carotenoids.

There are hundreds of carotenoids beyond beta-carotene. The most prevalent in the U.S. diet is lycopene, which is found in tomatoes and tomato sauce-based foods. Lycopene is important for retinal health, but is already present at healthy levels in most people.

Of greater interest are the macular pigment or xanthophyll carotenoids, lutein and zeaxanthin, which are deficient in the U.S. diet. Lutein is found naturally in leafy

Tip

Because chickens are fed lutein and zeaxanthin to make their egg yolks more yellow, eating commercially raised eggs (preferably free-range) is one way to add these nutrients to the diet. The fat in the eggs also promotes absorption of lutein.

cause a number of problems, ranging from an orange skin tone to liver or kidney dysfunction. Several studies have now shown an association between supplemental beta-carotene and an increased risk of lung cancer in smokers⁷⁻⁹ or an increase in mortality with beta-carotene supplementation.¹⁰ Eating diets rich in beta-carotene, however, does not increase the risk of lung cancer.¹¹

High levels of beta-carotene vitamin A can also compete

green vegetables and eggs. Zeaxanthin is found in orange and yellow peppers and certain berries, such as goji berries, that aren't commonly eaten in Western society.

Carotenoids in general are crucial for skin, retinal, and crystalline lens health. Lutein and zeaxanthin, in particular, are found in high concentrations in the macula, where they help to filter blue light to sharpen vision, enhance contrast, and reduce glare. The additional antioxidant capa-

bilities of these xanthophylls, combined with their ability to trap short-wavelength light may serve to protect the outer retina, RPE, and choriocapillaris from oxidative damage.¹²

Like all carotenoids, lutein and zeaxanthin are fat-soluble, so they require dietary fat for absorption and transport. Too much adipose body fat, though, inhibits transport of lutein and zeaxanthin—storing the nutrients in the fat tissue instead. Women and obese people, therefore, will have higher requirements for xanthophyll intake compared to men and thinner individuals.

A number of observational studies have indicated that dietary lutein and zeaxanthin may have a protective effect against AMD.¹³⁻¹⁸ Higher vs. lower intake of dietary lutein, for example, reduced the risk of AMD by 43% to 57%.^{13,14}

There is also an association between xanthophyll concentrations in the retina and AMD. Bone showed an 82% lower risk of AMD with higher concentrations of lutein and zeaxanthin in the retina.¹⁹ Conversely, average levels of lutein and zeaxanthin are 32% lower in eyes with AMD than in normal elderly control eyes.²⁰ Oral supplementation does increase the concentration of these macular pigments in the retina.²⁰⁻²³

Minerals

Zinc. Zinc is an antioxidant mineral that is important in many functions, including taste, smell, vision, growth development, DNA-RNA

Tip

CONSIDERING CONTRAINDICATIONS

- *Before adding high doses of a potentially blood-thinning supplement, such as vitamin E or omega-3s, to a patient who is on warfarin or other blood thinners, ask the patient to discuss the pros and cons with their cardiologist or general practitioner. Note that AREDS2-type supplements are not considered high dosage.*
- *For patients with kidney and/or liver dysfunction, use caution when recommending high levels of beta-carotene or high doses of other supplements.*

synthesis, wound healing, cell division, and cell repair. Of importance for the eye, zinc mobilizes vitamins A and E from the liver so they can be transported to the retina.

Oysters provide the highest concentration of dietary zinc. Other dietary sources include red meats, nuts (especially cashews), some poultry, and fortified cereals. Because iron and zinc compete, and carbohydrates in the United States are also fortified (by law) with iron, the RDA for zinc is very difficult to obtain through diet alone, so supplementation is recommended. The upper limit for safe supplementation is 40 mg/day.

Dietary intake of zinc is inversely associated with incident AMD.¹ Supplementation appears to provide significant benefits: In the Age-Related Eye Diseases Study (AREDS) the reduction in risk of progression to advanced AMD in patients with moderate AMD at enrollment was about 21% for those taking zinc supple-

ments only, comparable to taking all of the other AREDS ingredients in combination.³

There are some known adverse effects with higher levels of zinc supplementation, including an increase in urinary tract infections^{3,24} and decreased copper absorption. Zinc may be associated with cognitive function, although no clear association between zinc and Alzheimer's has ever been found.

Because of the copper deficiency associated with zinc supplementation, small amounts of copper are often added to zinc supplements. Otherwise, copper is generally not a desirable supplement, as it is a known oxidant that builds up in the RPE, where it enhances vascular endothelial growth factor. Copper plumbing ensures that most Americans get plenty of this mineral from their water supply alone.

Selenium. Selenium is another mineral cofactor for antioxidant enzymes that fight oxidative damage. It works

FAQ

Q: *What is the best form of Omega 3? Essential fatty acid supplementation can be confusing. Should it come from flax seed or fish oil? How much do patients really need? What constitutes a “high quality” fish oil supplement? Should they look for the triglyceride form or are the synthetic ethyl ester forms ok?*

A: *In fish, these compounds are present in the triglyceride form. Both the “natural” triglyceride and the “synthetic ethyl ester” supplement forms are processed and distilled. When the fish oils are processed and molecularly distilled to make supplements, the fatty acid bond breaks apart, creating an ethyl ester. This is often called “synthetic fish oil.” For the triglyceride supplements, an additional processing step re-attaches the triglyceride enzyme. Most of the studies confirming the benefits of fish oil over the past 15 years were conducted with the ethyl ester form.*

One study showed more rapid absorption of the triglyceride form, but over a 24-hour period, there is little difference in serum levels between these forms. Other research has indicated an advantage in absorption of the triglyceride form, but this small advantage can be overcome by maintaining a regular intake level of traditional ethyl ester fish oils.

The most important factor in choosing a fish oil supplement is the effective EPA and DHA content. In a 1000-mg capsule, it is possible to have only 180 mg of EPA and 120 mg of DHA—a total of 300 mg of the “good stuff”—with the rest just oil. The recommended 1,000 mg means 1,000 mg of EPA/DHA. Patient education is important, because most patients under-consume these supplements. The capsules are large; the clinician’s recommendations may not correspond to the package labeling; and different brands can have widely varying DHA/EPA content. It is often easier to provide a specific product so that you know patients are getting the right amount.

Flaxseed oil may be beneficial, but it is poorly converted to EPA (especially in males) and therefore not the best source of omega-3.

Most people recommend 1,000 mg (1 g) or more daily for antioxidant and anti-inflammatory benefits. However, a recent paper noted that certain genetic subsets need only about 300 mg per day. Genetics research may tell us more in the future about who is most likely to respond and whether mega-doses are really needed.

with vitamin E to maintain RPE health and function. Brazil nuts and tuna are among the foods with the highest concentrations of selenium. It is typically most available from plant sources, but the amounts of selenium can vary widely depending on the soil in which the plants are grown. Other than in certain areas such as the northwestern plains, most Americans generally do not consume enough selenium. Selenium toxicity is rare.

Omega 3 Fatty Acids

Omega 3 fatty acids have tremendous systemic anti-inflammatory benefits; in the eye, they support the photoreceptor membranes.

They are usually consumed in the form of alpha linoleic acid (ALA), which metabolizes down to polyunsaturated, longer-chain fatty acids known as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These in turn metabolize into the prostaglandin E3. The most important dietary source of EPA/DHA is fatty cold water fish, but fish consumption is dismally low in the United States overall (and especially fatty, cold water fish consumption). There are vegetable sources of ALA (e.g., flaxseed oil), but the conversion rate to EPA and DHA from these sources is much lower than from fish oil.

Dietary consumption of omega-3 fatty acids is inversely related to the incidence of macular degeneration, with an increase in risk of AMD of between 45% and 75% for peo-

ple with low dietary intake.²⁵⁻²⁹ Most recently, the Women's Health Study found that in a large cohort of women who did not have a diagnosis of AMD at baseline, regular consumption of DHA/EPA and fish was associated with a significantly decreased risk of incident AMD and may be of benefit in primary prevention of AMD.³⁰ Higher dietary intake of omega-3 fatty acids has also been associated with decreased incidence of dry eye in the Women's Health Study.³¹

The only major concern with fish oil supplementation is the remote potential for interaction with warfarin, aspirin, high-dose vitamin E and polyphenols such as ginkgo biloba. For example, a 2004 case report described increased bleeding in a patient on warfarin on low-dose fish oil of 1000 to 2000 mg/day (300 to 600 mg EPA/DHA).³² However,

a small randomized, controlled study conducted earlier found no significant effect on the anti-coagulation status of patients receiving chronic warfarin therapy with fish oil doses of as much as 3,000-6,000 mg per day.³³

Other Compounds. A balanced diet includes many other nutrients that likely contribute to ocular health. Many Americans, for example, are deficient in vitamin D, which humans synthesize through the skin during sunlight exposure. While profoundly important for overall systemic health, studies of the ocular benefits of vitamin D are not definitive.

The B vitamins fulfill many systemic needs. The Women's Health Study, with more than 5,000 patients, found a decreased prevalence of AMD among patients who were taking a folic acid/vitamin B complex supplement.³⁴ B vitamins are

also thought to play a role in the prevention of glaucoma by maintaining the myelin sheets surrounding the optic nerve.

The tripeptide glutathione is important because it regenerates both vitamin C and vitamin E. This sulphur-containing antioxidant, a small molecule that permeates all cells, cannot itself be digested by humans, but dietary sources of glutathione precursors include pungent food such as onions and garlic. Glutathione is very highly concentrated in the anterior epithelium of the crystalline lens. Any form of cataract, whether from radiation, drugs, malnutrition or other etiology, includes a decrease in glutathione in the lens, and then subsequent opacification of the lens.^{35,36}

These compounds warrant further research; there is not yet enough data to support ocular health-related recommendations.

PART 2: Modifying Age-Related Disease Progression

It has been hypothesized that cumulative oxidative damage to the retina and lens are key processes involved in the development of age-related eye diseases like AMD and cataract. It makes sense, therefore, that nutrients with antioxidant effects could be used to prevent or treat these conditions.

AMD

Dry AMD affects roughly 85% to 90% of the more than 10 million Americans over age 55 with macular degeneration.

Millions more are at risk for developing AMD. Risk factors include increasing age, female gender, genetic factors, smoking, and high body mass index (BMI), among others.³⁷ There is no cure and, left untreated, patients with AMD are at risk for progression and significant vision loss.

Beginning in 1992, researchers began looking specifically at the role of nutrition and nutritional supplementation in ocular health. The National Eye Institute-supported Age-

Related Eye Disease Study (AREDS), which enrolled nearly 5,000 patients between 55 and 80 years old, was designed to learn more about the natural history and risk factors of AMD (and cataract) and to evaluate the effect of high doses of antioxidants and zinc on the progression of these diseases over 5 years or more.

The 3,640 AREDS subjects with at least early signs of AMD were classified by severity, from no AMD to advanced AMD. In each severity group,

Table 1: AREDS and AREDS2 Supplement Dosage (Daily)

	AREDS	AREDS2
Vitamin A (beta-carotene)	28,640 IU	None or 28,640 IU
Vitamin C	452 mg	500 mg
Vitamin E	400 IU	400 IU
Zinc	69.6 mg	25 mg or 80 mg
Copper	1.6 mg	2 mg
Lutein	--	10 mg
Zeaxanthin	--	2 mg
Omega-3 fatty acids	--	1,000 mg 650 mg EPA 350 mg DHA

subjects were randomized to receive antioxidants only, zinc only, antioxidants plus zinc, or placebo, with the dosage as described in *Table 1*. Subjects were followed for at least 5 years; some reports now follow them out to 10 years.

The results indicate that high levels of antioxidants and zinc significantly reduce the risk of advanced AMD and its associated vision loss in those with intermediate AMD or advanced disease in one eye (see *Table 2*). Given that 1.6 million people fall into these risk groups, the public health impact of this magnitude of effect is enormous.

The supplements were not shown to have a significant effect on progression of earlier stage AMD or on the development or progression of cataract. Category 1-2 AMD patients have a low risk to begin with and may take

longer than the course of the AREDS study to develop advanced disease. There have now been more than 30 published reports from this trial.

In 2006, the NEI launched AREDS2 to see if a modified combination (see *Table 1*) of vitamins, minerals, and fish oil can further slow the progression of vision loss from AMD. More than 4,000 subjects were randomized to one of 4 groups: placebo, lutein/zeaxanthin, DHA/EPA from fish oil, and lutein/zeaxanthin plus fish oil. In addition, subjects in all 4 groups were offered an AREDS-type antioxidant supplement as the standard of care. Participants who chose to take an antioxidant supplement were further randomized to the original AREDS1 formula or to one of three new formulas with low zinc, no beta-carotene, or low zinc and no beta-carotene. Smokers

were randomized to one of the groups without beta-carotene. Finally, all subjects who were taking a daily multivitamin supplement were asked to replace it with Centrum Silver. Results are expected in 2013.

A number of other prospective studies have added to the evidence base for nutritional supplementation to modify disease progression in AMD:

CARMIS (Carotenoids and Antioxidants in age-Related Maculopathy Italian Study). Randomized, controlled trial in 27 subjects with maculopathy and reduced visual function. Short-term supplementation with carotenoids and antioxidants, including lutein, zeaxanthin, and astaxanthin resulted in significant improvement in central retinal function after 12 months of treatment.³⁸

LAST/LAST II (Lutein Antioxidant Supplementation Trial). In both intervention groups, (10 mg lutein only and 10 mg of lutein plus a broad-spectrum vitamin and mineral supplement), visual acuity improved and macular pigment optical density (MPOD) increased from baseline in patients with atrophic ARMD.³⁹ Moreover, the highest increases in MPOD over time occurred in patients with lower baseline values of MPOD.⁴⁰

LUXEA (Lutein Xanthophyll Eye Accumulation) Study. In a randomized, prospective, controlled study, 6 months of daily supplementation with zeaxanthin, lutein, or a combination of the two improved

mesopic contrast acuity and low-light visual performance.⁴¹

TOZAL (Taurine, Omega-3 Fatty Acids, Zinc, Antioxidant, Lutein) Study.

This study of short-term (6 months) supplementation with antioxidants and omega-3 fatty acids provides evidence that such treatment can improve visual acuity. In the study, 77% of subjects experienced a gain in best-corrected visual acuity (BCVA).⁴² The supplement includes 28,640 IU of Vitamin A, of which 18,640 is from natural food sources, 452 mg vitamin C, 200 IU of vitamin E, 69.6 mg of zinc, 1.6 mg of copper, 400 mg of taurine,

180 mg EPA and 120 mg DHA, 8 mg of lutein, and 400 mcg of zeaxanthin.

ZVF Study (Zeaxanthin and Visual Function). In older male patients with AMD, zeaxanthin-induced foveal macular pigment elevation mirrored that of lutein and provided complementary distinct visual benefits by improving foveal cone-based visual parameters, whereas lutein enhanced those parameters associated with gross detailed rod-based vision, with considerable overlap between the two carotenoids.⁴³

Cataract

A number of studies have suggested that a diet high in

antioxidants, particularly vitamin C, might be protective against cataract.⁴⁴⁻⁴⁶ Recently, higher plasma concentrations of lutein and zeaxanthin were correlated with lower risk of cataract.⁴⁷

Not surprisingly, researchers have been interested in whether supplementation can delay or prevent cataracts. Several studies suggested that long-term use of vitamin E supplements might reduce the development or progression of age-related cataract^{48,49} and in the Physicians Health Study, men who took multivitamin supplements had a decreased risk of cataract.⁵⁰

Table 2: AREDS Key Results			
	Antioxidants Plus Zinc	Antioxidants Only	Zinc Only
CATEGORY 1 No AMD A few small or no drusen	Risk not evaluated		
CATEGORY 2 Early AMD Several small drusen or a few medium-sized drusen in one or both eyes; <2% chance of progression	No benefit		
CATEGORY 3 Intermediate AMD Many medium-sized drusen or one or more large drusen in one or both eyes	Reduced risk of developing advanced AMD by about 25%	Reduced risk of developing advanced AMD by about 17%	Reduced risk of developing advanced AMD by about 21%
CATEGORY 4 Advanced AMD Advanced dry or wet AMD in one eye	Reduced risk of vision loss by about 19%	Reduced risk of vision loss by about 10%	Reduced risk of vision loss by about 11%
Cataract		No benefit	

Table 3: Expert Algorithm: Nutritional Support for Ocular Health, by AMD Status

<p>Everyone <i>Maintain general ocular and systemic health</i></p>	<ul style="list-style-type: none"> • Eat a balanced diet with lots of fruits, vegetables, whole foods and essential fats • Exercise and maintain healthy weight • Don't smoke • Take a good full-spectrum multi-vitamin
<p>Adults 50+ Interest in performance vision</p>	<ul style="list-style-type: none"> • Continue above recommendations • 50+ exam • Add lutein (≥6 mg) and zeaxanthin for visual function • Add 500–1,000 mg DHA/EPA fish oil
<p>Pre-AMD, Early AMD <i>Adults with AREDS Category 1–2 AMD and/or significant risk factors (e.g., family history, smoker, high BMI, etc.)</i></p>	<ul style="list-style-type: none"> • Continue above recommendations • Nutritional counseling • Genetic testing • Consider increasing antioxidants
<p>Moderate to Severe AMD <i>AREDS Category 3–4</i> <i>Highest risk of progression</i></p>	<ul style="list-style-type: none"> • Continue above recommendations • Replace antioxidants with AREDS1 formulation with or without beta-carotene (depending on smoking status) as long as there is no contraindication <p>-OR-</p> <ul style="list-style-type: none"> • Replace all above supplements (except multi-vitamin) with AREDS2 formulation that includes lutein, zeaxanthin and DHA/EPA from fish oil

However, AREDS did not show any cataract-related benefits to supplementation.⁵¹ A later analysis of men enrolled in the Physicians Health Study and randomized to long-term

supplementation with vitamin C (500 mg/day) vs. placebo or vitamin E (400 IU on alternate days) or placebo showed no benefit to either supplement in delaying or preventing

the development of cataract after 8 years.⁵²

AREDS 2 will further explore the impact of nutritional supplementation on cataract development.

PART 3: Nutritional Recommendations in Clinical Practice

Our consensus recommendations, broken down by AMD status, are summarized in *Table 3*, above.

Moderate to Advanced AMD

For patients with moderate to advanced dry AMD, the

AREDS evidence is clear that supplementation is beneficial. This is the group of patients, therefore, for which our deci-

sion making is the easiest.

Category 3 includes those with many medium-sized drusen or one or more large drusen. In AREDS, this was further defined as drusen between 63 μm and 124 μm . Clinically, when one begins to see 12–15 drusen coalescing, or any non-central geographic atrophy, that should be considered Category 3.

Category 4 is the more advanced stage, with pigmentary changes, decrease in visual acuity to less than 20/30, geographic atrophy, and/or wet AMD in one eye. Patients with advanced AMD in one eye have a risk of progression to the contralateral eye of 42%.

For these patients, the current standard of care is an AREDS formulation that (except for smokers) includes beta-carotene but does not include macular xanthophylls that weren't commercially available at the time of the original study. The exact AREDS formulation (PreserVision, Bausch + Lomb) is available commercially, as are other supplements with very similar ingredients.

However, the Blue Mountains Eye Study pointed to a higher risk of macular degeneration with increased beta-carotene levels, perhaps because high-dose beta-carotene competes with the absorption of crucial lutein and zeaxanthin.⁵³

The Physician's Health Study compared patients taking beta carotene vs. placebo over 12 years and found no significant differences in the prevalence

of AMD over time. With these studies, and the association of high-dose beta-carotene with lung carcinogenesis, it makes sense to consider cutting back on supplemental sources of beta-carotene.

We anticipate the AREDS2 data are likely to support eliminating beta-carotene and adding lutein, zeaxanthin and fish oil.

Many clinicians would choose to make those modifications already with an AREDS2-type formula that includes 2 mg of zeaxanthin, 10 mg of lutein, and 1 gram of DHA/EPA.

Many people consider it reasonable to continue AREDS' high levels of zinc, pending AREDS2 results. Also, it is important to talk about modifiable risk factors, like diet/BMI, exercise, smoking, controlling blood sugar and hypertension.

Zeaxanthin may play a role in improving actual retinal treatment outcomes. In a recent study by Peralta, patients undergoing triple therapy for AMD (PDT with dexamethasone and bevacizumab injections) required fewer treatment cycles to achieve anatomic stabilization of choroidal neovascularization when they took high levels (20 mg/day) of an oral zeaxanthin supplement.⁵⁴

Early AMD or AMD Risk Factors

Since AREDS found no effect of the antioxidant or zinc supplements on progression of early AMD, it is less clear what, if anything, we should be recommending for patients

with Category 2 AMD—and even less clear what should be recommended to those patients who have significant risk factors for AMD but do not yet have the disease.

According to AREDS, those Category 1 or 2 patients have a less than 2% chance of progression to advanced AMD. However, there may be certain groups within that population who are genetically predisposed and at higher risk. Genetic testing, along with low contrast visual acuity and glare recovery testing, may provide some insight into subclinical disease and even into how likely individuals are to respond to certain nutrients.

One aspect to consider is that the AREDS definitions were drusen-based, using outdated imaging technology. Newer spectral domain OCT and RPE autofluorescence imaging, along with genetic testing, will likely provide earlier structural confirmation of disease. These measures may indicate that other people who don't meet the AREDS drusen definition are actually at high risk and would benefit from nutritional supplementation or behavioral modifications.

We believe that, much as we change our care for the pre-diabetes patient who has significant risk factors, we should really be doing the same thing for AMD and beginning to encourage lifestyle changes (including improving nutrient intake through food) and supplementation to optimize ocular health. However, there is much less of a consensus in

the medical literature on this.

For AREDS category 1–2 patients, one may want to consider a good multivitamin to support retinal health, 500 to 1,000 mg of EPA/DHA from fish oil, and nutritional counseling. Most would add lutein and zeaxanthin to this regimen, as well. If there is a family history of AMD or three or more risk factors for AMD, one might want to also consider a broader array of nutrients.

Maximizing Performance

A truly forward-thinking clinician may want to consider how diet and nutritional supplementation can improve visual function, even before there are signs or symptoms of disease.

We believe that a 50+ exam, as detailed below, offers an opportunity to use nutritional supplementation to enhance visual function. Limiting vision testing to Snellen acuity is likely to underestimate the number of people with visual impairments. In most patients in the 50+ age group, contrast sensitivity, glare recovery, and glare disability testing will uncover visual disabilities that directly affect everyday functioning and even public safety.

Decreasing visual function affects the ability to move and drive safely in dim lighting or other visually compromising conditions. Self-described driving ability on the VFQ-25 was notably associated with baseline pre-supplementation macular pigmentation. Linear regression modeling suggests

that self-described ability to safely drive a car was strongly associated with final macular re-pigmentation post supplementation ($p=0.02$).⁵⁵ Any opportunity to enhance visual function and safety in such situations is a triple win—for the patient, for the practitioner, and for the public at large.

At the other end of the spectrum, macular carotenoids—and particularly zeaxanthin, which is more densely distributed in the central cone-rich fovea—are directly related to visual acuity functioning and shape discrimination. The nutrients may affect sports performance and other skills such as hunting, for instance. Foveal integrity, beyond visual acuity, can now be evaluated with a very sensitive test, the Retina Foundation of the Southwest's Shape Discrimination Test.⁵⁶ This measure can be used to detect loss of function due to AMD or identify opportunities to enhance function for high performance. Patients of any age who want to enhance visual performance may also want to consider supplementation with lutein, zeaxanthin, and omega-3 fatty acids.

Incorporating Nutrition into Clinical Care

The eyes are a window into the body and are affected by many of its physical maladies. Improving ocular health is likely to have a positive effect on systemic health (and vice versa).

As primary eye care providers, we can and should be talking about diet, exercise and

nutritional supplementation with our patients, when appropriate. People may not expect to hear about these topics from us, but given the growing consensus that diet and exercise affect risk factors for age-related eye diseases such as AMD, we would be remiss to ignore them. The Carotenoids in Age-Related Eye Disease Study (CAREDS), for example, recently showed that having a combination of 3 healthy lifestyle behaviors (healthy diet, physical activity, and not smoking) was associated with 71% lower odds for AMD compared with having high-risk scores.⁵⁷

Our patients care deeply about maintaining visual function. Yet, while there is widespread awareness today of the importance of diet and exercise in prevention of heart disease and cancer, the average person is unaware that they can also affect eye health and vision.⁵⁸ Particularly with susceptible individuals, dietary advice can help them postpone or prevent the vision-disabling consequences of AMD as they age.⁶

The first thing we can do is to encourage patients to improve their diet by consuming more vegetables, fruits, fish and whole foods—the best sources of many essential nutrients. We can discuss body mass index (BMI) as a risk factor and encourage patients to move more. An aggressive exercise regimen is not necessary; moderate walking or swimming conveys many benefits. And we would be well-advised to educate patients about nutritional supplementation.

Nutritional supplements represent an attempt to substitute for what is missing or inadequate in the diets. One might consider them “second best” to obtaining nutrients from dietary sources. But even people who eat a relatively healthy diet are likely to be deficient in a number of nutrients that are critical for ocular health. As people age, it makes sense to consider supplementation, not only to reduce disease risk, but to maximize visual function.

While it can seem daunting to incorporate nutrition counseling into a busy clinical practice, we offer a number of simple strategies for doing so (*see sidebar* at right). Chief among these is instituting a 50+ exam in your practice.

The 50+ Eye Exam. We strongly recommend introducing an adult 50+ examination in your practice, with an emphasis on optimizing vision for the second half of life. This is the ideal time to introduce a more comprehensive exam, during which visual function can be tested, disease risk factors assessed and nutritional status more carefully evaluated. Use this exam to guide recommendations, as discussed in the previous section and in *Table 3*.

The diagnostic testing one might want to consider in this exam includes contrast sensitivity, photo-stress glare-recovery testing, and macular pigment ocular density (MPOD). Diet assessment, nutritional counseling, or genetic testing may also be added, depending upon the practitioner and patient.

There are several options for

Practical Pearls for Working Nutritional Advice Into a Busy Practice

Basic Education

- *Start simply stating to every patient that nutrition affects the quality of your vision and your eye health.*
- *In your history, specifically ask about vitamins or supplements.*
- *Add a few simple questions to identify patients with gross deficiencies who are good candidates for nutritional supplementation (How many servings of fruit and vegetables do you eat daily? Green leafy vegetables? When was the last time you ate fish?).*
- *Provide in-office literature on nutrition and the eyes (source: www.ocularnutritionssociety.org).*
- *Using a quick smart phone app, calculate patients' BMI, based on their reported weight and height, and discuss BMI as a risk factor and the need for higher doses of ocular nutrients.*
- *With elderly patients, encourage “movement” not “exercise” – tracking steps with a pedometer is a great way to move more.*

Take it Up a Notch

- *Recommend and/or sell supplements from your office based on patient needs and potential contraindications.*
- *Bring in a local nutritionist for monthly/quarterly nutrition and lifestyle counseling.*
- *Refer to and co-manage patients with a local nutritionist.*
- *Add baseline and serial glare and contrast testing.*
- *Position props in the office: A poster with key ocular nutrients is good; plastic food items illustrating good foods (broccoli, salmon, etc) are even better.*

Become a Nutritional Whiz

- *Offer a full review and analysis of vitamins and supplements.*
- *Construct handouts from www.choosemyplate.gov.*
- *Refer to external lab for serum testing and urinalysis and review results.*

testing contrast sensitivity or low-contrast acuity. Among the simplest is a card with high-

contrast print on the front, low-contrast print on the back, available from several optical

Tip

A patient who is plagued by photophobia in the absence of any ocular inflammation, should have macular pigment ocular density (MPOD) testing. Appropriate supplementation with carotenoids and synergistic fish oil reduces symptoms within a 3-month period in most cases.

supply houses. A difference in the number of lines read on each side indicates potential loss of contrast sensitivity. Various low-contrast projected charts are available. And of course, there is the full contrast sensitivity testing (Stereo Optical Functional Vision Analyzer or the Vector Vision CSV-1000) that has been used in many clinical trials.

The photostress glare recovery test (PSGR) involves exposing an individual eye to intense light, or retinal bleach, for a set duration and measuring the time for visual acuity to recover. This transient state of insensitivity is subjectively perceived as a scotomatous afterimage. The actual reduction in visual acuity results from photopigment depletion and the recovery time is dependent on the rate of photopigment regeneration, independent of neural mechanisms. Furthermore, the return of retinal sensitivity is dependent on resynthesis of visual pigments in the outer retinal segments.⁵⁹ Any nutrient, drug or disease that affects the photoreceptors, adjacent retinal pigment epithelium or choroid is also expected to prolong the recovery of sensitivity following glare exposure.⁶⁰

The Newsome Macular Disease Detection (MDD2) device (Health Research Sciences, LLC, Lighthouse Point, Fla.) is a portable, hand-held diagnostic device that allows the clinician to test both eyes of a patient in less than 5 minutes. In recent studies of this device used on 515 eyes, prolonged recovery time from a flash stimulus to the retina is correlated with worse vision and with the presence of macular disease.⁶¹

Macular pigment ocular density (MPOD) is an increasingly important metric. MPOD has been identified as an independent risk factor for AMD. It provides a way to measure and benchmark macular pigments and also to measure improve-

ments after dietary changes or supplementation. In a society where “knowing your numbers” is the norm, MPOD is a good tool to increase patient awareness and perhaps even compliance.

Serum testing can provide an indication of overall antioxidant capacity, homocysteine oxidant levels, essential fatty acid balance and the C-reactive protein systemic inflammation status.

Conclusions

Supplementation with high levels of antioxidants and zinc is the standard of care for patients with moderate to advanced AMD. Research continues into the role of these nutrients, along with EPA and DHA from fish oil, lutein, and zeaxanthin for AMD, cataract,

dry eye, and maintenance of healthy visual function.

Educating yourself and your patients about dietary nutrition and supplementation is a valuable service to your patient and society that will also enhance your clinical practice.

Patient Education Resources

- Ocular Nutrition Society (www.ocularnutritionociety.org)
- Nutritional analysis survey available to ONS members
- www.eyefoods.com or Eyefoods: A Food Plan for Healthy Eyes by Laurie Capogna, O.D., and Barbara Pelletier, O.D.
- <http://www.bausch.com/en/Vision-and-Age/60s-Eyes/Seniors-Eye-Health>
- National Heart Lung & Blood Institute (NHLBI) BMI Calculator (or other similar free smart phone apps)
- www.choosemyplate.gov

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