

Nutrient Supplementation for Age-related Macular Degeneration, Cataract, and Dry Eye

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Abstract

There have been enormous advances in the past decade for the treatment of age-related macular degeneration (AMD); however, these treatments are expensive and require frequent follow-up and injections which place a tremendous burden on both the healthcare system and patients. Consequently, there remains considerable interest in preventing or slowing the progression of AMD requiring treatment. Epidemiological studies have shown that diet is a modifiable AMD risk factor, and nutrient modification is a particularly appealing treatment for AMD due to the perceived universal benefit and relatively low expense. Recently, the age-related eye disease study part two (AREDS2) was concluded and demonstrated further benefit with the addition of lutein and zeaxanthin as a replacement for the β -carotene of the previous generation formulation. The addition of omega-3 essential fatty acids did not show an added benefit. This review aims to highlight some of the evidenced based body of knowledge that has been accumulated from recent studies regarding the use of nutritional supplements and their effect on AMD, cataracts, and dry eyes.

Keywords: Age-Related Macular Degeneration; Carotenoids; Nutrition; Supplements

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INTRODUCTION

In the past decade, there has been tremendous advance in the treatment of age-related macular degeneration (AMD), but the introduction of anti-angiogenic agents has not been without substantial costs. The approved medications are expensive, and visits for intravitreal injections can be frequent, imposing an ever growing burden on healthcare systems, on physician practices, and on patients and their families. Thus, there is still considerable interest in preventing or slowing the progression of AMD through interventions against modifiable risk factors. Epidemiological studies have shown that smoking and diet are two of the most consistently identified modifiable AMD risk factors. Dietary modification through nutritional counseling is particularly appealing due to its universal applicability and its relatively low expense, but major dietary and lifestyle changes can be difficult to achieve in the

elderly population at risk for visual loss. This means that dietary supplements of vitamins, minerals and other nutritional factors are an attractive intervention for AMD and other age-related eye diseases as long as a firm evidenced-based body of knowledge exists to support their use.

It is not unusual for patients and eye care providers to commonly refer to these supplements as “eye vitamins,” but many of their key components do not fit the strict definition of a vitamin, which is an organic compound required by an organism as a vital nutrient in limited amounts and for whom a deficiency state reproducibly results in a clinically defined pathological condition.^[1] By convention, there are thirteen universally recognized vitamins, but there are numerous other non-vitamin nutrients linked with improved ocular function and health including trace minerals, dietary lipids and plant pigments such as carotenoids and polyphenols

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that are typically included in supplements targeted for promotion of eye health and protection against eye disease.

The first commercially available vitamin supplements were produced around 1940. Prior to that time, all needed vitamins were obtained solely through food intake; however, dietary modifications to meet ocular supplementation needs occurred long before when the ancient Egyptians recognized that feeding a person liver, an excellent source of Vitamin A essential for production of functional photoreceptor pigments, could cure night blindness. Today, dietary supplements are frequently used to ensure that adequate amounts of ocular nutrients are obtained on a daily basis but in some cases, the complex interactions between elevated levels of vitamins and other nutrients in the body are just now being elucidated. Unwanted effects can occur with taking high doses of even essential vitamins or if the person taking them has certain health conditions.^[2] For example, a study published in 2009 found that antioxidant Vitamins, C and E, which are often used in high doses in eye supplements, may actually decrease the benefits of exercise.^[3] Additionally, contradictory conclusions have been reached by different studies when a large, double-blind trial in 2011^[4] found that Vitamin E supplementation increased the risk of prostate cancer in healthy men, while a previous study in 1998^[5] had shown a decreased risk of prostate cancer with Vitamin E supplements.

Today, more than ever, eye doctors are being asked to advise an increasingly aware patient population regarding nutrition and vitamin supplements related to vision. Most of the current recommendations regarding the use of eye vitamin supplementation to support macular health have been gleaned from a pair of large, randomized controlled studies known as the age-related eye disease study (AREDS) 1 and 2. These studies suggest that nutritional supplements are a promising means of delaying the leading cause of elderly blindness in developed countries, that is, advanced AMD. In addition, there is some evidence that vitamin supplementation may be beneficial in delaying cataract progression and treating dry eyes. Studies are currently underway evaluating their usefulness in treating glaucoma and diabetic retinopathy, the number one cause of blindness among the working population.

EPIDEMIOLOGIC STUDIES

While it has been shown that extreme vitamin deficiencies can directly cause retinal dysfunction in animal experiments,^[6] large epidemiologic studies in humans are needed to determine if diet alone or modest nutritional supplementation can influence ocular diseases. For starters, everyone consumes vitamins on some level, so the effect of supplementation depends on the amount of a vitamin already being consumed. While randomized

trials with defined end-points are the gold standard, these results can be misleading. One reason is that trial participants for the most part have good diets, and they may not show an effect of supplementation that might be exhibited in those with poorer diets. Additionally, trials on eyes may be too short for an effect to be demonstrated or may focus on persons at high risk for a disease or only those with an existing disease. Such trials may make it difficult to apply findings later to those with average risk. Generally, positive results of such trials are compelling, while negative results are difficult to interpret.

AGE-RELATED MACULAR DEGENERATION

Age-related macular degeneration remains the leading cause of elderly blindness in developed countries. Multiple genetic and environmental factors have been implicated in the pathogenesis of this complex disease. Age, smoking, genetics, diet, obesity, hypertension and hypercholesterolemia are the most recognized risk factors. Among these, aging and smoking have been demonstrated to be the most consistent non-genetic risk factors. Increasing pack years of cigarettes smoked is directly correlated with an increasing risk of AMD; the risk is roughly doubled when smokers are compared to those who have never smoked.^[7] As such, smoking cessation should always be recommended to those with evidence of AMD. Ethnicity also plays a role according to a 10 years longitudinal study, the Multi-Ethnic Study of Atherosclerosis (MESA), reporting a lower prevalence of AMD in blacks than in whites with the overall prevalence varying from 2.4% in African Americans, 4.2% in Hispanics, and 4.6% in Chinese as compared to 5.4% in whites.^[8]

Compared to other organs, the eye is uniquely susceptible to oxidative stress given its high consumption of oxygen, high content of polyunsaturated fatty acids, and exposure to visible light.^[9] The formation of reactive oxygen species leads to the oxidation of docosahexaenoic acid (DHA) which is thought to be a major pathway of cellular damage and photoreceptor degeneration in AMD.^[10] This mechanistic understanding of AMD has led to therapeutic strategies to reduce oxidative damage by cessation of smoking, limiting alcohol intake, avoiding obesity, regular exercise, and of course, the implementation of supplemental antioxidant eye vitamins. Additionally, there has been recent interest in supplementation with compounds possessing anti-inflammatory properties such as the omega-3 fatty acids, eicosapentaenoic acid (EPA) and DHA.

The age-related eye disease study (AREDS),^[11] sponsored by the National Eye Institute, evaluated AMD progression in participants supplemented over an average of 6.3 years with randomization at entry to 1 of 4 treatment categories of dietary supplements at levels well above recommended daily allowances:

Placebo; antioxidants (β -carotene 15 mg, Vitamin C 500 mg, and Vitamin E 400 IU); zinc (80 mg as zinc oxide and copper 2 mg); and antioxidants and zinc combined. These nutrients were chosen based on the best nutritional knowledge of eye disease in the 1980s when the AREDS study was conceived. A seminal study performed in Utah had recently shown a beneficial effect of zinc supplementation in AMD patients,^[12] Vitamins C and E were readily available antioxidants abundantly present in ocular tissues, and β -carotene was a major commercially available Vitamin A precursor which was known to be less toxic at high doses than Vitamin A itself.

Patients were characterized during enrollment with retinal images and varied from those with normal eyes to those with advanced AMD. Disease level was then classified by investigators based on the category of AMD in the patient's worse eye: AREDS category 1 (no AMD) consisted of fewer than 5 small ($<63 \mu\text{m}$) drusen; category 2 (mild AMD), multiple small drusen, non-extensive intermediate ($63\text{--}124 \mu\text{m}$) drusen, pigment abnormalities, or a combination; category 3 (intermediate AMD), at least 1 large ($>125 \mu\text{m}$) druse, extensive intermediate drusen, or geographic atrophy not involving the center of the macula; and category 4 (advanced AMD), central geographic atrophy or neovascular AMD in 1 eye or visual loss resulting from AMD, regardless of the lesion type.

The 5 years results of the AREDS study showed that supplementation with antioxidants and zinc combined, reduced the risk of progression to advanced AMD by approximately 25% in those with intermediate AMD or advanced AMD in one eye.^[11] The risk of losing three or more lines of vision was also reduced by 19% with this treatment. It was concluded from this study that those with extensive intermediate drusen, at least one large druse, non-central geographic atrophy in one or both eyes, advanced AMD or vision loss because of AMD in one eye, and without contraindications such as smoking, should take an AREDS supplement of antioxidants plus zinc. It should be noted however, that to date routine supplementation with antioxidant vitamins or minerals has not been demonstrated to prevent the onset of AMD in patients who do not have AREDS category 3 or 4 disease.^[13]

By the time the original AREDS study was published in 2001, there had been considerable progress in the molecular understanding of ocular nutrients. First it was recognized that the dose of β -carotene used in the study was likely to present a significant risk of lung cancer development in smokers based on several large randomized trials published while AREDS was in progress. Second, ongoing biochemical studies clearly identified several common dietary constituents that were abundantly concentrated in the macula and whose dietary consumptions were epidemiologically linked with decreased risk of AMD in the AREDS population and in other cohorts – the xanthophyll carotenoids commonly found in dark

green leafy vegetables and orange or yellow fruits and vegetables, lutein and zeaxanthin, and the omega-3 fatty acids abundantly present in fish oil, EPA and DHA. Out of over 600 carotenoids in nature, only lutein and zeaxanthin and their metabolites are present in the foveal region of the human eye where they form the yellow pigment of the macula lutea. These natural blue-light screening antioxidants have been associated with decreased risk of AMD in multiple epidemiological studies, and their unique localization to the fovea implies a potentially important physiological function in visual performance and in preservation of macular health. Likewise, photoreceptor outer segments contain the highest percentage of omega-3 polyunsaturated fatty acids in the body.

Based on the afore mentioned concerns about β -carotene in smokers and the progression in knowledge of ocular nutrition, the National Eye Institute initiated the AREDS2 study which enrolled its first patient in 2006 and published its results in 2013. It assessed the effects on cataracts, AMD, and moderate vision loss of oral supplementation with 10 mg lutein + 2 mg zeaxanthin, and/or 650 mg EPA + 350 mg DHA. Additionally, a secondary randomization was also performed in which study participants were given either: 1) the original AREDS formula, (2) AREDS formula minus β -carotene, (3) AREDS formula with low dose zinc (25 mg), or (4) AREDS formula with no β -carotene and low dose zinc.

This secondary randomization was included because high levels of zinc supplementation in the original AREDS formula was thought to be associated with significantly more hospitalizations due to genitourinary conditions and self-reported anemia even though overall mortality was not affected by zinc supplementation during the study.^[11] 80 mg was tested in the original AREDS formula because it was the dose used in an earlier trial that suggested benefit.^[12] The AREDS2 study evaluated a lower 25 mg dose as more recent research had suggested this may be the maximal level absorbed by the gut.^[14] β -carotene was removed from two arms in the secondary randomization for multiple reasons. First, two different randomized controlled clinical trials had demonstrated an increase in lung cancer rates and mortality in cigarette smokers supplemented with β -carotene.^[15,16] Secondly, previous animal^[17] and human^[18,19] studies had suggested that simultaneous administration of high doses of β -carotene and lutein + zeaxanthin may suppress serum and tissue levels of lutein + zeaxanthin because of competitive absorption of carotenoids.

The AREDS2 planners set an ambitious goal of achieving a 25% incremental improvement on the benefits of the already successful AREDS formula, and unfortunately, they did not achieve the pre-specified primary positive endpoint when each of the three active supplementation arms was compared individually with the control group, but pre-specified secondary analyses of the main effects of lutein and zeaxanthin

produced statistically and clinically significant positive results. On the other hand, main effect analysis of the data from AREDS2 showed that the addition of omega-3 fatty acids was neither harmful nor beneficial. Adding lutein + zeaxanthin to the AREDS formula resulted in an additional beneficial effect of about 10% beyond the effects of the original AREDS formulation in reducing the risk of progressing to advanced AMD, and when β -carotene was removed, the incremental benefit increased to 18%, possibly due to amelioration of competitive absorption effects.^[20] Those who derived the most benefit from the addition of lutein + zeaxanthin were those in the lowest quintile of dietary lutein and zeaxanthin intake. Furthermore, despite proscriptio against β -carotene supplementation in current smokers, β -carotene was still associated with a greater risk of lung cancer in AREDS2 participants (2% vs. 0.9%), especially in those who had previously been smokers. This finding is clinically relevant, as 50% of participants in AREDS and AREDS2 with AMD were former smokers, and 91% of those who developed lung cancer in AREDS2 were former smokers. On the other hand, there was no increased risk of lung cancer with lutein + zeaxanthin supplementation.

Finally, comparison of low-dose zinc versus high-dose zinc displayed no statistically significant effect. The authors concluded that there was insufficient evidence to provide a clinical recommendation at this point regarding changing the dose to 25 mg. Given the results of this study, it should be expected that most supplement makers will soon remove β -carotene from the eye vitamin formula and replace it with 10 mg of lutein and 2 mg of zeaxanthin certainly for smokers and former smokers, and for simplicity and uniformity of message this formulation can be recommended to nonsmokers as well. AREDS2 did not find evidence to support the addition of omega-3 fatty acids to the formula at this point; however, other studies have demonstrated a benefit from increased omega-3 intake,^[21] so clinicians are left to individually counsel patients regarding omega-3 supplementation, especially if these patients normally consume very little fish in their diets.

AGE-RELATED MACULAR DEGENERATION (GENOTYPE SPECIFIC TREATMENT)

Recent understanding regarding the genetics of heritable mutations associated with AMD has shed much light on the pathogenesis of the disease and implicated several important biological pathways such as complement pathways, cholesterol and lipid metabolism pathways, extracellular/collagen matrix pathways, oxidative stress pathways and angiogenesis signaling pathways.^[22-24] An international collaborative effort recently reviewed over 17,000 AMD cases and compared them with 60,000 matched controls of European and Asian ancestry and revealed 19 AMD loci.^[25]

The question remains as to how many of these associated variants are causal, and further evaluation of the functional characterization of genes associated with these variants may provide biological relevance to our understanding of the pathogenesis of AMD.

Some of the known biological features of AMD genetic risk factors predict that specific components of the AREDS formulation would be more beneficial. A recent study re-analyzed the AREDS results in conjunction with genotype data and evaluated the effectiveness of the original AREDS formula and concluded that the estimated potential benefit of using genotype specific nutritional therapy could have more than doubled the reduction in AMD progression rate compared with treatment with the AREDS formula over a 10 years period.^[26] They felt that patients with 1 or 2 complement factor H (CFH) risk alleles derived maximum benefit from antioxidants alone as zinc negated the benefits of antioxidants. Additionally, patients with age-related maculopathy sensitivity 2 (ARMS2) risk alleles derived maximum benefit from zinc-containing regimens, with a deleterious response to antioxidants. They also proposed that individuals homozygous for CFH and ARMS2 risk alleles derived no benefit from any category of AREDS treatment. As possible explanations for this effect, they noted that patients with a known CFH mutation might be predicted to respond more poorly to an eye vitamin supplement containing zinc as CFH binds zinc, which can neutralize its ability to inactivate complement component 3b.^[27-29] Additionally, ARMS2 localizes to mitochondria, and might potentially affect oxidative phosphorylation and the generation of oxygen free radicals that could interact with antioxidants such as Vitamins C and E.^[30,31]

This *post-hoc* analysis must be interpreted with caution, however, as the genotype specific subgroups were often very small which necessitated complicated statistical modeling with wide confidence intervals, and their conclusions may not apply to newer AREDS2 recommendations. Moreover, their biochemical explanations require additional *in vitro* and *in vivo* studies to prove their clinical relevance, and further confirmatory studies of the influence of AMD risk genotypes on response to nutritional supplements are required before their recommendations can enter mainstream clinical practice. As additional studies are performed, it is likely that we will see improved outcomes from genotype-directed therapy in the future. Of course, this would also necessitate genetic testing becoming readily available for all patients with AMD in order to categorize their genetic variants.

CATARACTS

Age-related cataracts remain the leading cause of blindness throughout the world.^[32] Several previous studies have evaluated risk factors felt to be associated with cataract

development such as: Smoking,^[33] diabetes,^[34,35] sunlight exposure,^[36,37] educational level,^[38] body mass index,^[39,40] refraction,^[41] and estrogen replacement therapy,^[42,43] however, most supplementation trials have tested the effect of high-dose antioxidants such as Vitamin C, Vitamin E, and β -carotene.^[44-50] Since this review has the goal of discussing the role of vitamin supplements in treating diseases of the eye, only trials relating to supplements will be discussed.

Recently, AREDS report number 32^[45] published results which demonstrated that Centrum use amongst AREDS study patients was associated with a decreased risk of nuclear cataract. These findings were consistent with an earlier report based on a propensity score analysis of cataract and Centrum use in the AREDS population.^[51] They also agreed with a large, randomized clinical trial^[44] recently performed in Italy which showed a reduction in the development or progression of nuclear opacities; however, this trial differed from other trials in that it also showed a significant increase in the development or progression of posterior subcapsular (PSC) opacities. Interestingly, even though significant changes were noted in cataract progression in study participants, there were no significant effects on functional end-points such as visual acuity or cataract surgery. Identifying which individual supplements or combination of supplements within Centrum vitamins contribute to the protective effect on nuclear cataract remains an area of investigation.

Perhaps the study that showed the most promising benefits from vitamin supplementation on cataracts was performed in rural China^[52] where it demonstrated a 36% reduction in the prevalence of nuclear cataract in persons 65–74 years old after 5 years. Study participants were divided into two arms with the study arm receiving 2 centrum tablets and 15 mg of β -carotene daily compared with those assigned to a placebo formulation. While these results were more statistically significant than other studies performed in western populations, the trend seems to be the same with a decrease in nuclear cataracts and a possible increase in PSC opacities. Additionally, one may conclude that more nutritionally deprived populations seem to derive the most benefit from multivitamin supplementation, although further evaluation is needed.

Interestingly, lutein and zeaxanthin are the only carotenoids that have been detected in the lens.^[53] The AREDS2 results showed daily supplementation with lutein/zeaxanthin had no statistically significant overall effect on rates of cataract surgery or vision loss.^[54] Taking multivitamins may slow the development of age-related cataracts, but since this link in most appears weak, at best, patients should consider taking multivitamins on the basis of overall health benefits or risks.

DRY EYE SYNDROME

Dry eye syndrome (DES) is one of the most prevalent ocular conditions in the world. Worldwide epidemiologic

studies have shown prevalence rates ranging from 14.6% to 57.5%.^[55] DES results in ocular discomfort and can lead to decreased functional visual acuity. Rapid tear evaporation, inadequate tear production and inflammation of the ocular surface have all been associated with dry eyes.

One school of thought for treatment of DES is that meibum lipid composition can be influenced by increasing dietary lipid intake in an effort to manage meibomian gland dysfunction (MGD). Therefore, it is recommended that oral supplementation with omega-3 essential fatty acids (EFAs) can be a therapeutic option for patients with MGD. It has been demonstrated that breakdown of omega-3 EFAs leads to suppression of inflammation, and the breakdown of omega-6 EFAs promotes inflammation.^[56,57] Two hypotheses exist as to why supplementation with omega-3 EFAs can alleviate MGD. The first proposes that the breakdown of omega-3 EFAs competes with the same enzymes that are used to breakdown omega-6 EFAs and essentially inhibits the ability to breakdown omega-6 EFAs, thus leading to decreased inflammation along the eyelid margin. The second hypothesis is that supplementation with omega-3 EFAs influences fatty acid composition and promotes tear stabilization while preventing blocked meibomian ducts.^[58]

Current data support the use of systemic omega-3 fatty acid supplements for DES, although there is a lack of large randomized, controlled, double-blinded studies evaluating their efficacy.^[59] One such study on 71 patients with mild to moderate dry eye symptoms demonstrated a non-statistically significant improvement in Schirmer test, tear break-up time, and fluorescein and lissamine green staining in patients who took oral polyunsaturated fatty acid supplements.^[60] Another study suggested that higher dietary intake of omega-3 fatty acids is associated with a decreased risk of dry eye syndrome in women.^[61]

Omega-3 fatty acids include alpha-linolenic acid in addition to DHA and EPA. They are found in high amounts in cold water fish and flaxseed oil.^[62] There are no formal recommendations or FDA approved formulations for dietary consumption of EFAs in the treatment of eye disease or the promotion of eye health, but many ophthalmologists currently recommend treatment with 1000 mg of flaxseed oil daily (typically divided in three doses) or another form of omega-3 EFAs.^[63-65] Additionally, the American Heart Association (AHA) currently recommends at least two servings of fish high in omega-3 fatty acids per week for heart health.^[66] It appears likely that many benefits are associated with a diet rich in omega-3 fatty acids including heart health, AMD, and DES. Future studies will hopefully provide outcome measures of the use of different types of EFAs compared in a standardized fashion. The potential exists to modify ophthalmic preferred practice guidelines much the same way that the AREDS study has done for macular degeneration. The limited studies to date suggest that a well-designed,

multicenter, randomized, controlled trial of EFAs would be welcomed and could provide important insight on the benefits of using omega-3 EFAs as a supplement for DES.

There have been a number of important studies affirming the relationship of diet and nutrition to the treatment, prevention, and/or slowing progression of a number of age-related ocular diseases. It is important that any advice given to patients regarding lifestyle modifications and particularly recommendations on the benefits of nutritional supplementation be informed by the best available research evidence. When we understand this evidence, we can help educate our patient populations to the link between nutrition and eye-health. Since nutrients are more conceptual, and thus invisible to consumers, a single page write-up or a stand-alone pamphlet can be very helpful to encourage the best diet/health practices for healthy vision. They also can be valuable in initiating a discussion with patients on overall health beyond the eyes themselves.

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