INTRODUCTION

The genomic revolution has brought with it a swell in the interest of those genetic, environmental and nutritional factors that predispose one to health or illness. Inherent in this is an assessment of how dietary changes and supplements may play a role in maximizing health. Specific for eye and vision care, ocular conditions that are likely to be nutritive-responsive are of particular interest. The hope is to extend usable vision and reduce visual morbidity. Never before has technology, science, and healthcare been so poised for action and answers. It is for these reasons that the interest in ocular nutrition, ocular antioxidants and nutritive-responsive ocular conditions continues to surge.

There is currently intense interest in the possible role that antioxidants may provide prevention, retardation and possible reversal of these disorders. This interest is secondary to some of the favorable in vivo and human clinical trial outcomes. Among the most critical issues facing eyecare providers is reducing the likelihood of manifesting the ocular disorder or prolonging its time of arrival. The specific nutrients that follow, listed along with each disorder, represent only those with a compelling body of evidence-based research or preliminary promising potential. This manuscript is designed to provide the reader with current scientific understanding and clinical opinion of nutrition in eyecare. A glossary is provided at the end, to be referenced as needed.

A. Free Radical Generation, Antioxidant Response

Free radicals have been established as one of the more important contributors to ocular pathology. Free radicals are produced as a result of both normal-physiological, as well as pathological, biochemical reactions. Oxidants such as the superoxide radical, hydrogen peroxide, the hydroxyl and lipid peroxide radicals, will cause damage if not neutralized by antioxidants. Antioxidants are defined as substances that counteract the effects of oxidation, whether oxidants are produced by normal or aberrant biochemical pathways. Well-known antioxidants such as vitamin C, E or beta carotene, indiscriminately quench free radicals, restoring biological homeostasis and mitigating oxidative damage. It is generally accepted that increasing dietary or supplemental antioxidants decreases oxidative insult, and should positively affect the outcome of chronic disorders.

In the following discussions all Dietary Reference Intake levels (DRI) are current recommendations of the Food and Nutrition Board of the Institute of Medicine, unless otherwise indicated.

B. Age-related Cataract

Background

Cataractogenesis is ordinarily a result of free radical accumulation, secondary to ultraviolet exposure, physiological processes and loss of inherent antioxidant defense systems. These processes induce lens protein alterations (enzyme inactivation, denaturation, protein aggregation and eventual cell membrane lysis), causing light scatter and clinically manifesting as cataract. The bulk of nutritional research pursuits have been dedicated to studying the role that antioxidants may provide as far as prevention, retardation and possible reversal of primary age-related cataract (ARC).

Vitamin C

Major contribution: Ascorbate (vitamin C) is a central contributor to the native...
antioxidant defense system of the lens, working to quench free radical formation and also known to be involved in the regeneration of reduced vitamin E.6

Evidence Base: In a case-controlled study of 350 patients, those who consumed greater than 300 mg/d of vitamin C over a five year period were found to have one-third the risk of nuclear sclerosis relative to age-matched controls with no vitamin C intake.7 The use of vitamin C supplements for ≥ 10 years resulted in a 77% lower prevalence of early lens opacities, and an 83% lower prevalence of moderate lens opacities.10 Another study determined that the odds of nuclear opacity were 66% lower for Vitamin C users with intakes of 240-300 mg/d.14

DRI: The current recommended dosages of vitamin C for an adult male is 90 mg/d, and adult female is 75 mg/d; however, it is generally accepted that 500 mg/d is a more appropriate intake level for the prevention of chronic ocular disease such as primary ARC.7,15

Lutein/Zeaxanthin

Major contribution: Carotenoids, such as lutein and zeaxanthin, are powerful antioxidants, particularly at low partial pressures such as the reduced partial pressures found at the crystalline lens core. Carotenoids represent one of the most common antioxidants in the lens.

Evidence Base: Dietary intake of spinach (lutein/zeaxanthin dense), rather than carrots (beta carotene dense), was associated with a lower cataract risk and inversely related to cataract extraction. This points to the likelihood of lutein or zeaxanthin contributing to the protective association between total carotenoid intake and reduced risk of cataract.15 A more recent analysis of this same population showed those with the highest lutein and zeaxanthin intakes had a 22% decreased risk of cataract extraction.16 Among specific foods high in carotenoids, broccoli and spinach (lutein/zeaxanthin-rich) were most consistently associated with a lower risk of cataract.17

These findings were supported in a recent publication suggesting that consumption of vegetables rich in lutein and zeaxanthin offers 10 times more protection than alpha tocopherol from ultraviolet induced lens cell damage that is typically associated with cataract formation.18

DRI: No current standard has been established, although prevailing scientific evidence suggests that consuming 6 mg/d of dietary lutein/zeaxanthin may decrease the risk of certain types of ocular disease, including cataract.19-21

C. Dry Eye Syndrome/Ocular Surface Health

Background

Dry eye syndrome (DES) is a recalcitrant, life-long condition, frequently affecting the patient’s quality of life. It tends to worsen with time. Regardless of the etiology, DES is ultimately an ocular surface inflammatory disorder.22,23 Nutritional intervention strategies have been aimed at restoring tear production, reducing tear evaporation, rectifying abnormalities in mucin and lipid constituents, and generally reducing ocular surface inflammatory indices.

Omega Three Fatty Acids (O3FA)

Major contribution: Generally speaking, omega three fatty acids (O3FAs) are proposed to decrease ocular surface inflammation and enhance oil production from the meibomian glands, thereby decreasing evaporative tear loss.24,25 This particular type of polyunsaturated fatty acid (PUFA) is thought to promote anti-inflammatory prostaglandins and anti-inflammatory leukotrienes, as well as suppress tumor necrosis factor alpha, a regulatory factor in lacrimal gland apoptosis.25,26

Evidence Base: Researchers analyzed the dietary questionnaires of over 30,000 female health professionals, who provided information on diet and dry eye status.27 Results from the study indicated that intake of O3FA found in fish oil, and tuna consumption in particular, reduced the risk of DES. This was a landmark study suggesting an active role for dietary O3FA and a reduced risk for dry eye.27

DRI: A DRI has not been established for specific types of O3FAs. However an adequate intake level (AI) level has been set for O3FA at 1.6 g/day for adult males and 1.1 g/day for adult females.

Vitamin A

Major contribution: Retinoids (Vitamin A and pro-vitamin A) have an important role in epithelial cell health, contributing to normal cell growth, differentiation, and baseline ocular surface maintenance such as mucus and goblet cell production.28,29 Deficiencies of this vitamin have been associated with decreases in hemidesmosomes, which may promote epithelial sloughing, as well as decreases in goblet cell production.28,30

Evidence Base: Vitamin A has been identified as a necessary component for ocular health.31 Clinical trials evaluating vitamin A-containing artificial tears report a high degree of improvement in patients with keratoconjunctivitis sicca (KCS).32,33 In 2004, a small clinical trial reported improved signs of dry eye in those patients taking a vitamin A-based topical emulsion.34

DRI: The current recommended dosage is 3,000 IU/day for adult males, and 2,333 IU/day for adult females.32,33

Vitamin B12

Major contribution: This essential vitamin is integral to the growth and health of the epithelial cells of mucous membranes. Vitamin B12 is a vital co-enzyme in the production of DNA and RNA, driving mechanisms for cell growth and repair, and thus promoting a healthy ocular surface.35 Vitamin B12 absorption is reduced with age and, therefore, local supplementation may be desirable. Artificial tear formulations containing B12 are commercially available, such as Nutratear™.

Evidence Base: In vivo experiments have shown local ocular application of B12 solution to triple the rate of corneal healing.36 Early data from studies of vitamin B12 ocular topical drops have been encouraging. Patients showed relief from ocular surface irritation and good tolerability for the B12 formulation.37 Further masked studies are required to confirm and extend these early reported beneficial effects of vitamin B12 in DES.

DRI: The current level is 2.4 mcg/d for adult males and females.35

D. Age-related Macular Degeneration

Background

Age-related macular degeneration (AMD) is the leading cause of blindness in people ages 65 years and older.3,5,8 There are three main theories contributing to the pathophysiology of AMD, among these: oxidative stress, impairment to choroidal circulation, and degradation of Bruch’s membrane. AMD is most likely multifactorial, precipitated by oxidative stress and free radical formation secondary to UV radiation, age, systemic disease, and nutritional factors.7 The very process of aging, with its relative increase in oxidative load and decrease in native antioxidants, fosters the development of AMD. It is for this reason that antioxidant intervention and nutritionally supportive measures are of particular interest.

Targeted Antioxidant Combination

Major contribution: Synergy among antioxidants has been proposed and conti-
ues to be studied.^{11,19} Antioxidant combinations may deliver more diverse free radical quenching capacity than singular supplements.

**Evidence Base:** In the Age Related Eye Disease Study (AREDS) AMD arm,^{11} there was a clinically significant effect of supplementation for those patients with moderate to advanced disease, in preventing further progression. Patients with intermediate or advanced AMD, who took the daily formulation of: beta carotene, vitamin C, alpha-tocopherol, and zinc/cupric oxide, showed a 25% reduction in the rate of progression.^{11} The treatment benefit was manifest although the sample was relatively well nourished.^{38} The AREDS led to mainstream changes in the clinical management of AMD. Additionally, in the TOZAL (Taurine, O3FA, Zinc, Antioxidant, Lutein) study, visual acuity was reported to stabilize or improve in 76% of the study patients with atrophic AMD, after receiving the nutritional formulation for six months.^{39} The complete formulation consisted of daily: 10,000 IU vitamin A, 18,640 IU beta carotene, 452 mg vitamin C, 200 IU vitamin E, 70 mg zinc oxide, 1.6 mg of copper, 400 mg taurine, 300 mg O3FA, 8 mg of lutein and 400 mcg of zeaxanthin. These study results complement the AREDS findings, pointing to the use of targeted antioxidant combinations as a viable therapeutic tool for atrophic AMD.

**DRI:** The high-dose AREDS formula ranges from five-fold (vitamin C) to 17-fold (alpha tocopherol) the recommended daily allowance. The AREDS formula is: daily supplementation of 15 mg beta carotene, 500 mg vitamin C, 400 IU alpha-tocopherol, and 80 mg of zinc oxide/2 mg of cupric oxide.^{11}

**Vitamin E (tocopherol)**

**Major contribution:** Photoreceptor outer segments have a greater percentage of fatty acids and higher levels of vitamin E when compared to most other tissues.^{40,41} Fatty acids are highly susceptible to lipid peroxidation and it is therefore suspected that sufficient levels of vitamin E help protect the retinal photoreceptors from oxidative insult.^{41} Alpha tocopherol is the most biologically active member of the vitamin E group, and is highly effective against lipid peroxidation.

**Evidence Base:** A significant protective effect was observed between dietary vitamin E and AMD in the Baltimore Longitudinal Study of Aging.^{42} In this study, patients with higher plasma concentrations of vitamin E had a 57% lower prevalence of AMD.^{43} This protective effect was also observed in the Eye Disease Case Control Study Group which examined 421 eyes with severe AMD and compared these subjects to 615 controls. The prevalence of AMD among those with higher serum vitamin E concentrations was 40% lower.^{44} Finally, the Pathologies Oculaires Liées à L’Age study found a significant AMD risk reduction for those subjects with higher plasma levels of vitamin E.^{45} **DRI:** A 22.5 IU/day dose for adult males and females is acceptable. However, clinical trials have utilized a range of 200-400IU/d, that is thought to be more consistent with clinically therapeutic levels.^{42}

**Lutein/zeaxanthin**

**Major contribution:** Lutein and zeaxanthin belong to a subset of hydroxylated carotenoids known as xanthophylls. This additional hydroxylation may expand the antioxidant capabilities of these particular carotenoids.^{46} Lutein and zeaxanthin are abundant in the retina and other ocular tissues such as aqueous, lens, and vitreous.

**Evidence Base:** A pilot study examined three different forms of dietary supplementation: 60 g of spinach and 150 g of corn (lutein-rich, zeaxanthin-rich), spinach (lutein-rich) alone, or corn (zeaxanthin-rich) alone, in addition to the usual daily diet.^{47} Most subjects showed a measurable increase in macular pigment density after four weeks of the modified diet. In a separate pilot study, the subjects consumed 30 mg of lutein per day for 140 days.^{48} This increased measurable macular pigment density, enhancing quenching ability (30-40%) of harmful blue light wavelengths. Resulting from these studies, an important concept has emerged, that increasing dietary intakes of lutein/zeaxanthin can increase density of protective macular pigment.^{48} A recent cross-sectional study determined the risk of atrophic AMD to be significantly higher in people with lower plasma concentrations of zeaxanthin.^{49} Additionally, the Carotenoids in Age-Related Eye Disease Study, determined that higher intakes of lutein plus zeaxanthin (≥3 mg/d) lowered the risk for intermediate AMD.^{50} The Lutein Antioxidant Supplementation Trial determined that lutein alone and lutein plus other antioxidants improves visual function in patients with established atrophic AMD.^{51} Finally, the newest ongoing randomized clinical trial to evaluate the effects of oral supplementation on AMD progression is AREDS 2, providing 10 mg of lutein and 2 mg of zeaxanthin per day.^{52} **DRI:** No current standard has been established although prevailing scientific evidence suggests that consuming 6-10 mg/d of dietary lutein/zeaxanthin may decrease the risk of AMD progression.^{19,21,51,52}

**E. Optic Nerve Health:**

**Glaucoma**

**Background**

Primary open angle glaucoma (POAG) describes a type of progressive, multifactorial optic neuropathy, and is a major health concern due to its insidious nature. Recent prevalence estimates in the U.S. suggest that 2.22 million Americans over the age of forty have this form of glaucoma.^{54} For these reasons, there is particular interest in nutritional approaches to improve blood flow, reduce intraocular pressure, thwart free-radical induced optic nerve insult, and generally improve the stability of the neuropathy.

**O3FA**

**Major contribution:** Higher intake levels of O3FA increased aqueous outflow facility, thereby decreasing IOP in animal models.^{55} Furthermore, a deficiency in certain types of long chain PUFA, including O3FA, are thought to impair ocular micro-circulation, creating conditions favorable to this type of optic neuropathy.^{56,57} Therefore sufficient levels of O3FA are linked with improvements in microcirculation and ultimately enhanced blood flow, as well as potentially enhancing aqueous outflow.^{55} **Evidence Base:** Research in animal models has shown that increasing O3FA intake can cause a significant decrease in intraocular pressure compared to diets that are not rich in O3FAs.^{58} Additionally, when plasma fatty acid composition was compared in POAG patients versus non-POAG siblings, glaucoma subjects were found to have reduced levels of O3FAs.^{57} Lastly, a complex of O3FA (docosahexaenoic acid-rich), tocopherol and B vitamins taken for 90 days was shown to expand measurable visual field in a small subset of glaucoma patients.^{59} **DRI:** A DRI has not been established for specific types of omega three fatty acids. However an AI level has been set O3FA at 1.6 g/day for adult males and 1.1 g/day for adult females.
Ginkgo Biloba
Major contribution: Ginkgo biloba extract (GBE) has multiple attributes which enhance its therapeutic potential for treating non-IOP dependent pathways of POAG. Among these attributes: reducing platelet aggregation, minimizing glutamate toxicity, quenching free radicals, nitric oxide inhibition, and reducing blood viscosity.

Evidence Base: Animal model studies show that GBE is effective in reducing retinal ganglion cell neurotoxicity secondary to chronic moderately elevated IOP. Blood flow velocity in the ophthalmic artery has been shown to significantly increase in individuals taking 120 mg/d of GBE, with no reported side effects. No such effect was measured in those subjects receiving placebo. DRI: No current DRI has been established. However the study cited above indicates that 120 mg/d might be effective.

F. Retinitis Pigmentosa
Background
This group of inherited, progressive retinal dystrophies is known to affect 50,000-100,000 people in the United States and a total of 1.5 million people worldwide. There is currently no effective treatment for retinitis pigmentosa (RP) and modern advances in gene therapy and retinal implants have met with limited success. For this reason, interest in supplements and other means of reducing the rate of retinal degeneration are of particular interest to vision scientists and the eyecare community.

Vitamin A
Major contribution: The role of vitamin A in the visual transduction cycle makes this a key member for full photoreceptor function and retinal processing. Inadequate levels of vitamin A can impair the visual cycle, resulting in known deficiencies in dark adaptation.

Evidence Base: The daily intake of 15,000 IU vitamin A palmitate, over a five-year period, reduced the rate of electroretinogram decline in retinitis pigmentosa. Importantly, this study revealed that 400 IU of daily vitamin E, contributed to functional vision decline in RP.

DRI: Dosages of 15,000 IU/d of vitamin A, for adult male and female patients (who are not of childbearing age) with RP, are considered safe and are recommended. Women of childbearing age should not take high dose vitamin A, as studies have shown this can increase the risk of birth defects, particularly in the first trimester. However, routine monitoring of liver function and fasting serum vitamin A should be utilized to monitor for toxicity.

Lutein
Major contribution: The relative abundance of lutein and zeaxanthin in the retina and their contributions to macular pigment density and antioxidant activity are well documented. Chronic retinal dystrophies and degenerations, therefore, are natural targets for further investigations of these specific xanthophylls.

Evidence Base: A pilot study reported lutein supplementation (40 mg/d for nine weeks, 20 mg/d for 17 additional weeks) to improve nyctalopia in patients with RP. Unfortunately the number of subjects was small and no placebo controls were included. A study conducted by the Wilmer Eye Institute randomized 34 adult RP patients into two groups and followed them for 48 weeks. One group received lutein for 24 weeks, followed by placebo for the other 24 weeks; the other group received the reverse treatment. The results showed improvements in visual field, visual acuity and reduction in the rate of visual decline.

DRI: No DRI has been established. However, clinical trials have utilized 10 mg of lutein per day for long term treatment of patients with RP, and up to 40 mg per day for short term treatment.

Table 1 summarizes appropriate dosages of the various supplements, based on the existing literature.

DISCUSSION AND CONCLUSION
The fact that increasing dietary levels of specific nutrients can increase target tissue levels is a significant breakthrough in this field of study. The key is in determining the highest therapeutic, least toxic, plasma levels for ascorbate, tocopherols, carotenoids and other antioxidants to deliver the necessary concentration to the desired target ocular tissue, crystalline lens, retina, etc. The next steps should be to determine what length of time is necessary to prevent formation or stall progression of disorders like AMD or cataract and at what daily dosages.

The most effective antioxidants investigated thus far with respect to the retardation of age-related cataract are vitamin C, lutein and zeaxanthin based therapies. Supplementary inclusion of O3FA continues to show promising results regarding ocular surface health and DES. There may be a role in the future for topical application of vitamin A or B12 to promote epithelial health. Studies have shown antioxidant combination supplements, lutein and zeaxanthin, and O3FA-antioxidant combination supplements, most consistently provide protective effects against AMD. More specifically, the antioxidant combination of ascorbate, tocopherol, beta carotene and zinc, known as the AREDS formula, is now considered part of the standard of care. The effects of lutein, zeaxanthin, and O3FA supplementation will be further studied in the new AREDS 2 ongoing clinical trial. Dietary supplementation with GBE and O3FA has demonstrated improvement in visual field and ocular blood flow in POAG patients. These nutrients have therapeutic potential for treating IOP-dependent and IOP-independent glaucoma mechanisms. Finally, vitamin A and lutein have shown consistent enhancements in visual field and decreases in the rate of ERG decline in retinitis pigmentosa.

Trials have also established daily vitamin E as having deleterious effects on the progression of RP. Clearly the field of antioxidant and nutritional influences on ocular health is expanding and evolving. With the aging of the population, and natural increase in the prevalence of age-related eye disease, nutritional supplementation in ocular disease is emerging as a valid therapeutic approach. Should future randomized clinical trials show that age-related cataracts can be prevented, or at least attenuated, and age-related macular degeneration is indeed a nutritive-responsive disorder, the ramifications for reduction of visual morbidity and its consequences, are truly exciting.

The author has no financial or other interest in any of the products discussed herein.
**Table 1: Clinical Guidelines for Supportive Therapeutic Nutrients in Certain Ocular Diseases**

<table>
<thead>
<tr>
<th>Ocular Disorder</th>
<th>Supplement</th>
<th>Therapeutic Intake Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Related Cataract</td>
<td>vitamin C</td>
<td>500 mg/d</td>
</tr>
<tr>
<td></td>
<td>lutein/zeaxanthin</td>
<td>6 mg/d</td>
</tr>
<tr>
<td>Dry Eye Syndrome</td>
<td>omega three fatty acids</td>
<td>1.6 g/d males</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 g/d females</td>
</tr>
<tr>
<td></td>
<td>topical vitamin A or B12</td>
<td>As directed on the bottle</td>
</tr>
<tr>
<td>Age Related Macular Degeneration</td>
<td>antioxidant combination (AREDS formula)</td>
<td>Daily: 15 mg beta carotene, 500 mg vitamin C, 400 IU alpha-tocopherol, 80 mg zinc oxide, and 2 mg cupric oxide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6-10 mg/d</td>
</tr>
<tr>
<td>Primary Open Angle Glaucoma</td>
<td>ginkgo biloba extract</td>
<td>120 mg/d</td>
</tr>
<tr>
<td></td>
<td>omega three fatty acids</td>
<td>1.6 g/d males</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 g/d females</td>
</tr>
<tr>
<td>Retinitis Pigmentosa</td>
<td>vitamin A</td>
<td>15,000 IU/d for males, and females who are not of childbearing age monitor toxicity</td>
</tr>
<tr>
<td></td>
<td>lutein</td>
<td>10 mg/d</td>
</tr>
</tbody>
</table>

**GLOSSARY**

**Adequate Intake (AI) level**: one of the dietary reference intake (DRI) guidelines proposed by the Food and Nutrition Board of the National Institute of Medicine. It is used as a target nutrient intake for individuals, particularly when a recommended dietary allowance (RDA) has not been established. The AI helps to define the nutrient intake necessary to maintain a healthy nutritional state.

**AREDS formula**: A multivitamin-mineral formula comprised of beta carotene, vitamin C, vitamin E, zinc and copper, that has been linked to a reduction in risk of progression for patients with moderate or advanced AMD.

**ascorbate; vitamin C**: carotenoids: a group of organic pigments, one of the most known is beta carotene

**Dietary Reference Intakes (DRI)**: the most recent set of nutrition recommendations established by the Food and Nutrition Board of the Institute of Medicine. The formerly referenced and more widely known, U.S. Recommended Dietary Allowance (RDA) is now but one component of the new DRI. The DRI values are specific for each life stage and gender group.

**docosahexanoic acid (DHA)**: a type of omega three fatty acid

**eicosapentanoic acid (EPA)**: a type of omega three fatty acid

**Food and Nutrition Board**: a board established by the U.S. Institute of Medicine to study issues of national food supply, food safety, and to establish guidelines for adequate nutrition.

**free radicals**: highly reactive chemical species with unpaired electrons

**ginkgo biloba**: a medicinal herb whose leaves are often used in the form of a standardized extract (GBE)

**lutein**: a specific type of hydroxylated carotenoid, known as a xanthophyll, with distinctive light-absorbing properties

**lipid peroxidation**: oxidative destruction of lipids, most often degradation of PUFA's

**omega three fatty acid (O3FA)**: an essential fatty acid, and specific type of long chain polyunsaturated fatty acid (PUFA); i.e., fatty acids that contain more than one double bond

**Recommended Dietary Allowance (RDA)**: the average daily intake level of a nutrient that is sufficient to meet the requirements of nearly all (97-98%) healthy individuals.

**Retinoids**: a class of compounds related to vitamin A
tocopherol: a sub-family of vitamin E
xanthophyll: a yellow pigment and type of modified carotenoid
zeaxanthin: a specific type of hydroxylated carotenoid, known as a xanthophyll, with distinctive light-absorbing properties. Zeaxanthin and lutein are isomers.

**References**


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