Nutritional Supplementation and Ocular Health

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EVIDENCE OF EFFICACY

Introduction

Age-related ocular disorders are leading causes of visual impairment and blindness in the US and worldwide. Nearly 2 million Americans over the age of 40 suffer from age-related macular degeneration (AMD), and another 7 million with large drusen are at high risk.[1] Over 20 million people in the US have cataracts.[2] By 2020, AMD and cataract prevalence are expected to increase to 3 million and 30 million people, respectively.[1,2]

Research has shown that genetic, environmental, and dietary factors interact to influence the development of AMD.[3-5] Heightened risk for AMD has been associated with smoking, obesity, sedentary lifestyle, suboptimal nutrition, and comorbidities common among the elderly population, such as hypertension.[3,4,6] These and other factors can enable inflammation, oxidative stress, and proteolysis that may cause or contribute to degenerative changes in the aging retina.[3,5,7]

An emphasis on identifying nutritional correlates of health and disease prevention is growing in basic science, epidemiologic, and clinical research. The typical Western diet, characterized by moderate to high intake of meats, sweets, and refined grains, has been shown to be proinflammatory and damaging to cells over time.[8] By contrast, diets high in fruits, vegetables, whole grains, legumes, and fish—and rich in antioxidant vitamins, carotenoids, omega-3 polyunsaturated fatty acids, and other nutrients—have been associated with reduced rates of cardiovascular and neurodegenerative disease, cancer, AMD, and cataracts.[7,9-12] Micronutrients may synergistically protect cells against damage from oxidative stress and inflammation.[8-10]

In the field of ophthalmology, observational studies have shown that individuals who report diets rich in certain nutrients experience lower rates of cataracts and AMD across a range of populations. In particular, high intake of fish and omega-3 polyunsaturated fatty acids, and foods high in antioxidant vitamins and carotenoids (such as lutein and zeaxanthin) have been associated with reduced risk for age-related ocular diseases.[13-17]

The use of vitamin, mineral, and other dietary supplements as a means to correct inadequate micronutrient intake or otherwise improve health is a widespread practice in the developed world and among the elderly population.[18-20] In a survey of patients attending a Michigan-based general ophthalmology practice (N = 397, mean age 58 years), 58% reported nearly daily multivitamin intake. In the same study, patients reported that their preferred source of information about vitamins was their primary care practitioner (26%), friends and family (22%), and the media or the internet (22%)—rarely their ophthalmologist (2%). Only 5% reported discussing vitamins with their ophthalmologists.[18] Ophthalmologists familiar with research on nutritional supplementation are in a strong position to bridge the communication gap with patients and help them make sound choices.

Highlights of Dietary and Nutritional Supplement Research

Antioxidant vitamins, beta-carotene, and zinc

Human beings are unable to synthesize micronutrients classified as vitamins, and so must derive them through diet or supplementation. Antioxidant vitamins C (ascorbic acid) and E (alpha-tocopherol) protect cells via their function as free-radical scavengers. Free radicals are molecules that possess an unpaired electron, making them highly reactive and able to create oxidative stress damaging to cellular membranes.[21,22] Both vitamins C and E also support proper immune functioning.[20,23] Additionally, vitamin C supports collagen synthesis and tissue repair; vitamin E protects endothelial cells within blood vessels against platelet aggregation.[22,23]

Carotenoids comprise a class of more than 600 distinct antioxidant compounds found in orange, yellow, or red foods. Beta-carotene, a carotenoid prevalent in food, readily undergoes cleavage within the body to become vitamin A. Intake of provitamin A carotenoids, including beta-carotene, as well as alpha-carotene and beta-cryptoxanthin, is responsible for up to one-third of daily dietary vitamin A, the rest of which is typically ingested directly as retinol.[24] Vitamin A, or retinol, is essential for vision and immune function, among others, and deficiencies in it can cause xerophthalmia and night blindness.[21]

Zinc is a mineral essential for proper enzymatic and immune function, protein and DNA synthesis, and other vital cellular functions. Zinc serves as a cofactor to over 100 enzymes, including superoxide dismutase, an important regulator of reactive oxygen species such as superoxide anion. Zinc cannot be stored in the body and so must be ingested in small amounts daily for optimal health.[25] In order to reduce the risk for zinc-induced copper deficiency anemia, the essential trace mineral copper is often added to supplemental zinc formulations.

Research related to antioxidant vitamins, beta-carotene, and zinc in eye health

In a landmark prospective study of a nutritional intervention for ocular health, the Age-Related Eye Disease Study (AREDS), high-dose antioxidant vitamins and minerals were shown to slow the progression of AMD and vision loss among patients with intermediate-size or larger drusen.[26] AREDS provided the first evidence from a large, randomized, controlled trial for a role of nutritional supplementation with vitamins C, E, beta-carotene, zinc, and copper in the management of dry AMD, and to date, represents the only intervention available with the potential to slow disease progression in many patients.[3] Some progress is also being made toward identifying patients with genotypes that increase their chances of responding to nutritional therapy. Genotypic subanalysis of AREDS participants revealed that those who possessed a "low-risk" variant of the gene for complement factor H (CFH), a suspected immune component of AMD pathophysiology, derived a protective benefit from zinc-containing regimens, whereas those with the "high-risk" variant of the gene experienced disease progression.[3,5] In a separate study known as the Nutrition and Vision Project, nutritional data gathered prospectively over 13 to 15 years among 478 healthy women supported an association between dietary vitamin C intake and a reduced risk for cataract development. Also significantly protective of the lens were beta-carotene, vitamin E, folate, riboflavin, lutein, and zeaxanthin.[16]

Xanthophylls (lutein and zeaxanthin)

Most dietary carotenoid compounds do not undergo conversion to vitamin A, but exert an effect on the body in their predigested form.[24] Among them, two members of the xanthophyll family—lutein and zeaxanthin—form principal components of macular pigment in human eyes, and are central to maintenance of ocular health.[27] Xanthophylls are not synthesized by animals, and are derived in the diet mainly through ingestion of yellow or orange plant foods, such as corn, orange peppers and oranges, and green leafy vegetables such as spinach.[28]

The presence of two hydroxyl groups in their chemical structure renders them more polar than

other carotenoids, which alters their solubility, disposition, and function.[28-30] As yellow pigments, they may also be important to the filtration of damaging high-energy blue light in the lens and macula.[28]

Research related to xanthophylls (lutein and zeaxanthin) and eye health

Macular density, also called macular pigment optical density (MPOD), has been shown to decline with advancing age and is reflective of reduced xanthophyll concentrations. Low macular density been shown to correlate with increased AMD risk.[31,32]

A link between xanthophyll intake and reduced AMD risk is strengthened by epidemiologic data. In an analysis of dietary histories among AREDS participants, higher dietary xanthophyll intake was shown to significantly correlate with reduced risk for AMD.[17] In a separate cohort study, higher plasma xanthophyll levels were associated with reduced rates of AMD and cataract.[33]

Research prospectively evaluating lutein and zeaxanthin supplementation has yielded favorable results to date. In two studies among patients with AMD, supplementation with lutein resulted in higher macular density, at levels comparable to unaffected peers.[32,34] In one of these studies, patients with lower levels of baseline macular density had the most improvement with xanthophyll supplements.[34]

Omega-3 fatty acids

Polyunsaturated fatty acids are essential for a wide range of activities in the body. They comprise two classes distinguished by their chemical structures: omega-3 fatty acids, including short-chain alpha-linolenic acid (ALA) and long-chain molecules docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); and omega-6 fatty acids, principally linoleic acid (LA). ALA is available only through the diet in nuts and seeds—it is especially abundant in flaxseeds and flaxseed oil—and is metabolized in the body into EPA and DHA. DHA and EPA can be synthesized in the body and are also available in foods, mainly fish and organ meats.[35]

Molecules derived from EPA are critical in downregulating the sometimes excessive immune response to injury, infection, and stress, and they serve to protect against inflammatory and cardiovascular diseases. DHA is concentrated in outer segments of photoreceptors and at neural synapses, so it is important in the maintenance of normal central nervous system and ocular physiology.[35,36] DHA may also play a role in immune regulation.[37]

The omega-6 fatty acid LA is converted to the proinflammtory molecule arachidonic acid in the body. LA is abundant in many staples of the typical American diet, including meat, vegetable oils, and processed foods. The average ratio of omega-6 to omega-3 fatty acid intake each day may be as high as 10:1, far in excess of an optimal ratio (between 3:1 and 4:1).[35,37] In an effort to optimize protective benefit, increased omega-3 intake should ideally be accompanied by reduced omega-6 intake.

Research related to omega-3 fatty acids and eye health

Numerous cohort studies have shown that diets rich in omega-3 fatty acids have been associated with lower rates of AMD development.[13,14,37] The benefit conferred by omega-3 fatty acid intake is thought to relate to a lower and healthier ratio of omega-6 to omega-3 fatty acids, and indeed, in populations with increased omega-3 consumption, the protective benefit was often cancelled out by excessive omega-6 consumption.[37] Furthermore, the Blue Mountains Eye Study revealed a reduced risk of cataract among patients who reported high dietary levels of several nutrients, including polyunsaturated fatty acids.[15]

There is an interest in the effects various vitamin combinations can have on AMD progression. In vitro evidence suggests that, when exposed to a combination of carotenoids and omega-3 fatty acids, ocular photoreceptors undergo healthy differentiation and are protected from cell death induced by oxidative stress.[30] Clinical studies have shown that supplementation with combined lutein, zeaxanthin, and omega-3 fatty acids results in robust xanthophyll plasma levels and improves MPOD and visual acuity in AMD patients.[38,39] A second large, prospective, NIH-sponsored trial (AREDS 2)

will evaluate the role of various combinations of lutein, zeaxanthin, and omega-3 fatty acids along with standard and modified AREDS formulas (antioxidant vitamins and zinc).[40]

B Vitamins

B vitamins comprise a diverse family of water-soluble molecules which affect ocular tissue via a variety of possible mechanisms. Folic acid and vitamins B6 and B12 have been shown to reduce homocysteine levels, which may affect vascular endothelial integrity and be a factor in neovascular AMD development.[36] High doses of niacin, for example, have been shown to increase arterial flow in the retina in patients with AMD.[41] Riboflavin is a precursor to an enzymatic cofactor important to the health of crystalline lens. Deficiencies in riboflavin and folic acid have been associated with increased risk for cataract formation.[42]

Research related to B vitamins and eye health

Generous intake of dietary B vitamins, with or without supplements, has been associated with reduced cataract rates in observational studies.[15,16] In the Nurses' Health Study, women who reported increased intake of riboflavin and folate experienced a significantly lower incidence of nuclear cataract over the ensuing 13 to 15 years.[16] Similarly, the Blue Mountains Eye Study in Australia revealed a significant inverse relationship between dietary niacin, thiamin, and riboflavin intake and nuclear cataract prevalence.[15] When only supplement use was considered, lower rates of nuclear cataract were associated with thiamin, folate, and cyanocobalamin supplementation, as well as use of a multivitamin. Additionally, lower rates of cortical cataract were seen among those taking supplemental thiamin, folate, cyanocobalamin, or niacin.[43]

The Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) followed over 5,000 female healthcare workers with high cardiovascular risk for an average of 7 years, after blinded randomization to receive daily vitamin B supplementation or placebo. The group taking B vitamins had significantly lower rates of total and visually significant AMD, starting at 2 years of treatment.[44]

Selenium and ocular health

Selenium is found in high concentrations in retinal cells, and serves as a cofactor to antioxidant enzymes, particularly glutathione peroxidase. High dietary consumption of selenium has been associated with a range of health benefits in cohort studies.[20] Although the significance is not clear, selenium has been shown to be low in whole blood in AMD patients, and in serum and aqueous humor in cataract patients.[42,45]

Beta-carotene and lung cancer risk

Other than the potential for reversible yellow skin discoloration (carotenodermia) high dietary intake of beta-carotene is not commonly associated with adverse effects. Although it is a provitamin, beta-carotene is not thought to contribute to toxic accumulation of vitamin A.[46]

However, in the 1990s, evidence from two large, prospective, placebo-controlled trials, the Alpha Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study in Finland (N > 29,000), and the beta-Carotene And Retinol Efficacy Trial (CARET) in the US (N > 18,000), showed increased rates of lung cancer among high-risk patients (smokers, former smokers, and persons exposed to asbestos) taking daily beta-carotene-containing vitamin regimens.[47,48] In those studies, subjects received beta-carotene at daily doses of 20 mg and 30 mg, respectively. This has led to recommendations that patients at risk for lung cancer avoid taking beta-carotene.

Increased risk for cancer has not been associated with beta-carotene supplementation within the general, non-smoking population. In the Physicians' Health Study, healthy male physicians (N = 22,000), 11% of whom smoked, were randomized to receive either beta-carotene 50 mg every other day, or placebo. Subjects were followed for an average of 12 years, and no significant outcome differences were noted in cancer incidence, cardiovascular disease outcomes, or death.[49]

Vitamin E and prostate cancer risk

Due to conflicting findings from randomized, controlled trials, it is unclear whether high doses of supplemental vitamin E increases risk for some cancers. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) examined the potential effect of a daily regimen of oral vitamin E supplementation, selenium, both combined, or placebo, on the incidence of prostate cancer in healthy men over 50 (N = 35,533). Supplementation of vitamin E 400 IU/day as a single ingredient was associated with an increased incidence of prostate cancer (hazard ratio [HR] 1.17, $P = 0.008$); however, men who received vitamin E plus selenium had similar rates of prostate cancer as placebo-treated men (HR 1.05, $P = 0.46$).[50]

Several prospective trials have shown no significant effect on prostate cancer risk with supplemental vitamin E. These include the Physicians' Health Study II (vitamin E dose 400 IU every other day), and a subanalysis of AREDS (400 IU daily).[51,52] One trial (ATBC) demonstrated a reduced rate of prostate cancer among patients who took vitamin E 50 mg daily.[47] No evidence of increased prostate cancer rates has emerged from monitoring of the ongoing AREDS 2 trial, in which all non-placebo treated patients are receiving vitamin E 400 IU.[52]

Zinc and urinary adverse events

Risks associated with zinc supplements are typically anemia, reduced HDL cholesterol, and gastric upset. Among participants in the AREDS trial, in which patients received antioxidant vitamins and zinc supplementation, adverse events were uncommon. However, an increased proportion of patients treated with zinc underwent hospitalization for reasons related to the genitourinary tract. Overall, 7.5% of participants were hospitalized for genitourinary complaints (compared with 4.9% in the placebo arm; $P = 0.001$). Rates were higher among men taking zinc, of whom 8.6% had genitourinary hospitalizations compared with 4.4% of men not treated with zinc ($P = 0.001$). No increase in serious adverse events was seen among patients in the intervention arm.[26]

For subjects taking zinc alone, urinary tract infections and urinary stones were the most common types of events requiring hospitalization. Interestingly, infection rates were lower among patients taking both zinc and antioxidant vitamins.[53]

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Antioxidants | Zinc

AMD

This large, double-blind, placebo-controlled, multicenter trial demonstrated for the first time that antioxidant vitamin and zinc supplementation can slow AMD progression and vision loss among high-risk groups.

The NIH-sponsored Age-Related Eye Disease Study (AREDS) trial investigated the clinical course, prognosis, and risk factors of AMD. This analysis included 3,640 patients, aged 55 to 80 years, who had any of the following findings on fundoscopic examination: extensive small drusen, intermediate drusen, large drusen, noncentral geographic atrophy, or pigment abnormalities in one or both eyes; or advanced AMD or vision loss in one eye. Patients were randomized to one of four treatment arms: (1) vitamin C 500 mg, vitamin E 400 IU, and beta-carotene 15 mg; (2) zinc 80 mg as zinc oxide, and copper 2 mg as cupric oxide; (3) both regimens combined; and (4) placebo. Patients were followed clinically and with color fundus photography for an average of 6.3 years.

Results showed that the group treated with vitamins A, C, E, zinc, and copper (arm 3) had significantly better outcomes compared with placebo for reduced AMD progression (odds ratio [OR] 0.72). Supplement use conferred even greater benefit among patients with more advanced disease at baseline—with reductions in disease advancement (OR 0.66 vs placebo) and lower rates of visual loss (OR 0.73). Among this higher-risk group, significant delays in AMD progression were also observed with vitamins A, C, and E supplementation (arm 1; OR 0.76) and zinc and copper (arm 2; OR 0.71) compared with placebo.

Preliminary identification of the human macular pigment. Bone RA, Landrum JT, Tarsis SL. *Vision Res.* 1985;25(11):1531-5.

Xanthophylls

This laboratory investigation involving extracts from human donor eyes revealed the principal composition of macular pigment: lutein and zeaxanthin.

Pigment extraction and purification from human macular tissue yielded two major products, MP1 and MP2, which were evaluated via high-performance liquid chromatography (HPLC) on three separate stationary phases. In all instances, chromatograms of the macular purification products were indistinguishable from previously reported chromatographic spectra of lutein and zeaxanthin, as well as that of freshly eluted plant-based lutein and zeaxanthin standards. When macular and plant-derived pigments were co-injected—MP1 with lutein, and MP2 with zeaxanthin—single chromatographic peaks were observed, signifying identical composition. Further biochemical and chromatographic studies confirmed that MP1, like lutein, reacted to methanol and hydrochloric acid by producing two new compounds. In contrast, MP2, like zeaxanthin, did not react.

It was also observed that, although the ratio varied from eye to eye, lutein and zeaxanthin were present in comparable amounts in macular tissue, and in some instances zeaxanthin was dominant. This research supports findings from previous work suggesting that these carotenoids are exclusively derived from dietary sources. The authors speculate that the presence of lutein and zeaxanthin in retinal pigment may provide a photo-protective function against oxidative stress.

Macular pigment and risk for age-related macular degeneration in subjects from a northern-European population. Beatty S, Murray IJ, Henson DB, Carden D, Koh H, Boulton ME. *Invest Ophthalmol Vis Sci.* 2001;42:439-46.

Xanthophylls

AMD

This was among the first studies to correlate macular density with AMD risk.

Researchers in northwest England determined macular pigment optical density (MPOD) among two groups of subjects with categorical AMD risk factors: (1) advanced age, and (2) the presence of AMD in the opposite eye. For the investigation based on age, 46 subjects without evidence of ocular disease on ophthalmic examination, aged 21 to 81 years (mean age 51) were included. For the second analysis, nine patients with advanced neovascular AMD in one eye, and no evidence of AMD in the fellow eye (high-risk eye) were recruited, along with controls matched for age, sex, iris color, smoking history, and lens density. All participants underwent MPOD assessment by a psychophysical measure known as heterochromatic flicker photometry.

As analyzed by regression analysis and analysis of variance, optical density among healthy volunteers significantly declined with advancing age (right eye $P = 0.0006$, left eye $P < 0.0001$). For the second group of subjects, those with unilateral AMD, statistical analyses revealed high-risk eyes had mean MPOD about half that of standard-risk eyes of matched controls, despite similar rates of other ocular characteristics including nuclear opalescence, nuclear color, cortical opacification, and posterior subcapsular cataract. Authors speculated that age-related decreases in MPOD, such as those observed in their study, may relate to inadequate uptake of retinal carotenoids—due to dietary intake deficiencies or reduced retinal ability to absorb, transport, or accumulate these nutrients—or to their excessive utilization, due to mounting oxidative stress, resulting in depletion.

Resonance Raman measurement of macular carotenoids in normal subjects and in age-related macular degeneration patients. Bernstein PS, Zhao D, Wintch SW, Ermakov IV, McClane RW, Gellerman W. *Ophthalmology*. 2002;109:1780-7.

Xanthophylls

AMD

This was among the first studies to directly measure macular lutein and zeaxanthin density in living patients, revealing significantly lower macular carotenoid levels among patients with AMD compared with healthy, age-matched peers. It also correlated a history of high-dose lutein supplementation with normalized macular density.

In this population-based cohort study, 63 patients with AMD (93 eyes) and without other significant ocular morbidity were recruited at the University of Utah School of Medicine, along with 138 healthy control subjects (220 eyes). Patients were interviewed regarding supplementation practices and stratified accordingly. All subjects underwent macular examination of carotenoid levels with resonance Raman spectography, a technology considered highly sensitive and specific in the detection of macular pigments.

Results showed that in normal subjects, macular carotenoid intensity significantly declined with advancing age up to 60 years ($P < 0.001$, one-way ANOVA). Among patients with AMD who were not taking lutein supplements, mean lutein and zeaxanthin levels were 32% lower than comparator eyes in healthy, age-matched controls ($P = 0.001$). AMD patients supplementing with lutein ≥ 4 mg/day had significantly higher macular lutein and zeaxanthin levels compared to age-matched AMD patients who were not supplementing ($P = 0.038$, two-sided *t*-test). Macular lutein/zeaxanthin levels among AMD patients who reported supplementation with high-dose lutein were similar to that of normal subjects ($P = 0.829$).

Plasma lutein and zeaxanthin and other carotenoids as modifiable risk factors for age-related maculopathy and cataract: The POLA Study. Delcourt C, Carriere I, Delage M, Berberger-Gateau P, Schach W, and the POLA Study Group. *Invest Ophthalmol Vis Sci*. 2006;47:2329-35.

Xanthophylls

AMD

A population-based study in Southern France showed that higher plasma levels of the xanthophylls—zeaxanthin in particular—correlated with a reduced risk for age-related ocular diseases.

Residents of Sete, France (N = 899), aged ≥ 60 years, provided fasting blood samples and underwent baseline ophthalmic exam including visual acuity, slit lamp examination, and 50° color retinal photography. Plasma levels of lutein, zeaxanthin, 3′-dehydro-lutein, and other carotenoids were assessed.

Individuals with high plasma levels (≥ 80th percentile) of lutein (≥ 0.41 µM), zeaxanthin (≥ 0.09 µM), or both, had significantly lower rates of AMD compared to individuals with lower levels. High plasma levels of zeaxanthin and 3′-dehydro-lutein were significantly associated with reduced risk for nuclear cataract. Most notably, high levels of zeaxanthin correlated with a 93% reduction in AMD risk ($P = 0.005$) and a 75% reduction in nuclear cataract risk ($P = 0.004$). Associations between AMD or cataract and alpha-carotene, beta-carotene, beta-cryptoxanthin, and lycopene were not found in this study.

The relationship of dietary carotenoid and vitamin A, E, and C intake with age-related macular degeneration in a case-control study. AREDS Report No. 22. SanGiovanni JP, Chew EY, Clemons TE, et al, for the Age Related Eye Disease Study Research Group. *Arch Ophthalmol*. 2007;125(9):1225-32.

Xanthophylls

Antioxidants | Zinc

AMD

An extensive AREDS dietary database showed that intake of lutein/zeaxanthin—to a greater extent than other nutrients examined—was associated with significantly reduced rates of AMD.

At enrollment in AREDS, 4,519 patients completed a validated food frequency questionnaire, in which the frequency and serving size of 90 itemized foods over the past year was recalled. Dietary nutrient content per patient was calculated using National Cancer Institute's DIETSys software. After adjusting for age, sex, calorie intake, and other variables, consumption of each nutrient was correlated with AMD severity. Additionally, subjects were grouped by quintiles according to nutrient consumption for vitamin A, retinol, beta-carotene, alpha-carotene, beta-cryptoxanthin, lutein/zeaxanthin, lycopene, vitamin C, and alpha-tocopherol. For each nutrient studied, risk for geographic atrophy and neovascular AMD among the highest quintile (20% of subjects consuming the most) and lowest quintile (20% consuming the least) were compared.

Results showed that high intake of vitamin A and lutein/zeaxanthin correlated with significantly lower rates of AMD, as characterized by extensive intermediate or large drusen (group 3), geographic atrophy (group 4), or neovascularization (group 5). After adjustment for multiple variables, lutein/zeaxanthin were the only nutrients significantly associated with reductions in the three most advanced disease groups. Furthermore, in a separate analysis, lutein/zeaxanthin intake of the highest quintile remained the only independent nutritional predictor of reduced risk among patients with neovascular AMD (OR 0.65 compared with lowest intake; $P \leq 0.05$) and geographic atrophy (OR 0.45; $P \leq 0.05$).

LAST II: Differential temporal responses of macular pigment optical density in patients with atrophic age-related macular degeneration to dietary supplementation with xanthophylls. Richer S, Devenport J, Lang JD. *Optometry*. 2007;78:213-9.

Xanthophylls

AMD

This analysis of the Lutein Antioxidant Supplementation Trial (LAST) showed that patients who benefited most from supplementation with lutein, vitamins, minerals, and antioxidants were those with lowest baseline macular pigmentation.

LAST was a randomized, double-blind, placebo-controlled trial in which a largely male US veteran population (mean age 75 years) with atrophic AMD (N = 90), were treated with placebo or one of two daily supplement regimens: (1) lutein 10 mg, or (2) lutein 10 mg plus broad-spectrum antioxidants including bioflavinoids, vitamins, minerals, and amino acids. Patients were followed with serial macular pigment optical density (MPOD) measurements by heterochromatic flicker photometry over the course of 12 months.

Researchers found significantly improved MPOD measurements among both of the treated groups compared with baseline and compared with placebo. Rates of MPOD increase were not different between the two treatment arms, indicating that lutein was the nutrient underlying the change. Among all lutein-treated patients, those with the lowest baseline MPOD values saw the greatest increases in MPOD, signifying a potential benefit for supplementation within this higher-risk population.

Omega-3 long-chain polyunsaturated fatty acid intake and 12-y incidence of neovascular age-related macular degeneration and central geographic atrophy: AREDS report 30, a prospective cohort study from the Age-Related Eye Disease Study. SanGiovanni JP, Agron E, Meleth D, et al. *Am J Clin Nutr*. 2009;90:1601-7.

Omega-3s

AMD

Consumption of foods rich in omega-3 fatty acids may reduce the risk for development of advanced stages of AMD.

In a nested cohort study of the large, multicenter AREDS trial, 1,837 patients at moderate to high risk for progression to advanced AMD were identified, and baseline dietary reports of omega-3 fatty acid intake were analyzed. Patients were followed for AMD progression over 12 years with annual stereoscopic color photographs.

Over the course of the 12-year period, 20% of patients developed central geographic atrophy (CGA) and 32% developed neovascular (NV) AMD. Compared with those reporting lowest omega-3 fatty acid intake, patients who reported the highest intake (median 0.11% of total caloric intake) had a 30% lower likelihood of progressing to CGA or NV AMD. For combined DHA and EPA intake, OR = 0.65 (95% CI: 0.45, 0.92; $P \leq 0.016$) for CGA and 0.68 (95% CI: 0.49, 0.94; $P \leq 0.020$) for NV AMD. These results support the idea that omega-3-fatty acids in food or supplements may counteract inflammatory aspects of AMD pathophysiology.

These data build upon prior AREDS reports associating dietary omega-3 fatty acid and fish consumption with reduced risk for neovascular AMD. Inverse associations between neovascular AMD and total dietary omega-3 long-chain polyunsaturated fatty acids (OR 0.61), docosahexaenoic acid (OR 0.54), and broiled and baked fish (OR 0.61) were shown at baseline.[54] At six years, habitual consumption of dietary omega-3 long-chain polyunsaturated fatty acids was shown to decrease risk of progression from bilateral drusen to central geographic atrophy.[55]

Dietary fat and risk for advanced age-related macular degeneration. Seddon JM, Rosner B, Sperduto RD. *Arch Ophthalmol*. 2001 Aug;119:1191-9.

Omega-3s

AMD

Diets high in fish and omega-3 fatty acids and low in omega-6 fatty acids were associated with reduced risk for AMD in a US multicenter, case-control study.

In order to better understand the relationship between specific types of dietary fats and AMD, the Eye Disease Case-Control Study analyzed semi-quantitative food frequency questionnaires from 349 patients, aged 55 to 88 years, with advanced neovascular disease diagnosed in the previous year. Matched control subjects (N = 504) were patients with ocular disease attending the same clinics, but with no evidence of AMD.

Compared with controls, patients with AMD reported significantly lower intake of omega-3 fatty acids and fish ($P = 0.05$), and higher intake of omega-6 fatty acids or linoleic acid. Among patients who consumed high amounts of omega-6 fatty acids, the benefit afforded by omega-3 fatty acid consumption was lost, underscoring the importance of consuming a higher ratio of omega-3 to omega-6 fatty acids. Increased rates of AMD correlated with consumption of vegetable fats (mostly processed, OR 2.22, $P = 0.007$ for the trend), monounsaturated fats (OR 1.71, $P = 0.03$), polyunsaturated fats (OR 1.86, $P = 0.03$), and linoleic acids ($P = 0.02$).

Cigarette smoking, fish consumption, omega-3 fatty acid intake, and associations with age-related macular degeneration: The US Twin Study of Age-Related Macular Degeneration. Seddon JM, George S, Rosner B. *Arch Ophthalmol*. 2006;124:995-1001.

Omega-3s

AMD

Consistent with earlier findings within a different population (Seddon et al, 2001), this study of elderly American male twins confirmed that a favorable ratio of dietary omega-3- to omega-6 fatty acid reduces the risk of AMD development.

One year prior to this publication, the authors showed that, among US veteran twin males born between 1917 and 1927 (N = 840), AMD risk was a product of both genetic and environmental influences.[56] A subset of the cohort evaluated in that study, derived from National Academy of Sciences/National Research Council World War II Veteran Twin Registry, was evaluated in this case-control study to assess the influence of behavioral (smoking) and nutritional factors (fish consumption and fat intake) on AMD.

Pairs who were concordant or discordant for AMD, and pairs in which both twins were unaffected were included (N = 681). Evaluations included ophthalmic examination, retinal photography, risk-factor questionnaire, and a validated, standardized food frequency questionnaire, with questions about portion size and multivitamin/supplement use.

Results were remarkable for reduced AMD risk among those with high fish consumption (≥ twice per week) compared to those with low consumption (< once per week; OR 0.64; $P = 0.04$). High intake of omega-3 fatty acids was also found to be protective (OR = 0.56 between fourth and first quartiles of intake). The benefit of high omega-3 fatty acid intake was retained among those with lower omega-6 fatty acid intake (below the median), but high omega-3 fatty acid intake was not beneficial among men with high omega-6 fatty acid intake. This is congruent with prior research that points to a protective role of the proper ratio of dietary omega-3 to omega-6 fatty acids, rather than the quantity of either component alone. Also significant was the finding that veterans with a history of smoking or current smoking were at higher risk for AMD (OR 1.74; $P = 0.007$).

The LUTEGA Study: lutein and omega-3 fatty acids and their relevance for macular pigment in patients with age-related macular degeneration (AMD). Jentsch S, Schweitzer D, Hammer M, Lang GE, Dawczynski J. Poster presented at the Association for Research in Vision and Ophthalmology Meeting; May 1-5, 2011; Ft. Lauderdale FL.

Xanthophylls
Omega-3s
AMD

A long-term supplement regimen of lutein, zeaxanthin, and omega-3 fatty acids improved macular pigment optical density (MPOD) and visual acuity among patients with AMD.

In a double-blind, placebo-controlled trial, 172 patients over 50 were randomized to receive one of two dosing regimens of lutein, zeaxanthin, and omega-3 fatty acids over a 12-month period. Patients in arm 1 received lutein 10 mg; zeaxanthin 1 mg; and omega-3 fatty acids, including docosahexaenoic acid (DHA) 100 mg, and eicosapentaenoic acid (EPA) 30 mg per day. Patients in arm 2 received twice the dose as arm 1: lutein 20 mg, zeaxanthin 2 mg, and DHA 200 mg EPA 60 mg per day. A control group received placebo.

After 1 year of supplementation, all MPOD measurements (volume, area, maximum, and mean) in both supplemented groups increased significantly compared with baseline values and compared with placebo ($P < 0.001$ for MPOD volume). By contrast, MPOD declined significantly among placebo-treated patients. Visual acuity was also significantly improved at 12 months in both treatment groups compared with baseline ($P = 0.001$ in arm 1; $P < 0.001$ in arm 2), and compared with placebo ($P = 0.006$ and $P = 0.038$, respectively). Plasma concentrations of lutein rose in dose-dependent manner among treated patients, and declined among placebo-treated patients. Authors concluded that lutein, zeaxanthin, and omega-3 fatty acid supplementation stabilized or improved macular pigment density and visual acuity, likely by exerting a protective effect on the macula.

Oral supplementation of lutein/zeaxanthin and omega-3 long chain polyunsaturated fatty acids in persons aged 60 years or older, with or without AMD. Huang LL, Coleman HR, Kim J, et al. *Invest Ophthalmol Vis Sci*. 2008;49:3864-9.

Xanthophylls
Omega-3s
AMD

A small-scale, prospective, randomized, controlled trial documented that serum levels of lutein and zeaxanthin can be increased with oral supplementation and are unaffected by the addition of omega-3 fatty acids. This study and the 2001 AREDS trial formed the basis for the AREDS 2 trial.

Forty patients over age 60 were enrolled, with mild to advanced AMD or no disease. After baseline assessments, patients were treated for 6 months with lutein 10 mg and zeaxanthin 2 mg daily, and either 1 g per day of omega-3 fatty acids (docosahexaenoic acid [DHA] 350 mg and eicosapentaenoic acid [EPA] 650 mg), or placebo. The stated objectives were to assess serum levels of all agents, correlate those with macular pigment density and visual acuity assessments, and identify potential adverse events.

Researchers found that serum lutein and zeaxanthin levels increased during the first month and plateaued for the next 5 months of treatment. Levels returned to baseline values by 3 months following discontinuation. Compared with placebo, the addition of DHA and EPA was not associated with changed serum lutein or zeaxanthin levels. Serum lutein levels, but not zeaxanthin levels, were significantly lower among patients with AMD compared with those without AMD. No changes in visual acuity were noted over the 9-month follow-up period, and neither macular findings nor serious adverse events were reported.

AREDS 2: Ongoing (http://clinicaltrials.gov/ct2/show/NCT00345176?term=AREDS2&rank=1)

Xanthophylls
Omega-3s
AMD

Definitive roles of lutein, zeaxanthin, and omega-3 fatty acids in the prevention of AMD and cataract progression are currently under investigation in AREDS 2.

AREDS 2 is a second large-scale, NIH-sponsored, phase III, randomized, controlled trial of nutrient effects on AMD development and vision loss in at-risk individuals. In contrast to the first AREDS, AREDS 2 will evaluate xanthophylls, omega-3 fatty acids, and both in combination. Researchers intend to enroll 4,000 subjects, aged 50 to 85 years, with either bilateral large drusen, unilateral large drusen and advanced AMD, or bilateral advanced AMD at baseline. Further, AREDS 2 has been designed to show the effects of partially modifying the original AREDS formula, including omission of beta-carotene and reduced zinc dose. Cataract development will also be tracked.

Enrollment was completed in June 2008, and patients will be followed for 5 to 6 years. Data are not available at the time of this printing.

Whole blood selenium in exudative age-related maculopathy. Mayer MJ, van Kuijk FJGM, Ward B, Glucs A. *Acta Ophthalmologica Scandanavica.* 1998;76:62-7.

B vitamins | Selenium
AMD

Patients with neovascular AMD were found to have low whole blood selenium levels, compared with age-matched controls.

Based on knowledge that selenium is a cofactor in antioxidant mechanisms and can be demonstrated in high concentrations in retinal tissue, this small study aimed to understand whether whole blood levels correlated with AMD presence. Ten patients with neovascular AMD and nine controls, aged 61 to 76 years, were evaluated. Whole blood samples, chosen over plasma in consideration of selenium in red blood cells, revealed significantly reduced mean levels of selenium among AMD patients (186.6 µg/L), compared with those without AMD (207.0 µg/L, $P = 0.018$ ANOVA). This was the case despite a greater proportion of participants in the AMD arm who were taking selenium supplements (7 of 10) compared with controls (1 of 9). The reason for the discrepancy was not known, although possible explanations include differences in diet, environment, or occupational exposures.

In a second arm of this study, blood selenium concentrations among four healthy volunteers, aged 24 to 47 years, were measured for 6 months on selenium supplementation (80 µg per day of sodium selenate), after a 14-month unsupplemented baseline period. In this population, selenium supplementation showed no sustained elevations in whole blood selenium levels. Authors concluded the lack of observable response to supplementation may be related to the use of an inorganic form of the compound, and that studies with organic selenium were warranted.

Effect of niacin on retinal vascular diameter in patients with age-related macular degeneration. Barakat MR, Metelitsina TI, DuPont JC, Grunwald JE. *Curr Eye Res*. 2006;31:629-34.

B vitamins | Selenium

AMD

Niacin may benefit AMD patients by increasing retinal arterial flow.

Niacin, a B vitamin, has known lipid-lowering and vasodilatory effects. This trial was conducted to explore the potential of niacin as a therapeutic agent for ischemic vascular diseases of the eye. A randomized, double-blind, placebo-controlled crossover trail of 12 AMD patients examined vascular effects of single-dose niacin at baseline, and at 30 and 90 minutes post-dose, compared with placebo. Participant eyes had evidence of large bilateral drusen, and no evidence of neovascularization. Authors reported that, due to adverse events of nausea and flushing, the niacin dose (not stated) given to the first six patients was reduced to 250 mg in the subsequent six patients.

Fundoscopic photography of retinal vasculature revealed a 5.3% average increase in diameter of the inferior temporal artery at 30 minutes ($P = 0.05$), and 5.8% increase at 90 minutes ($P = 0.003$) post-niacin. In contrast, significant diameter changes in superior temporal and inferior temporal veins were not observed. Authors concluded that niacin has a vasodilatory effect on retinal arteries.

Folic acid, pyridoxine, and cyanocobalamin combination treatment and age-related macular degeneration in women: The Women's Antioxidant and Folic Acid Cardiovascular Study. Christen WG, Glynn RJ, Chew EY, Albert C, Manson JE. *Arch Intern Med*. 2009;169(4):335-41.

B vitamins | Selenium

AMD

A large, prospective, randomized, double-blind, placebo-controlled trial, the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS), showed that AMD rates among women at high risk for vascular disease could be reduced by 35% to 40% with B vitamin supplementation.

WAFACS enrolled female healthcare professionals over the age of 40 years who were at increased cardiovascular (CV) risk due to current disease or at least three CV risk factors, and randomized them to receive either placebo or a combination of folic acid 2.5 mg daily, pyridoxine hydrochloride 50 mg daily, and cyanocobalamin 1 mg daily. Among them, 5,205 without evidence of AMD at baseline were included in this analysis and followed for development of AMD.

Over the course of 7.3 years of follow-up, women treated with vitamin B supplementation experienced significantly lower incidence of total AMD (OR 0.66; 95% CI, 0.47-0.93 [$P = 0.02$]), and vision-impairing AMD (OR 0.59; 95% CI, 0.36-0.95 [$P = 0.03$]). Benefit from vitamin supplementation emerged at approximately 2 years and 4 years of treatment for reduction of total and visually significant AMD, respectively. Although not studied in this trial, a proposed mechanism for the vitamin B effect may be reduction of serum homocysteine, which has been associated with increased AMD risk in epidemiologic studies.

Long-term nutrient intake and early age-related nuclear lens opacities. Jacques PF, Chylack LT, Hankinson SE, et al. *Arch Ophthalmol*. 2001;119:1009-19.

Antioxidants | Zinc
CATARACT

The Nutrition and Vision Project (NVP)—the first study to correlate prospective, long-term, serial nutritional data with lens opacity outcomes—demonstrated that several nutrient variables, in particular high vitamin C intake, were associated with reduced nuclear cataract incidence in non-diabetic women.

The NVP aimed to correlate usual nutrient intake with risk of age-related lens opacification among Boston-based participants in the Nurses' Health Study (NHS). Subjects with neither diabetes nor a prior diagnosis of cataract were enrolled. Four hundred seventy-eight women, aged 53 to 73 years, underwent detailed ophthalmic exam and analysis of plasma antioxidant concentrations, as well as analysis of five food frequency questionnaires collected over the previous 13 to 15 years for the purposes of the NHS, providing the basis for calculating total nutrient intake from food and supplements.

Researchers found significant inverse correlations between intake of vitamin C ($P = 0.003$), riboflavin ($P = 0.03$), and folate ($P = 0.005$) and incidence of nuclear cataract. After adjusting for intake of other vitamins, only vitamin C emerged as an independent predictor of lens health. Women who took vitamin C supplements for at least 10 years had 43% to 64% lower rates of nuclear cataract. Cataract rate comparisons between upper and lowermost nutrient quintiles favored higher intake of beta-carotene ($P = 0.04$), vitamin E ($P \leq 0.03$), and lutein/zeaxanthin ($P \leq 0.04$).

Diet and cataract: The Blue Mountains Eye Study. Cumming RG, Mitchell P, Smith W. *Ophthalmology*. 2000;107:450-6.

Antioxidants | Zinc
B vitamins | Selenium
CATARACT

This large, population-based, cross-sectional study showed that high intake of certain micro- and macronutrients—vitamin A, niacin, thiamine, riboflavin, polyunsaturated fats, and protein—may protect against the development of cataracts.

The Blue Mountains Eye Study collected and analyzed dietary and ocular data on residents of an urban community near Sydney, Australia, aged 49 to 97 years, median age 65 years. On enrollment, participants completed a 145-item food frequency questionnaire detailing dietary habits over the past year, including portion size and supplement use. The 2,900 subjects who provided complete dietary histories were included in the analysis. They then underwent ophthalmic assessment and lens photography for detection and grading of cataract.

Results showed that, after adjustment for potentially confounding factors, high intake of vitamin A (OR 0.5, $P = 0.001$), niacin (OR 0.6, $P = 0.008$), thiamine (OR 0.6, $P = 0.03$), riboflavin (OR 0.5, $P = 0.01$), and protein (OR 0.5, $P = 0.009$) significantly correlated with protection against nuclear cataract. Among specific vegetables, spinach approached statistical significance in reducing rates of nuclear cataract (OR 0.7, $P = 0.07$). Intake of polyunsaturated fats was associated with reduced rates of cortical cataract (OR 0.7, $P = 0.02$), which persisted after adjustment for age, sex, education, smoking, diabetes, hypertension, corticosteroid use, and solar UV damage to skin ($P = 0.007$). None of the studied nutrients correlated with protection against posterior subcapsular cataract.

Use of vitamin supplements and cataract: The Blue Mountains Eye Study. Kuzniarz M, Mitchell P, Cumming RG, Flood VM. *Am J Ophthalmol*. 2001;132:19-26.

Antioxidants | Zinc
B vitamins | Selenium
CATARACT

An extension of the Blue Mountains Eye Study described above (Cumming et al, 2000), this analysis revealed reduced cortical and nuclear cataract prevalence with vitamin supplementation and increased duration of multivitamin use. It was the first study to correlate supplemental vitamin B12 and folate use with reduced cataract risk.

Among 2,873 participants, aged 49 to 94 years, enrolled in the Blue Mountains Eye Study, data regarding use of supplements —including dose, frequency, and duration of multivitamins and individual vitamins—were extracted from validated questionnaires. Diet-derived nutrients were not taken into account in this analysis. Nutrient exposure from supplement use was compared with findings on ophthalmic exam.

In this urban Australian population, 33% of participants reported taking supplements of some sort. Cortical cataract, observed in 22% of participants, was inversely associated with thiamine dose (OR 0.7, $P = 0.02$), niacin dose (OR 0.7, $P = 0.04$), folate dose (OR 0.6, $P = 0.01$), and vitamin B12 dose (OR 0.7, $P = 0.03$). Among subjects reporting multivitamin use, greater duration of use strongly correlated with reduced cortical cataract development ($P = 0.03$).

Nuclear cataracts were diagnosed among 12% of participants, and were less common among participants who took multivitamins regularly (OR 0.6, $P = 0.05$; $P = 0.02$ for the trend), and those on long-term vitamin A (OR 0.4, $P = 0.01$; $P = 0.06$ for the trend). Higher doses of thiamine (OR 0.6, $P = 0.03$), folate (OR 0.4, $P = 0.03$), and vitamin B12 (OR 0.3, $P = 0.01$) also appeared protective against nuclear cataract. Posterior subcapsular cataracts were seen in 6% of participants, and were not influenced by multivitamin use. Pyridoxine use (OR 1.6, $P = 0.05$) and daily doses of thiamin greater than 4.4 mg (OR 1.6, $P = 0.04$) were associated with slightly higher rates of posterior subcapsular cataracts.