

**COMPLEMENTARY THERAPY ASSESSMENT
ANTIOXIDANT SUPPLEMENTS AND
AGE-RELATED MACULAR DEGENERATION
LIMITED REVISION JANUARY 2002**

SUMMARY

INTRODUCTION TO THE TOPIC

The role of antioxidant supplements in the development of age-related macular degeneration (AMD) has received a great deal of interest. Antioxidants are found naturally in food and include vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), carotenoids, selenium, and zinc. Antioxidants neutralize the damage to cells caused by free radicals and may be relevant to AMD if oxidative damage to the retina leads to AMD.

CONCLUSIONS

A prospective, randomized, controlled clinical trial supports the use of antioxidant vitamins and minerals in patients with intermediate-risk non-neovascular AMD to reduce the rate of progression to advanced AMD. Intermediate-risk AMD was defined by the Age Related Eye Disease Study (AREDS) Group as patients with extensive medium-sized drusen or one or more large drusen (≥ 125 microns) in one or both eyes. The role of antioxidant supplements in the prevention of AMD or in slowing progression of AMD for those with the early stages of the disease has not been adequately answered in randomized, controlled trials. Observational studies have returned conflicting results. It is possible that there are long-term risks in high levels of supplementation of specific antioxidants.

Patients with intermediate AMD in one or both eyes and patients with advanced AMD in one eye only or vision loss due to AMD in one eye should consider taking antioxidants plus zinc on a daily basis. The dosages used in AREDS were as follows: vitamin C, 500 mg; vitamin E, 400 IU; beta-carotene, 15 mg (approximately 25,000 IU vitamin A); zinc 80 mg as zinc oxide; and copper, 2 mg, as cupric oxide. Copper should be taken with zinc because high-dose zinc is associated with copper deficiency anemia. Smokers probably should not use beta-carotene because previous studies have suggested an association with lung cancer and beta-carotene in smokers. All patients can be encouraged to maintain a healthy diet, with consumption of fresh fruits and vegetables, for a variety of health benefits.

BENEFITS

The AREDS evaluated treatment for patients without AMD, and patients with small drusen, pigmentary changes, or nonextensive intermediate drusen, but the rate of progression to advanced AMD was too low to assess treatment effect.

Intermediate-risk AMD was defined by the AREDS Study Group as patients with extensive medium-sized drusen or one or more large drusen (≥ 125 microns) in one or both eyes. Advanced AMD was defined as geographic atrophy involving the center of the macula (fovea) or features of choroidal

neovascularization. For patients with intermediate AMD in one or both eyes and for patients with advanced AMD in one eye only or vision loss due to AMD in one eye, the AREDS results showed that supplementation with antioxidants and zinc reduced the risk of developing advanced AMD by 25%. The results for reduction in vision loss from advanced AMD were statistically significant only for the combination of zinc and antioxidant treatment.

A Cochrane Library systematic review included one randomized controlled study that demonstrated a positive, if limited, effect of a nutritional supplement on vision and progression of AMD. In this study, people in the zinc-treated group were less likely to lose 10 or more letters on the ETDRS chart than controls were. The other studies found no beneficial effect or a benefit of marginal statistical significance. In the Cochrane report, the one randomized controlled trial of supplements for prevention of AMD showed no apparent effect.

RISKS

The adverse effects and toxicity, if any, of supplementation with antioxidants over a long-term period (10 years or more) is unknown. There were no statistically significant serious adverse effects associated with treatment in the AREDS; however, hospitalizations for genitourinary disorders were more frequent for male and female participants receiving zinc. Zinc sulfate supplementation may depress copper levels and cause copper deficiency anemia, so copper should be taken with high-dose zinc. There are two randomized controlled trials of supplementation in groups of people at high risk for cancer (smokers and asbestos-exposed workers) where high levels of beta-carotene were associated with significantly higher cancer incidence and mortality rates. One theory on the risk of supplementation with a single product is that protection may require multiple nutrients consumed in a balanced combination at nutritional doses.

The cost of using antioxidant supplements can be significant and is seldom covered by health insurance. The quality of supplements can vary by manufacturer and absorption can be affected by a variety of dietary factors.

REPORT

DESCRIPTION OF ANTIOXIDANT SUPPLEMENTS

Antioxidant substances are found naturally in food and include vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), carotenoids, anthocyanidins, selenium, and zinc. Carotenoids, nutrients that are not classified as vitamins, include beta-carotene, alpha-carotene, the lycopenes, lutein, and zeaxanthin. The carotenoids are found in leafy green vegetables, corn, kiwi, and many other green, red, or yellow fruits and vegetables. The anthocyanidins are responsible for the blue color of blueberries and bilberries. Antioxidants neutralize the damage to cells caused by free radicals, and may be relevant to AMD if oxidative damage to the retina leads to AMD. Many different brands of antioxidant supplements are sold singly and in various combinations as tablets, capsules, or sprays. The manufactured quality and formulation of the supplement can influence absorption and therefore potential benefit.

MECHANISM OF ACTION

The exact mechanism of antioxidant in the retina is unknown. A hypothesis is that damage to the retinal photoreceptors is caused by oxidation, leading to impaired function and eventually to degeneration of the macula. Antioxidants could prevent cellular damage in the retina by eliminating free radicals and harmful oxidants that are generated by light absorption and by normal metabolic processes.^{1,2}

DEFINITION OF THE PROBLEM

Age-related macular degeneration is a disorder of the macula that occurs most often in patients 50 years of age or older and is characterized by one or more of the following findings: drusen formation, retinal pigment epithelial (RPE) abnormalities, geographic atrophy of the RPE and choriocapillaris, and neovascular maculopathy. Although most people with macular degeneration have the non-neovascular (atrophic, or dry) form, the majority of patients with severe visual loss from AMD have the neovascular form associated with choroidal neovascularization (CNV) and/or pigment

epithelial detachment. Age-related macular degeneration is the leading cause of irreversible severe central visual loss in Caucasians 50 years old and older in the United States. As yet, there is no proven effective therapy for the non-neovascular form of AMD or for the majority of patients with neovascular maculopathy.

FDA STATUS/LEGAL STATUS

According to the NIH Office of Dietary Supplements,³ the Dietary Supplement Health and Education Act of 1994 defines dietary supplements as a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical; or a dietary substance for use to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above. Any of these must be intended for ingestion in the form of a capsule, powder, tablet, softgel, liquid, or gelcap, and must not be represented as a conventional food or as a sole item of a meal or the diet.

Dietary supplements are widely available through many commercial sources including health food stores, grocery stores, and pharmacies and by mail and on the Internet. Historically in the United States, the most prevalent type of dietary supplement was a multivitamin/mineral tablet or capsule that was available in pharmacies by prescription or "over the counter." Supplements containing strictly herbal preparations were less widely available. Currently in the United States, a wide array of supplement products are available, including vitamins, minerals, and other nutrients; botanical supplements; and ingredients and extracts of animal and plant origin, but producers of supplements are not allowed to attribute any potential health benefit to their products.

The Dietary Supplement Health and Education Act of 1994 limits the authority of the Food and Drug Administration (FDA) over these products since they are not classified as drugs. The FDA requirement for pre-market review of dietary supplements is less than that over other products it regulates, such as drugs and many additives

used in conventional foods. The FDA oversees safety, manufacturing, and product information such as claims, in a product's labeling, package inserts, and accompanying literature. The Federal Trade Commission, which oversees advertising, has issued advertising guidelines, and has taken a number of enforcement actions against companies whose advertisements contained false and misleading information.

SUMMARY OF EVIDENCE

Search Methods and Study Selection

MEDLINE and the Cochrane Library were searched using the keywords macular degeneration, nutrition, antioxidants, and vitamins. The MEDLINE search was restricted to review articles and to English language. A search of the Cochrane Controlled Trials Register and MEDLINE revealed two systematic reviews on this subject in the Cochrane Library. A search of MEDLINE for additional articles after the submission date of these papers was undertaken using the same keywords.

Statistical Issues and Study Design

The Age-Related Eye Disease Study (AREDS) is a multicenter, randomized, double-masked clinical trial of the effectiveness of daily supplementation with vitamin C, E, beta-carotene, and zinc versus placebo on the clinical course, risk factors, and prognosis for AMD.⁴ The study enrolled 4,757 individuals age 55 years to 80 years, and 90% of participants had at least 5 years of follow-up; mean follow-up time was 6.3 years. The daily supplement contained vitamin C, 500 mg; vitamin E, 400 IU; beta-carotene, 15 mg (approximately 25,000 IU vitamin A); zinc, 80 mg as zinc oxide; and copper, 2 mg as cupric oxide.

According to a Cochrane Library systematic review⁵ published in November 1998, there have been four published randomized trials where antioxidant vitamin and/or mineral supplementation, alone or in combination, for AMD was compared with a control group. Two of these studies are from the United States,^{6,7} one is from Austria,⁸ and one is from Switzerland.⁹ The Austrian study and one of the US studies⁷

used zinc sulfate 200 mg daily compared to placebo. The Swiss study and the second US study, the AMD Study Group,⁶ used a combination antioxidant product compared to placebo. These four trials were small; the number of participants for which data were analyzed ranged from 20 to 151 and the average age was 70 years. The trials used different outcome measures for visual function and AMD progression.

A second Cochrane Library review,¹⁰ substantively amended in July 1999, examined evidence supporting the role of supplements in preventing AMD. Only one randomized trial with reported outcomes was eligible for inclusion in the review. This study was added to a larger study of Finnish male smokers, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC trial).¹¹ In this subgroup of the ATBC trial of 941 subjects (50 to 69 years old), 5 to 8 years of supplementation with alpha-tocopherol or beta-carotene, alone or in combination, was compared to placebo. Only 14 participants were diagnosed with late AMD during the study, which limited the power to detect differences for this group, and 269 cases of early AMD were diagnosed during the study period.

A recent review article,¹² which summarized epidemiological studies of antioxidants and AMD, noted that these are mainly of cross-sectional, longitudinal, or case-control design, with no attempt to control subject intake of antioxidants. This paper reported the results of several large studies with combined participation of over 25,000 subjects. These data, as well as two of the randomized trials in the Cochrane Review, are discussed in another recent review paper.¹³

Two additional studies were not included in the review papers. One is part of the Blue Mountains Eye Study, a cross-sectional population-based study that included 2900 participants age 49 years and older.¹⁴ The second is the Pathologies Oculaires Liées à l'Age (POLA) Study, a population-based study of 1,791 participants.¹⁵

Observational studies have returned inconsistent results and must be interpreted with caution. In these studies there is no control on the intake of

antioxidants. Those who eat a diet rich in antioxidant substances or who use supplements and those who do not may differ in important ways that may not be adequately controlled for with statistical analyses.⁵ In cross-sectional and case-control studies, the temporal relationship between nutritional intake and AMD can be difficult or impossible to determine.

Specification of Level of Evidence

The AREDS and the studies cited in the Cochrane Reviews were randomized controlled trials, conducted in such a manner as to produce accurate and reliable data, and they are rated as Level I evidence.

ONGOING STUDIES

There are four large ongoing studies, three in the United States and one in Australia. The three trials in the United States will include AMD in the study outcomes. The Women's Health Study has randomized 39,876 women to low-dose aspirin and vitamin E. The Physician's Health Study II will randomize 15,000 male physicians to one of four groups, including beta-carotene and placebo groups. The Women's Antioxidant Cardiovascular Study has 8,171 women at high risk for cardiovascular disease randomized to vitamin C, E, folate, vitamin B6, and vitamin B12 supplementation.

In the VECAT study in Melbourne, Australia, a total sample of 1,204 people have been enrolled in a trial of vitamin E 500 IU/day and placebo over 5 years. The participants are enrolled based on their cataract status, but presence of AMD at baseline is known and AMD will be an outcome. This study has reported preliminary results in abstract form.

BENEFITS

The AREDS evaluated treatment for patients without AMD, and patients with small drusen, pigmentary changes, or nonextensive intermediate drusen, but the rate of progression to advanced AMD was too low to assess treatment effect.⁴

Intermediate-risk AMD was defined by the AREDS Study Group as patients with extensive medium sized drusen or one or more large drusen (≥ 125 microns) in one or both eyes. Advanced AMD was defined as geographic atrophy involving the center of the macula (fovea) or features of choroidal neovascularization. For patients with intermediate AMD in one or both eyes and for patients with advanced AMD in one eye only or vision loss due to AMD in one eye, the AREDS results showed that supplementation with antioxidants and zinc reduced the risk of developing advanced AMD by 25%. The reduction in risk for those taking zinc alone was 21% and for those taking antioxidants was 17%. Patients taking the antioxidant and zinc supplement had a 23% chance of developing vision loss from advanced AMD compared to a 29% chance of developing vision loss from advanced AMD for patients taking a placebo pill. The results for reduction in vision loss from advanced AMD were statistically significant only for the combination of zinc and antioxidant treatment.⁴

Of the four randomized controlled trials on supplements for AMD in the 1998 Cochrane Library review, one study (n = 151) demonstrated a positive, if limited, effect of a nutritional supplement on vision and progression of AMD.⁷ Patients in the zinc-treated group were less likely to lose 10 or more letters on the ETDRS chart than controls were and they had slower progression of disease.⁷ One study compared zinc with placebo (n=40) and found no beneficial effect on visual function or progression of AMD.⁸ The AMD Study Group compared an antioxidant complex with placebo (n=59) and found a positive effect, but the trial was too small to find a significant effect.⁶ The last study (n=20) found no difference in objective measures of visual functioning, but more people reported worse visual function in the control group. This study was also too small to detect differences.⁹

Investigators for the ATBC trial (included in the second Cochrane Library Review), the one randomized controlled trial of supplementation for primary prevention, found no association of either vitamin E or beta-carotene supplement with the development of early AMD.¹¹

Many observational studies have examined antioxidant micronutrients and AMD, but not always supplements per se. In a review article, Congdon points out the contradictory findings of studies and the need for prospective randomized clinical trials.¹² In the Blue Mountain Eye Study population (2,900 subjects 49 years old and older), Smith et al did not find associations between age-related maculopathy and dietary antioxidants, (Vitamins A, C, zinc, and carotene) either from diet alone or from supplements.¹⁴ In the POLA Study, a population-based study of 1,791 patients, an association was found between late AMD development and plasma vitamin E levels, but not with vitamin C or retinol.¹⁵

A preliminary analysis of data from VECAT showed little benefit to AMD prevention or progression from 4 years of vitamin E supplementation [Taylor HR, Tikellis G, Robman LD, et al. *Invest Ophthalmol Vis Sci* 42(Suppl):S311, 2001].

RISKS

The adverse effects and toxicity, if any, of supplementation with antioxidants over a long-term period (10 years or more) is unknown. There were no statistically significant serious adverse effects associated with treatment in the AREDS; however, hospitalizations for genitourinary disorders were more frequent for male and female participants receiving zinc.⁴ Some vitamins such as E can be toxic in higher levels. The recommendation for vitamin E is for the dosage used in the AREDS.

There are two randomized, controlled trials of supplementation in groups of people at high risk for cancer (smokers and asbestos-exposed workers) where high levels of beta-carotene were associated with significantly higher cancer incidence and mortality rates.^{16,17} One theory on the risk of supplementation with a single product is that protection may require multiple nutrients consumed in a balanced combination at nutritional doses.¹⁸

Zinc sulfate supplementation may depress copper levels and cause copper deficiency anemia, so copper should be taken with zinc. Zinc can cause

gastrointestinal symptoms, which may deter patients from taking the supplement.

The cost of using nutritional supplements can be significant and is seldom covered by health insurance. The quality of supplements can vary by manufacturer and absorption can be affected by a variety of dietary factors.

QUESTIONS FOR SCIENTIFIC INQUIRY

To understand the role of antioxidant supplements in the prevention and treatment of AMD, the following questions should be answered.

- What are the effects of biochemical oxidation on the eye?
- In what amount and in what combinations is supplementation beneficial? At what stage or age would supplementation be beneficial? How long would supplementation need to occur to remain effective?
- Which groups of people derive benefit from supplementation? Can we use objective testing to preselect these favorable responders?
- What constitutes an antioxidant-rich diet, and are there differences between consuming such a diet and taking supplements?

INFORMATION FOR PATIENTS

This material is excerpted from *An FDA Guide to Dietary Supplements*,¹² which is available at <http://vm.cfsan.fda.gov/~dms/fdsupp.html>.

- A healthy diet with a variety of fresh fruits and vegetables will have many overall benefits and may also contain many of the antioxidant vitamins and minerals.
- Consumers who use dietary supplements should always read product labels, follow directions, and heed all warnings.
- To help protect themselves, consumers should:
 - Look for ingredients in products with the U.S.P. notation that indicates that the manufacturer followed standards established by the United States Pharmacopœia.
 - Realize that the label term “natural” doesn’t guarantee that a product is safe.

- Supplement users who suffer a serious harmful effect or illness that they think is related to supplement use should call a doctor or other health care provider.
- If shoppers find dietary supplements with labels stating or implying the product can help diagnose, treat, cure, or prevent a disease, they should realize the product is being marketed illegally as a drug and as such has not been evaluated for safety or effectiveness.
- The majority of supplement manufacturers are responsible and careful. But as with all products on the market, consumers need to be discriminating. FDA and industry have important roles to play, but consumers must take responsibility, too.

CONCLUSIONS

Prospective, randomized, controlled clinical trials support the use of antioxidant vitamins and minerals in patients with intermediate-risk AMD to reduce the rate of progression to advanced AMD. The role of antioxidant supplements in the prevention of AMD or in slowing progression of AMD for those with the early stages of the disease has not been adequately answered in randomized controlled trials. Observational studies have returned conflicting results. It is possible that there are long-term risks in high levels of supplementation of specific antioxidants and minerals.

Patients with intermediate AMD in one or both eyes and patients with advanced AMD in one eye only or vision loss due to AMD in one eye should consider taking antioxidants plus zinc on a daily basis. The dosages used in AREDS were as follows: vitamin C, 500 mg; vitamin E, 400 IU; beta-carotene, 15 mg (approximately 25,000 IU vitamin A); zinc 80 mg as zinc oxide; and copper, 2 mg, as cupric oxide. Copper should be taken with zinc because high-dose zinc is associated with copper deficiency anemia. Smokers probably should not use beta-carotene because previous studies have suggested an association with lung cancer and beta-carotene in smokers. All patients can be encouraged to maintain a healthy diet, with consumption of fresh fruits and vegetables, for a variety of health benefits.

DEVELOPMENT OF COMPLEMENTARY THERAPY ASSESSMENTS

Complementary, or alternative therapies, are a growing part of health care in America. Americans spend an estimated \$14 billion a year on alternative treatments. Mainstream medicine is recognizing a need to learn more about alternative therapies and determine their true value. Most medical schools in the United States offer courses in alternative therapies. The editors of the *Journal of the American Medical Association* announced that publishing research on alternative therapies will be one of its priorities. The National Institutes of Health National Center for Complementary and Alternative Medicine has broadly defined complementary and alternative medicine as those treatments and health care practices not taught widely in medical schools, not generally used in hospitals, and not usually reimbursed by medical insurance companies. More scrutiny and scientific objectivity is being applied to determine whether evidence supporting their effectiveness exists.

In the fall of 1998, the Board of Trustees appointed a Task Force on Complementary Therapy to evaluate complementary therapies in eye care and develop an opinion on their safety and effectiveness, based on available scientific evidence, in order to inform ophthalmologists and their patients. A scientifically grounded analysis of the data will help ophthalmologists and patients evaluate the research and thus make more rational decisions on appropriate treatment choices.

The Academy believes that complementary therapies should be evaluated similarly to traditional medicine: evidence of safety, efficacy, and effectiveness should be demonstrated.¹⁹ Many therapies used in conventional medical practice also have not been as rigorously tested as they should be. Given the large numbers of patients affected and the health care expenditures involved it is important that data and scientific information be used to base all treatment recommendations. In this way, we can encourage high-quality, rigorous research on complementary therapies.²⁰

Ideally, a study of efficacy compares a treatment to a placebo or another treatment, using a double-masked controlled trial and well-defined protocol. Reports should describe enrollment procedures, eligibility criteria, clinical characteristics of the patients, methods for diagnosis, randomization method, definition of treatment, control conditions, and length of treatment. They should also use standardized outcomes and appropriate statistical analyses.

The goal of these assessments is to provide objective information of complementary therapies and provide a scientific basis for physicians to advise their patients, when asked.

To accomplish these goals, the assessments, in general, are intended to do the following:

- Describe the scientific rationale or mechanism for action for the complementary therapy.
- Describe the methods and basis for collecting evidence.
- Describe the relevant evidence.
- Summarize the benefits and risks of the complementary therapy.
- Pose questions for future research inquiry.
- Summarize the evidence on safety and effectiveness.

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ADDITIONAL RESOURCES

FDA Center for Food Safety and Applied Nutrition's Dietary Supplement Web page available at <http://vm.cfsan.fda.gov/~dms/supplmnt.html>

Federal Trade Commission available at <http://www.ftc.gov>

NIH/NEI Statement on Lutein and its Role in Eye Disease Prevention. Available at <http://www.nei.nih.gov/news/statements/lutein.htm>

NIH Office of Dietary Supplements available at <http://ods.od.nih.gov/index.asp>

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