Antioxidants and Zinc to Prevent Progression of Age-Related Macular Degeneration

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A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss: AREDS Report No. 8

Age-Related Eye Disease Study Research Group

Background: Observational and experimental data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss.

Objective: To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity.

Design: The Age-Related Eye Disease Study, an 11-center double-masked clinical trial, enrolled participants in an AMD trial if they had extensive small drusen, intermediate drusen, large drusen, noncental geographic atrophy, or pigment abnormalities in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye. At least 1 eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: (1) antioxidants (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) antioxidants plus zinc; or (4) placebo.

Main Outcome Measures: (1) Photographic assessment of progression to or treatment for advanced AMD and (2) at least moderate visual acuity loss from baseline (≥15 letters). Primary analyses used repeated-measures logistic regression with a significance level of .01, unadjusted for covariates. Serum level measurements, medical histories, and mortality rates were used for safety monitoring.

Results: Average follow-up of the 3640 enrolled study participants, aged 55-80 years, was 6.3 years, with 2.4% lost to follow-up. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52-0.98). The ORs for zinc alone and antioxidants alone are 0.75 (99% CI, 0.55-1.03) and 0.80 (99% CI, 0.59-1.09), respectively. Participants with extensive small drusen, nonextensive intermediate size drusen, or pigment abnormalities had only a 1.3% 5-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1063 participants were excluded (antioxidants plus zinc: OR, 0.66; 99% CI, 0.47-0.91; zinc: OR, 0.71; 99% CI, 0.52-0.99; antioxidants: OR, 0.76; 99% CI, 0.55-1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants plus zinc (OR, 0.73; 99% CI, 0.54-0.99). No statistically significant serious adverse effect was associated with any of the formulations.

Conclusions: Persons older than 55 years should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least 1 large druse, noncental geographic atrophy in 1 or both eyes, or advanced AMD or vision loss due to AMD in 1 eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc such as that used in this study.


Commentary by Lee M. Jampol, MD, and Frederick L. Ferris III, MD

AGE-RELATED MACULAR DEGENERATION (AMD) AND age-related cataract are leading causes of visual impairment and blindness in the United States. Approximately 1.7 million Americans have some intermediate or advanced AMD, and approximately 100,000 are legally blind from the disease.1 Cataract is even more common in the United States, requiring more than a million cataract operations per year.2,3 Nutritional supplementation with antioxidants, minerals, and other products is commonly used in the hopes of preventing or ameliorating AMD and cataract. To better understand the natural history of and risk factors for both diseases, the National Eye Institute, part of the National Institutes of Health, initiated a 10-year cohort study (Age-Related Eye Disease Study [AREDS]) of 4757 par-
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A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E and Beta Carotene for Age-Related Cataract and Vision Loss: AREDS Report No. 9

Age-Related Eye Disease Study Research Group

Background: Experimental and observational data suggest that micronutrients with antioxidant capabilities may retard the development of age-related cataract.

Objective: To evaluate the effect of a high-dose antioxidant formulation on the development and progression of age-related lens opacities and visual acuity loss.

Design: The 11-center Age-Related Eye Disease Study (AREDS) was a double-masked clinical trial. Participants were randomly assigned to receive daily oral tablets containing either antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) or no antioxidants. Participants with more than a few small drusen were also randomly assigned to receive tablets with or without zinc (80 mg of zinc as zinc oxide) and copper (2 mg of copper as cupric oxide) as part of the age-related macular degeneration trial. Baseline and annual (starting at year 2) lens photographs were graded at a reading center for the severity of lens opacities using the AREDS cataract grading scale.

Results: Of 4757 participants enrolled, 4629 who were aged from 55 to 80 years had at least 1 natural lens present and were followed up for an average of 6.3 years. No statistically significant effect of the antioxidant formulation was seen on the development or progression of age-related lens opacities (odds ratio = 0.97, P = .55). There was also no statistically significant effect of treatment in reducing the risk of progression for any of the 3 lens opacity types or for cataract surgery. For the 1117 participants with no age-related macular degeneration at baseline, no statistically significant difference was noted between treatment groups for at least moderate visual acuity loss. No statistically significant serious adverse effect was associated with treatment.

Conclusion: Use of a high-dose formulation of vitamin C, vitamin E, and beta carotene in a relatively well-nourished older adult cohort had no apparent effect on the 7-year risk of development or progression of age-related lens opacities or visual acuity loss.


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In the AREDS cataract study, there was no statistically significant effect of supplementation with antioxidants on the risk of progression of lens opacities overall (odds ratio [OR], 0.97; 99% confidence interval [CI], 0.84-1.11) or by type of lens opacity (such as nuclear, cortical, or posterior subcapsular events), or on the risk of cataract surgery (relative risk, 0.94; 99% CI, 0.77-1.14). The AREDS population was relatively well nourished and about two thirds of participants chose to supplement with a daily multivitamin containing RDA dosages of the study nutrients. These factors as well as length of participant follow-up, the specific antioxidants studied, or the dosages may have contributed to the negative finding. Based on the AREDS results, combined with the inconsistent results of other studies, it remains unclear whether antioxidants have a role in slowing the progression of lens opacity.

The AREDS AMD study found that, compared with placebo, both the combination of antioxidants plus zinc and zinc alone reduced the odds of developing advanced AMD in persons at risk of progression. However, the group with early AMD had only an estimated 1.3% probability of developing advanced AMD over a 5-year period, and with this low incidence rate, the study’s power to detect a possible treatment effect for early AMD was very low. There was no apparent effect of any of the treatments in slowing the rate of progression from early AMD to intermediate or advanced AMD. Because of these observations, the value of the routine use of antioxidants and zinc for early AMD remains uncertain.

The authors excluded participants with early AMD from the analysis and assessed treatment effects in participants at greater risk for progression to advanced AMD (n = 2556) and visual acuity loss (n = 2549). Because of the multiple outcomes and comparisons, the investigators used P < .01 to indicate statistical significance. Compared with placebo, the combination of antioxidants and zinc had the most consistent treatment benefit, reducing the risk of development of moderate visual acuity loss (OR, 0.73; 99% CI, 0.54-0.99) and development of advanced AMD (OR, 0.66; 99% CI, 0.47-0.91). The effect of zinc alone or antioxidants alone was intermediate between the combination and placebo. The ORs for risk of progression to advanced AMD and risk of visual acuity loss for zinc alone (vs placebo) were 0.71 (99% CI, 0.52-0.99) and 0.83 (99% CI, 0.62-1.11), respectively, and for antioxidants alone (vs placebo) ORs were 0.76 (99% CI, 0.55-1.05) and 0.85 (99% CI, 0.63-1.14), respectively. The study was not designed to discern among each of the 3 treatments (antioxidants, antioxidants plus zinc, or zinc alone).

Based on the consistency of the data, and the general lack of any clinically important and statistically significant serious adverse effects from these treatments, it is reasonable to conclude that persons found to have advanced AMD in one eye or intermediate AMD and who do not have contraindications (such as cigarette smokers wanting to avoid beta carotene) should consider supplementing with a combination of these antioxidants and zinc. The use of these supplements in patients with a strong family history of AMD, or with the early (before age 55 years) onset of drusen, is tempting but of unproven value.

The treatment benefit in AREDS was demonstrated despite the fact that this population is relatively well nourished and the majority took a multitreatment supplement. This is the first treatment shown to slow the progression of AMD and is a very important advancement in this field, one that could delay or prevent vision loss in many patients. The formulations of antioxidants and zinc used had no significant toxicity and appeared safe during a mean follow-up of 6.3 years. Persons who smoke should weigh the risks and potential benefits of taking a supplement containing beta carotene.

The safety of longer-term supplementation (>7 years) with these doses of vitamins and minerals is unknown. Antioxidants have so far proven disappointing in similar trials treating cardiovascular disease, stroke, and cancer. AREDS demonstrates that persons who are found by their eye care professional to have extensive intermediate drusen, large drusen, noncentral geographic atrophy in one or both eyes, or advanced AMD or vision loss due to AMD in one eye should consider supplementation with a combination of antioxidants and minerals such as those used in AREDS.10 However, the value of these supplements in persons at low risk of development of AMD remains uncertain.

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