

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

Arch Ophthalmol. 2001 (October);119:1417-1436

AREDS Report No. 8

Principal Investigator: Aaron Kassoff, MD

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, noncentral 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
- (2) at least moderate visual acuity loss from baseline (15 letters).

Results

Average follow-up of the 3,640 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.

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.

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, noncentral 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.

THESE AUTHORS ALSO NOTE:

"Age-related macular degeneration (AMD) is the leading cause of visual impairment and blindness in the United States and elsewhere among people 65 years or older."

"At present, there is no proven treatment that slows or prevents the development of advanced AMD."

"Oxidative damage to the retina may be involved in the pathogenesis of AMD."

This study on high-dose antioxidant and zinc supplements for AMD was done by the National Eye Institute (National Institutes of Health, Bethesda, Md) as a clinical trial of part of the Age-Related Eye Disease Study (AREDS).

This is a randomized clinical trial designed to evaluate the effect of high doses of zinc and selected antioxidant vitamins (5 to about 15 times the recommended dietary allowance [RDA]) on the development of advanced AMD in a cohort of older persons.

STUDY DESIGN

The 4 treatment interventions were double-masked and given as an oral total daily supplementation of antioxidants (500 mg of vitamin C, 400 IU of vitamin

E, and 15 mg of beta carotene), or zinc (80 mg of zinc as zinc oxide and 2 mg of copper as cupric oxide to prevent potential anemia), or the combination of antioxidants and zinc, or placebo.

Tablets were taken with food to avoid potential irritation of an empty stomach by zinc.

COMMENT

"Data from AREDS demonstrate that treatment with zinc alone or in combination with antioxidants reduced the risk of progression to advanced AMD"

Risk reductions for AMD by those taking antioxidants alone was 17%, and for zinc alone 21%.

"The risk reduction for those taking antioxidants plus zinc was 25%."

The probability of developing advanced AMD by 5 years among participants assigned to receive placebo varied within from about 27% to about 43%.

"Results to date find no statistically significant deleterious effect of antioxidants on mortality."

"The antioxidant formulation included only 3 antioxidants: beta carotene, vitamin E, and vitamin C. Individual effects of each of these components cannot be evaluated."

"AREDS was designed to assess whether active treatment with antioxidants and/or zinc could reduce the risk of developing advanced AMD."

The results are consistent in demonstrating that, compared with the placebo group, participants assigned to receive antioxidants plus zinc had the largest reduction of the risk of developing advanced AMD or visual acuity loss.

"Participants assigned to receive either zinc or antioxidants seem to have a lesser benefit from the study medication."

Although both zinc and antioxidants plus zinc significantly reduce the odds of developing advanced AMD, the only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to antioxidants plus zinc.

"Persons who smoke cigarettes should probably avoid taking beta carotene."

“Based on data from AREDS, 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, or noncentral GA in 1 or both eyes or those with 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.”

The AREDS investigators have no commercial or proprietary interest in the supplements used in this study.

KEY POINTS FROM DAN MURPHY:

- (1) Age-related macular degeneration is the leading cause of visual impairment and blindness in world for those 65 years or older.
- (2) There is no proven medical treatment that slows or prevents the development of age-related macular degeneration.
- (3) Oxidative damage to the retina may be involved in the pathogenesis of age-related macular degeneration. Antioxidants protect against oxidative damage.
- (4) Those using antioxidants plus zinc had the largest reduction of the risk of developing age-related macular degeneration or visual acuity loss.
 - (A) Risk reductions by those taking antioxidants alone was 17%.
 - (B) Risk reduction by those taking only zinc was 21%.
 - (C) Risk reduction for those taking antioxidants plus zinc was 25%.
- (5) The antioxidants used were :
vitamin C 500 mg; vitamin E 400 IU; beta carotene 15 mg.
- (6) The zinc used was 80 mg.
- (7) No significant or serious adverse effects were associated with any of the antioxidants or zinc formulas used.
- (8) This study clearly shows that zinc is especially important in preventing age-related macular degeneration.

The best book I have read to detail the necessity of antioxidants is:
The Antioxidant Miracle, By Lester Packer, Wiley& Sons, 1999.

