

Multivitamin-multimineral supplements and eye disease: age-related macular degeneration and cataract¹⁻⁴

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ABSTRACT

The prevalence and effects of age-related macular degeneration (AMD) and cataract are increasing dramatically as the proportion of elderly in our population continues to rise. A multivitamin-multimineral supplement with a combination of vitamin C, vitamin E, β -carotene, and zinc (with cupric oxide) is recommended for AMD but not cataract. Weak support exists for multivitamins or other vitamin supplements from observational studies of cataract. The results of observational studies suggest that a healthy lifestyle with a diet containing foods rich in antioxidants, particularly lutein and zeaxanthin, as well as n-3 fatty acids, appears beneficial for AMD and possibly cataract. The Age-Related Eye Disease Study II will evaluate some of these additional nutrients as dietary supplements in a randomized trial. *Am J Clin Nutr* 2007;85(suppl):304S-7S.

KEY WORDS AREDS, Age-Related Eye Disease Study, macular degeneration, cataract, antioxidants, eye

INTRODUCTION

The prevalence and effects of age-related macular degeneration (AMD) and cataract are increasing dramatically as the proportion of elderly in our population continues to rise (1-3). In 1984, in the Epidemiology Unit at the Massachusetts Eye and Ear Infirmary (MEEI), we began to explore whether diet or supplements could prevent or slow the progression of AMD and cataract. Our hypothesis involved oxidative mechanisms whereby daily insults such as pollution, smoking, sunlight, and even normal metabolic processes that lead to free radicals and oxidation could damage the retina and could theoretically be blocked by antioxidants such as those that occur in foods or supplements (4, 5). There was also much discussion at that time about the potential effect of vitamins on other chronic diseases such as cancer and heart disease.

THE DIETARY ANCILLARY STUDY

This Dietary Ancillary Study of the Eye Disease Case-Control Study (EDCCS) was designed to evaluate the relation between nutrition and AMD. The main EDCCS was directed by the National Eye Institute, and the Dietary Ancillary Study was directed by the Epidemiology Unit at MEEI, where the dietary questionnaire was designed for use by elderly individuals (6) and the dietary data were analyzed from the 5 centers. In the Dietary

Ancillary Study, lutein and zeaxanthin from foods were associated with a decreased risk of AMD, whereas β -carotene from foods was not (7). We also found that specific foods rich in lutein and zeaxanthin also decreased the risk of AMD. Leading the list of foods rich in lutein and zeaxanthin are kale, spinach, and collard greens, which prompted some lay press at the time to tout the benefits of Popeye's message about eating spinach. This finding also made sense biologically because lutein and zeaxanthin are the carotenoid pigments that are present in the center of the retina, called the macula (8). They may act as free radical scavengers and can filter the damaging rays of blue light. However, the results regarding supplement use were not strong in this Dietary Ancillary Study, with a small, nonsignificant association with multivitamins and vitamin C for ≥ 2 y but no association with vitamins A or E (7).

THE AGE-RELATED EYE DISEASE STUDY

The gold standard for evaluating supplements is a randomized controlled clinical trial, the Age-Related Eye Disease Study (AREDS), which was initiated in 1990 by the National Eye Institute (9, 10). It involved 11 centers in the United States and enrolled ≈ 5000 patients. Four AMD categories were defined on the basis of fundus photographs of the macula, ranging from no AMD to advanced disease. Cataract was assessed by photography of the lens. The study supplements were vitamin C (500 mg), vitamin E (400 IU), β -carotene (15 mg), and zinc oxide (80 mg) with cupric oxide (2 mg), and the patients were assigned to these 4 treatment groups in a factorial design. The antioxidant-zinc combination group had a 25% reduction in risk of progression to advanced AMD over 5 y and a 19% reduction in loss of ≥ 3 lines of vision over the same period. Because ≈ 8 million Americans are at risk of advanced AMD, $>300\,000$ persons could be saved from vision loss over 5 y if they all took these supplements (11). Based on AREDS and the observational studies of foods, many

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TABLE 1Relations between supplement use and age-related macular degeneration (AMD)¹

| | Subjects and study design | Nutrients | Results |
|------------------------------------|--|---|---|
| Randomized trials | | | |
| Newsome et al, 1988 (12) | 151 subjects (early AMD): 95 women, 56 men; duration: 12–24 mo | Zinc sulfate, 100 mg | Delay in visual loss |
| Stur et al, 1996 (13) | 112 subjects with wet AMD in one eye; 21 mo | Zinc sulfate, 200 mg | No effect on fellow eye |
| AREDS, 2001 (10) | 3640 subjects; 6.3 y | Vitamins C, E, and β -carotene; zinc alone; vitamins C, E, and β -carotene plus zinc; placebo | Antioxidants plus zinc, 25% reduction in progression at 5 y |
| Taylor et al, 2002 (14) | 1193 subjects; 4 y | Vitamin E, 500 IU | No effect on early AMD |
| Richer et al, 2004 (15) | 90 subjects randomly assigned; 12 mo | Lutein 10 mg; Lutein plus antioxidants; placebo | Improved visual function with lutein |
| Prospective cohort studies | | | |
| Vandenlandgenberg et al, 1998 (16) | Beaver Dam, 1709 subjects; 5-y incidence of early AMD | Foods and supplements combined | Carotenoids, vitamin E decreased risk of large drusen, zinc decreased risk of macular pigment abnormalities |
| Christen et al, 1999 (17) | PHS, 279 cases; 12.5 y of follow-up | Supplements, vitamins E and C, multivitamins | No significant effects |
| Flood et al, 2002 (18) | Australia, 1989 subjects, 192 cases of early AMD | Food and supplements combined | No beneficial effect |
| Cho et al, 2001 (19) | NHS, HPFS, 195 early AMD, 189 late AMD | Food and supplements | No association with zinc from food or supplements |
| Cho et al, 2004 (20) | NHS, HPFS, 464 early AMD, 316 wet AMD | Food and supplements | No association with antioxidant nutrients (food and supplements combined) (positive association with fruit, vegetables) |
| Case-control studies | | | |
| Seddon et al, 1994 (7) | Diet Ancillary Study, EDCCS, 356 advanced AMD cases, newly diagnosed, 520 controls | Food and supplements | Vitamins A, C, and E, no association (positive association with lutein and zeaxanthin from foods) |
| Teikari et al, 1998 (21) | ATBC, smoking males, end of trial exam, 269 cases, early AMD | Vitamin E, β -carotene, both, placebo | No effect |

¹ AREDS, Age-Related Eye Disease Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial; EDCCS, Eye Disease Case-Control Study; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; PHS, Physicians' Health Study.

clinicians now recommend that eligible patients with intermediate or advanced AMD in one eye take an AREDS-type supplement and consume a diet rich in antioxidants. Nutritional advice based on scientific studies, including foods and supplements, has had a major impact on the management of AMD.

SUPPLEMENT USE AND AMD

Our review of the literature regarding supplement use for both AMD and cataract included randomized trials, cohort studies, and case-control studies. As listed in **Table 1**, there were 5 randomized trials for AMD (10, 12–15), 5 cohort studies (16–20), and 2 case-control studies (7, 21). The largest and most robust study concerning supplements is AREDS, which found a reduction in the rate of progression of AMD with the use of a multivitamin-multimineral combination supplement (9).

SUPPLEMENT USE AND CATARACTS

Regarding the relation between cataract and supplements, a few randomized trials were initially designed to evaluate cataract (2 of these were in China) (10, 22, 23), and 3 other studies

evaluated cataract later in the clinical trials designed for other diseases (24–26) (**Table 2**). AREDS found no effect of the multivitamin-multimineral supplement on cataract progression, and all 3 trials that added cataract later in the study also found no effect. The other trials with cataract as the primary outcome found either a beneficial effect only in subgroups or a small decrease in progression. Several cohort studies had mixed results (27–34); some suggest a beneficial effect for vitamin C, multivitamins, and vitamin E, especially for longer use. Of 3 case-control studies (35–37), 2 supported vitamin C use of ≥ 10 y and 1 showed no effect. For cataract, therefore, the results are mixed, and the largest randomized trial done in the United States, AREDS, showed no beneficial effect of supplements containing vitamin C, vitamin E, β -carotene, and zinc with cupric oxide on development or progression of cataract (10).

THERAPEUTIC RECOMMENDATIONS

The therapeutic recommendations at this time include an AREDS-type supplement for persons with certain stages of AMD (intermediate disease or advanced disease in one eye) but not cataract. However, there have been concerns about some of

TABLE 2Relations between supplement use and cataract¹

| | Subjects and study design | Nutrients | Results |
|---|--|---|--|
| Randomized trials (primary outcomes) | | | |
| Sperduto et al, 1993 (22) | China, I, 2141 subjects; II, 3249 subjects | I, multivitamin-multimineral; II, retinol and zinc, riboflavin and niacin, vitamin C and molybdenum, selenium, vitamin E, and β -carotene | I, 36% ↓ nuclear cataracts (age 65–74 y); II, 44% ↓ nuclear cataracts in riboflavin and niacin group (age 65–74 y) |
| AREDS, 2001 (10) | 4629 subjects; 6.3 y follow-up | Vitamins C and E, β -carotene | No effect |
| Chylack et al, 2002 (23) | 297 subjects; 2–4 y follow-up | β -carotene, vitamin C, vitamin E | “Small” progression |
| Randomized trials (secondary outcomes) | | | |
| Teikari et al, 1998 (24) | 425 incident cataract extractions, ATBC | Vitamin E, β -carotene, both, placebo | No effect |
| Christen et al, 2002 (25) | PHS (men), cataract and cataract extractions | β -carotene (50 mg qod) | No effect |
| Christen et al, 2004 (26) | WHS (women), cataract and cataract surgery | β -carotene, vitamin E, aspirin | No effect of β -carotene |
| Prospective cohort studies | | | |
| Hankinson et al, 1992 (27) | NHS; 8-y follow-up, 493 cataract extractions | Food and supplements | Vitamin C supplements ≥ 10 y, RR = 0.55 |
| Seddon et al, 1994 (28) | PHS, 370 cataracts, 109 cataract extractions | Food and supplements | Multivitamins ↓ risk, RR = 0.73–0.79, vitamins C and E, no effect |
| Leske et al, 1998 (29) | 744 patients, nuclear changes | Food and supplements | Multivitamins ↓ risk, RR = 0.69; vitamin E ↓ risk, RR = 0.43 |
| Brown et al, 1999 (30) | HPFS (men), 840 cataract extractions; 8-y follow-up | Food and supplements | Retinol and vitamin A, no effect |
| Chasen-Taber et al, 1999 (31) | NHS (women), 1471 cataract extractions; 12-y follow-up | Food and supplements | Retinol and vitamin A, no effect |
| Chasen-Taber et al, 1999 (32) | NHS, 1377 cataract extractions; 12-y follow-up | Supplements | No effect, vitamin C ↓ risk (NS) for subgroups |
| Mares-Perlman et al, 2000 (33) | Beaver Dam, 3039 subjects; 5-y follow-up | Food and supplements | Multivitamins, vitamins C and E >10 y, 60% ↓ risk |
| Jacques et al, 2005 (34) | NHS, 408 women (subsample) | Diet and supplements 13–15 y before baseline | Vitamin E 10 y, followed progression (nuclear) |
| Case-control studies | | | |
| Jacques et al, 2001 (35) | NHS, 478 women (subsample), nuclear cataracts | Diet and supplements 13–15 y before baseline | Vitamin C, OR = 0.31 for 5th quintile; vitamin C 10 y, OR = 0.36 |
| Taylor et al, 2002 (36) | NHS, 492 women (subsample), cortical and posterior subcapsular cataracts | Diet and supplements 13–15 y before baseline | Vitamin C, OR = 0.43; vitamin C 10 y, OR = 0.40 (only for < 60 y old, cortical cataracts) |
| Case-control within clinical trial | | | |
| Teikari et al, 1997 (37) | 1828 evaluated end of trial (5–8 y) | Vitamin E, β -carotene, both, placebo | No effect |

¹ AREDS, Age-Related Eye Disease Study; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; OR, odds ratio; PHS, Physicians' Health Study; qod, every other day; RR, relative risk; WHS, Women's Health Study.

the components of the AREDS formula, namely β -carotene supplement use by smokers (38, 39), zinc (40), and vitamin E (41, 42). Observational studies showed that other nutrients derived from foods may also be important. The most consistent evidence relates to lutein and zeaxanthin (7, 8, 43) as well as dietary n–3 fatty acids (44–47). For this reason, the National Eye Institute launched a new randomized clinical trial called AREDS II, which will evaluate lutein and zeaxanthin, n–3 fatty acids, and alternate formulations for the AREDS I-type supplements in a secondary randomization (no β -carotene and a lower dose of zinc).

SUMMARY

In summary, a multivitamin-multimineral supplement with a combination of vitamin C, vitamin E, β -carotene, and zinc (with

cupric oxide) is recommended for AMD but not cataract. Observational studies for cataract provide only weak support for multivitamins or other vitamin supplements. The results of observational studies suggest that a healthy lifestyle with a diet containing foods rich in antioxidants, especially lutein and zeaxanthin, and n–3 fatty acids appears beneficial for AMD and possibly cataract. AREDS II will evaluate some of these additional nutrients as dietary supplements in a randomized trial.



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