Multivitamin-multimineral supplements and eye disease: age-related macular degeneration and cataract

Johanna M Seddon

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.

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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

1 From the Epidemiology Unit, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA.
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4 Address reprint requests to J Seddon, Epidemiology Unit, Department of Ophthalmology, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114. E-mail: jseddon@earthlink.net.
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). 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; 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
AREDS II, which will evaluate lutein and zeaxanthin, will launch a new randomized clinical trial called supplements in a secondary randomization (no fatty acids, and alternate formulations for the AREDS I-type diet). 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 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 secondary randomization.

The author had no financial interests to declare.

**REFERENCES**


