Antioxidants, Zinc, and Age-Related Macular Degeneration

Results and Recommendations

The patients arrive in our offices with plastic bottles and packets filled with pills of all sizes, shapes, and colors. In an attempt to prevent or ameliorate their age-related macular degeneration (AMD) they take vitamins including E, C, and A; minerals like zinc and selenium; carotenoids (beta carotene, lutein, zeaxanthin); and a variety of herbal supplements including gingko biloba and bilberry. They respond to articles in the lay press, in magazines, and on the internet, and to recommendations of their ophthalmologists and primary care physicians in hopes that these substances may help their AMD. Many take these, in addition to a myriad of other supplements for arthritis, vascular disease, and to prevent cancer. Many in the Baby Boom generation “attack” rather than wait for the inevitable progression of aging. They take these supplements prophylactically despite minimal or no signs of AMD. One ophthalmology colleague, a marathon runner, was taking some 80 pills each day in hopes of preventing the ravages of aging, until cardiac arrhythmias developed.

See also page 1417

How do we make sense of this dilemma of supplements for AMD? The National Eye Institute (Bethesda, Md) responded to this challenge more than a decade ago by organizing the Age-Related Eye Disease Study (AREDS) research group. Because of widespread usage of zinc at that time as a result of a small, randomized clinical trial1 that suggested that zinc might prevent AMD, zinc supplementation was included in the study. In response to observational studies suggesting that antioxidants might retard cataracts and AMD, and to the hypothesis (a popular one at that time) that ambient light and resultant oxidation in the retina might be a key factor in the development of AMD, antioxidant vitamins were studied. At that time, and even at the present time, supplementation for AMD remains enigmatic because the pathogenesis remains uncertain. We are largely ignorant as to whether AMD is a disease of the photoreceptors, retinal pigment epithelium, or the choroidal circulation. The role of light and other environmental factors is unclear. A strong genetic component is suggested by the clustering of the disease in families and the similarity of AMD to known genetic diseases (Sorsby dystrophy, Stargardt disease, and Malattia leventinese). Despite this uncertainty about the pathogenesis of AMD, AREDS organized a randomized, placebo-controlled trial to study high-dose supplement-

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2. Doses of vitamins C (500 mg), E (400 IU), and beta carotene (15 mg) that were many times the recommended daily allowance were grouped together as the antioxidant treatment. Zinc oxide (80 mg) was the second intervention. A 2 × 2 factorial design was used: patients were assigned to either placebo (1/4), antioxidants plus zinc (1/4), antioxidants alone (1/4), or zinc alone (1/4). At least 1 eye of each patient had to have a visual acuity of 20/32 or better. Patients could be enrolled with minimal or no drusen. Category 1 was included for concurrent studies of supplementation and cataract. Category 2 had multiple small drusen (<63 μm), nonextensive intermediate drusen (63-124 μm), or pigmentary changes. Category 3 had extreme intermediate drusen, any large drusen (≥125 μm), or noncentral geographic atrophy without advanced AMD. Category 4 had advanced AMD in one eye but not in the other eye.

Advanced AMD was defined as choroidal neovascularization, other exudative maculopathy, or geographic atrophy involving the center of the macula. The 2 primary outcome measures were (1) photographic assessment of progression to advanced AMD in an eye or (2) a moderate loss of vision from the baseline of 15 letters (doubling of the visual angle [eg, 20/30 to 20/60]). The group enrolled 3640 participants aged 55 to 80 years. Average follow-up was 6.3 years, and only a small percentage of patients were lost to follow-up. The study results strongly suggest that the antioxidant-zinc combination, as well as each supplement independently, was modestly effective for Categories 3 and 4 in preventing progression to advanced AMD. The combination of zinc and antioxidants was more effective than either one alone. Patients in Category 2 with extensive small drusen, nonextensive intermediate sized drusen, or only pigmented abnormalities had a very low incidence (1.3%) of progression to advanced AMD. Therefore, the study tells us nothing about the value of supplementation in these patients or in patients without even early lesions of AMD. Supplementation was not demonstrated to prevent progression from Category 2 to category 3 or 4. Excluding Category 2 patients, the estimated 5-year probability of progression to...
advanced AMD was 28% for placebo, 23% for antioxidants, 22% for zinc, and 20% for antioxidants plus zinc. Only the combination of zinc and antioxidants statistically reduced the odds of patients developing advanced AMD. The only statistically significant reduction of moderate visual loss occurred in patients assigned to antioxidants plus zinc. Most other secondary outcomes, however, showed a trend toward some benefit from zinc alone or antioxidants alone and suggested that the combination was more effective than either alone. Most of these results, however, did not achieve statistical significance. The study reviews evidence of toxicity of the treatment, and no statistically serious adverse effects or consequences were noted.

Are there weaknesses in this trial that could cast doubt on its conclusion that the supplements were effective? The exclusion of the subgroup of patients in Category 2 from many of the analyses because of the low incidence of primary outcome events is troubling because it occurred after review of the data. Despite the long follow-up (6.3 years) and the large number of patients, the trial was only marginally powerful enough to demonstrate the efficacy of the supplements. Many of the results demonstrate trends and do not reach the level of statistical significance that was selected for the trial (ie, \( P = .01 \)). This level was necessary because of the multiple outcomes and interim analyses performed. However, the results do demonstrate a consistent and cohesive picture of the modest efficacy of the zinc alone, the antioxidants alone, and more of an effect from the combination of the 2. We do not, of course, know whether 1, 2, or all 3 of the antioxidants are responsible for the beneficial effect.

How do we apply these results to our patients? The dosages of zinc and vitamins used in the trial are not reachable with diet alone or using common multivitamins like Centrum (Whitehall-Robins Healthcare, Madison, NJ). It still seems wise to recommend for all patients an overall balanced diet rich in fruits and vegetables. Many nutritional supplements presently available have uncertain quality control in their manufacture; the user has no assurance about what he or she is taking. The manufacture of reliable supplements is a necessity at this point.

Who should be taking these zinc and antioxidant supplements? The effectiveness of the supplementation will undoubtedly depend on factors such as age, duration of treatment, overall diet, and nutritional status. Yet AREDS shows that even well-nourished people can benefit. The detection of AMD in patients should now be a priority. I would conclude that those patients of any age who demonstrate extensive intermediate sized drusen, large drusen, or especially those who have advanced AMD in 1 eye, should consider taking a supplement containing these dosages of antioxidants and zinc. It seems desirable that this supplement should be taken indefinitely, though AREDS cannot determine ideal duration of treatment. It should be remembered that the adverse effects and toxicity of this treatment when used for long periods (longer than 10 years) remains uncertain.

Although AREDS did not prove efficacious for category 1 or category 2 patients because of the low incidence of the development of advanced AMD, it will be tempting to initiate antioxidants and zinc in other patients, such as those patients with a strong family history of AMD, or those who develop drusen at an age considerably younger than 55 years. Longer-term supplementation (eg, 10-20 years) might be effective in these patients, but AREDS data cannot answer this question. In view of previous studies suggesting that beta carotene might be harmful in smokers and may be associated with a greater risk of lung cancer,4,5 beta carotene should probably not be used by smokers and recent ex-smokers. An argument could be made that another carotenoid, lutein or zeaxanthin, could be substituted for beta carotene, but the value and risks of other carotenoids is unknown at this point.

The demonstrated benefit of the combination of antioxidants and zinc in protecting against progression to advanced AMD in AREDS was about 25% to 30%. All study groups, however, continued to progress toward advanced AMD. Other supplements like lutein or zeaxanthin are in widespread use, but their value remains uncertain. The long trial period and the large numbers of patients necessary to demonstrate efficacy will discourage other randomized trials of nutritional supplementation. Thus, AREDS solves only part of the dilemma of nutritional supplements. Like thermal photocoagulation and photodynamic therapy, nutritional intervention is not the final answer to AMD. Further advances will require a better understanding of the pathogenesis of the condition and the development of new interventions.

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REFERENCES