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Nutritional Supplements for Age-Related Macular Degeneration

Recent research into the relationship between nutrition and vision preservation suggests that the proper form of nutrients is as important as dosage.

BY MITCHELL S. FINEMAN, MD

THE AREDS TRIAL

The landmark study on nutrition for ocular health is the Age-Related Eye Disease Study (AREDS), which was published in 2001.[1] This was the first large, randomized trial to examine whether or not oral vitamin supplementation (specifically, vitamins C, E, beta carotene, and zinc) lowered the progression of age-related macular degeneration (AMD) and the risk of associated advanced vision loss. At the time, it was already well known that patients who ate a diet rich in leafy green vegetables had a lower risk of developing AMD. The study aimed to see if vitamin supplementation could mimic this effect in subjects who already had intermediate AMD or advanced AMD in one eye. The AREDS formula lowered the subjects' progression of AMD by 25% and reduced their vision loss due to advancing AMD by approximately 19% when compared to placebo.

THE AREDS 2 TRIAL

The AREDS2 trial,[2] the results of which were published in 2013, was born out of the desire to evaluate new nutrients that were thought to be beneficial for ocular health, and also to answer some questions raised by the original AREDS study. The inclusion criteria for this study was limited to people with intermediate AMD or advanced AMD in one eye, and the objective was to study whether these nutrients reduced the progression of the disease and advanced vision loss relating to AMD over 5 years.

One question was whether or not supplemental dietary carotenoids, specifically lutein and zeaxanthin, were of benefit in preventing progression of AMD. A second question was whether adding the omega-3 essential fatty acids (EFAs) eicosapentaeonic acid (EPA) and docosahexaenoic acid (DHA) in the ethyl ester form to the original AREDS supplement formula would affect AMD patients' progression to advanced AMD. Finally, the investigators evaluated the utility of beta carotene and the dose of zinc in the original AREDS study.

RANDOMIZATION IN THE AREDS2 STUDY DESIGN

Primary Randomization

The primary randomization in the AREDS2 trial was as follows: group 1: placebo; group 2: the original AREDS supplement formula plus lutein (10 mg) and zeaxanthin (2 mg); group 3: the original AREDS formula plus 1 g of ethyl ester omega-3 EFAs; and group 4: the original AREDS formula plus lutein, zeaxanthin, and ethyl ester omega-3 EFAs.

Compared with placebo, the groups that received lutein and zeaxanthin did not show a statistically significant reduction in the progression of AMD. However, these nutrients demonstrated value in the secondary analysis (see section below) in those subjects who did not receive beta carotene and those who had low levels of dietary lutein and zeaxanthin.

Supplementation with 1 gm of oral omega-3 EFAs in ethyl ester form showed no benefit (nor any detriment) in the treatment of AMD for either the primary or the secondary analyses. The inclusion of omega-3 EFAs in the AREDS2 was supported by multiple epidemiological studies linking the consumption of fatty fish (a rich source of omega-3 EFAs) to a lowered incidence or progression of AMD.[3-6] Also, an analysis of the original AREDS subjects' dietary habits showed a similar correlation.[7] Similarly, in 2013, Souied et al published a study[8] that found that those with lower amounts of the EFAs in their blood did not have protection against the advancement of AMD.

Because the AREDS2 study outcomes did not demonstrate a strong correlation between the dosed omega-3 EFAs and a reduction in the progression of AMD, the question remained whether this lack of effect was due to the form used (ethyl ester omega-3 EFAs) or the dosage administered (the omega-3 EFAs were dosed at 1,000 mg per day).

OMEGA-3 SUPPLEMENTATION—TYPE SEEMS TO MATTER

In nature, the long-chain omega-3 EFAs present in fish, such as EPA and DHA, exist as triglycerides (more than 98% of the

fats we ingest are in triglyceride form). Most omega-3 EFA supplements sold over-the-counter in the US are in the ethyl ester form, a byproduct of the way the fish oil is purified. Human studies have confirmed that the ethyl ester form has lower rates of absorption than the triglyceride form.[9]

Furthermore, Souied et al[8] concluded that an individual's level of omega-3 EFAs in the blood serum has greater clinical significance regarding the progression to neovascular AMD than the dosage of supplemental EFAs consumed. Blood serum levels of omega-3 EFAs are determined by genetic factors, absorption from consumed foods, and other dietary factors. Measurements of blood serum levels of omega-3 EFAs can be taken directly from the blood or indirectly calculated via saturation tests such as the omega-3 index test. One key study suggests that a reduction in sudden cardiac death is achieved when blood serum levels of omega-3 EFAs reach 8%.[10]

Does a higher blood lipid level of omega-3 EFAs correlate with the prevention of AMD? While we must be careful not to extrapolate such a conclusion, it does raise the issue that the omega-3 EFAs utilized in the AREDS2 trial may not have been dosed at an adequate level to see an effect.

Secondary Randomization

In a secondary randomization, AREDS2 subjects received the vitamins from the original AREDS trial. Within this randomization, there were four groups. Each group received 500 mg of vitamin C, 400 IU of vitamin E d-alpha tocopherol, and 2 mg of cupric oxide (copper). The groups' supplementation differed as follows: (1) 15 mg of beta carotene and 80 mg of zinc; (2) no beta carotene and 80 mg of zinc; (3) no beta carotene and 25 mg of zinc; and (4) 15 mg of beta carotene and 25 mg of zinc (Table 1).

The decision to test the removal of beta carotene from the formula makes scientific sense for at least two reasons. First, in contrast to lutein and zeaxanthin, beta carotene is not found in significant levels in the retina, and so its effect on preventing the progression of AMD was in question. Second, and more compellingly, was a study by Omenn et al[11] on the supplementation of beta carotene and vitamin A in smokers and workers exposed to asbestos that indicated that these individuals' risk of developing lung cancer increased with supplementation.

As noted in the primary randomization results, adding lutein and zeaxanthin to the original AREDS formula provided a greater benefit in suppressing AMD progression than simply removing the beta carotene. When these two carotenoids were given to the group randomized to no beta carotene, the result was a statistically significant reduction in the risk of advancement of AMD (18%) and a reduction in the risk of progression to neovascular AMD (22%).[2]

Finally, a reduced amount of daily zinc (25 mg) was tested because of the hypothesis that there was a limit to absorption at higher doses. The group that received less zinc in their formula showed no increase in the risk of progression to advanced AMD compared with the 80 mg found in the original AREDS formula.

TABLE 1. SUPPLEMENTATION USED IN AREDS2

	1	2	3	4
Vitamin C	500 mg	500 mg	500 mg	500 mg
Vitamin E	400 IU	400 IU	400 IU	400 IU
Beta-carotene	15 mg	0 mg	0 mg	15 mg
Zinc oxide	80 mg	80 mg	25 mg	25 mg
Cupric oxide	2 mg	2 mg	2 mg	2 mg

CONCLUSIONS

The AREDS and AREDS2 trial results have been extremely influential in determining the standard of care for vitamin supplementation in patients with intermediate AMD or advanced AMD in one eye. Keep in mind that vitamin supplementation has not been proven to reduce the risk of developing AMD in those who do not have it, or its worsening in those with only mild AMD. Regarding the effectiveness of omega-3 EFAs on the progression of intermediate AMD or advanced AMD in one eye, the only conclusions one should draw from the findings of the AREDS2 trial are that the form and dosage of the omega-3 EFAs used did not effectively lower patients' progression to advanced AMD over a 5-year period.

There is ample evidence from epidemiological studies to know that people who consume a diet rich in green leafy vegetables and other sources of zeaxanthin and lutein, as well as omega-3 EFAs from marine sources (oily fish), enjoy a reduction in the risk of progression of AMD. For patients who express a desire to preserve their visual function, I recommend a diet that includes these foods. If they cannot or are not willing to eat vegetables daily or oily fish at least twice per week, it is reasonable to recommend the consumption of dietary supplements that include these nutrients. ■

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