

Omega-3s and Angiogenesis

The AREDS study found an association between greater fish intake and reduced risk of AMD progression. AREDS 2 hopes to further qualify the relationship between dietary supplements and AMD.

BY EMILY Y. CHEW, MD

Age-related macular degeneration (AMD) is the leading cause of severe vision loss in the developed world. Because of a lack of effective treatments for AMD, and because evidence indicates that the pathogenesis of the disease may involve oxidative processes, there has been increased interest in the potential preventive role of nutritional supplementation.¹

The Eye Diseases Prevalence Research Group (EDPRG) identified AMD as the major cause of blindness among elderly people of European ancestry.² The EDPRG estimated that about 1.2 million US residents are living with AMD, and 970,000 are living with geographic atrophy, while 3.6 million people have bilateral large drusen. Within the next 20 years, these values are expected to increase by 50% with projected demographic shifts.²

LUTEIN ANTIOXIDANT SUPPLEMENTATION TRIAL

The Lutein Antioxidant Supplementation Trial found that visual function was improved with the use of supplements containing lutein or lutein together with other nutrients. The authors suggested that supplementation with lutein or lutein plus a broad spectrum of antioxidants, vitamins and minerals may play a role in the treatment of atrophic AMD.³

The Age-Related Eye Disease Study (AREDS), a multicenter, prospective, randomized clinical trial sponsored by the National Eye Institute, found that, in people at high risk for developing advanced AMD, supplementation with a high-dose combination of vitamin C, vitamin E, beta-carotene and zinc lowered the risk of developing advanced AMD by about 25% compared with placebo.⁴

Further study of nutritional supplementation for the

STUDY OBJECTIVES: AREDS 2

The objectives of AREDS 2 are to:

- Study the effects of high supplemental doses of the dietary xanthophylls (lutein and zeaxanthin) and omega-3 LCPUFAs (DHA and EPA) on the development of advanced AMD.
- Study the effects of these supplements on cataract and moderate vision loss (doubling of the visual angle or the loss of 15 or more letters on the ETDRS chart).
- Study the effects of eliminating beta-carotene in the original AREDS formulation on the development and progression of AMD.
- Study the effects of reducing zinc in the original AREDS formulation on the development and progression of AMD.
- Validate the fundus photographic AMD scale developed from the Age-Related Eye Disease Study.

Source: web.emmes.com/study/areds2/about/about.htm

prevention or delay of advanced AMD development is now being undertaken in a follow-up study, AREDS 2, which is currently enrolling patients. AREDS 2 will investigate additions to and alterations of the cocktail of micronutrients used in the first AREDS (See sidebar, Study Objectives: AREDS 2). In randomized fashion, the use of lutein and zeaxanthin instead of beta-carotene will be evaluated, as well as the addition of long-chain polyunsaturated fatty acids (LCPUFAs) of the omega-3 family.

AREDS REVIEW

This article reviews some of the findings of AREDS,

which has to date yielded 19 published reports, as well as approximately 70 abstracts and presentations at scientific meetings, and the rationale for undertaking AREDS 2.

LCPUFAS AND AMD

LCPUFAs are divided into two classes. Omega-3 LCPUFAs, predominantly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are acquired nutritionally from fish. Omega-6 LCPUFAs, mainly arachadonic acid (AA), are acquired nutritionally predominantly from red meat.

The role of these dietary lipids in the regulation of angiogenesis is not well defined beyond evidence from basic science. Structurally, DHA and AA are found in neural and vascular cell membrane phospholipids. EPA is found in the retinal vascular endothelium. Dietary LCPUFAs are released in the body as free fatty acids. LCPUFAs and their metabolites affect and are affected by metabolic factors, environmental factors and processes in the vascular and neural retina.

Experimental studies have shown that omega-3 LCPUFAs have the capacity to affect the production and activation of angiogenic growth factors.⁵⁻⁷

In addition to its interventional component, the first AREDS included an observational component that assessed participants' dietary intake. Investigators sought to determine whether nutrient or food intake levels were independently associated with AMD. To this end, a 90-item food frequency questionnaire was administered to participants at baseline, and intake of all nutrients, carotenoids, and dietary lipids was evaluated.⁸

The first AREDS included an observational component that assessed participants dietary intake.

The initial AREDS included 1,060 participants with intermediate drusen, 1,568 with large drusen, 658 with neovascular AMD, 119 with geographic atrophy and 1,115 participants who served as controls.

INITIAL STUDY OUTCOMES

At the end of the study period, analysis revealed that participants who ate fish twice a week had a reduced risk of developing AMD or of having it progress, in comparison with those who ate less fish.

When the intake of total omega-3 LCPUFAs was compared in participants with neovascular AMD and the control population with no drusen, those in quintile 5 (with the highest intake of total omega-3) were found to have a 40% reduced risk of developing AMD (odds ratio [OR]: 0.6; confidence interval [CI] 0.4-0.9) compared with those with the lowest intake.

Comparing DHA intake in those same two groups, participants in quintile 5 (the highest DHA intake) had a reduced risk of developing AMD (OR 0.54; CI 0.4-0.8) relative to quintile 1. Comparison of EPA intake yielded similar results (OR 0.75; CI 0.4-0.9). All of these differences were statistically significant.

Similar analysis was performed in the same two study populations for intake of broiled or baked fish. Participants who consumed more than one serving per week had a reduced risk of developing AMD (OR 0.64; CI 0.4-0.99) compared with those who ate no fish.

The investigators also analyzed red meat consumption and the effect of AA on risk reduction. In AREDS participants with neovascular AMD and the control population with no drusen, those in quintile 5 (who consumed the most red meat) showed only a trend toward a reduced risk (OR 1.54; CI 1.1-2.3) compared with those in quintile 1.

ASPIRIN AND AMD

Aspirin, a cyclooxygenase inhibitor, is involved in the mechanisms of vascular regulation, inflammation, and cell survival. The interaction of aspirin use and dietary intake of omega-3 was analyzed by AREDS investigators.⁹

Responses to a dietary questionnaire were used to analyze dietary lipid intake in 1,112 participants without AMD and 657 participants with neovascular AMD, and to identify participants who took aspirin five times a week for at least 3 consecutive months. Participants were stratified into quintiles for LCPUFA intake, and within each quintile, the duration of aspirin use, was analyzed.

Analysis showed that the percentage of participants with neovascular AMD decreased as the duration of aspirin use increased. Further, within each LCPUFA intake quintile, the percentage of participants with neovascular AMD decreased as the reported duration of aspirin use increased. The longer the duration of regular aspirin use, the lower the percentage of those with neovascular AMD. The highest proportion of people with neovascular AMD was seen in those with the lowest LCPUFA intake and no regular aspirin use.

In the AREDS population, regular aspirin use by itself was not an important risk reduction factor, but in

combination with EPA and DHA intake, it was protective against neovascular AMD. The protective effect was seen as quickly as 3 months after beginning daily use, and it was greater after 5 years of daily use.

AREDS 2 STUDY

The implications of food intake analysis in AREDS, although informative, are limited in strength because of the study's design. AREDS 2 is a multicenter, phase 3 randomized clinical trial designed to assess the effects of oral supplementation with high doses of macular xanthophylls (lutein and zeaxanthin) and/or omega-3 LCPUFAs for the prevention or delay of AMD, cataract and moderate vision loss.¹⁰

Lutein represents about 36% of all retinal carotenoids; zeaxanthin and meso-zeaxanthin each represent about 18%.

Lutein represents about 36% of all retinal carotenoids; zeaxanthin and meso-zeaxanthin each represent about 18%.¹¹ The two carotenoids had been considered for inclusion in the original AREDS formulation, but at the time of initiation of that study neither was readily available for manufacturing in a research formulation.

AREDS 2 will provide information on the clinical course, prognosis, and risk factors for development and progression of AMD and cataract. Other study goals include evaluating the effect of eliminating beta-carotene and/or reducing the amount of zinc in the original AREDS formulation on the progression and development of AMD.¹²

Enrollment for AREDS 2 began in November 2006 with the goal of enrolling 4,000 participants by February 2008. Ten centers will enroll about 150 patients each; other centers will enroll between five and 20 patients each.

INCLUSION CRITERIA

For inclusion in the study, participants must be between 50 and 85 years old, diagnosed at baseline with either large drusen in both eyes or large drusen in one eye and advanced AMD in the fellow eye. At baseline, participants must have sufficiently clear lenses to allow good quality fundus photographs.

Patients will be randomized to receive one of four study supplements daily: placebo, lutein/zeaxanthin,

DHA/EPA or lutein/zeaxanthin plus DHA/EPA. More information about the study can be found at www.areds2.org.

To date, studies linking nutritional supplements to reduced risk of cataracts are controversial.^{13,14} A multi-vitamin/multimineral supplement with a combination of vitamin C, vitamin E, beta-carotene, and zinc is recommended for reducing the risk of developing AMD, but not cataract.¹⁴ AREDS 2 will evaluate additional nutrients as dietary supplements to further understand the role of omega-3s in nutritional supplementation to prevent or delay the development of AMD and cataract. ■

Emily Y. Chew, MD, is the study chair of the AREDS 2 study. She is a member of the Division of Epidemiology and Clinical Research at the National Eye Institute. Dr. Chew may be reached at echew@nei.nih.gov or 301-496-6583.

1. Bartlett H, Eperjesi F. Age-related macular degeneration and nutritional supplementation: a review of randomised controlled trials. *Ophthalmic Physiol Opt*. 2003;23:383-399.
2. Friedman DS, O'Colmain BJ, Munoz B, et al for the Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol*. 2004;122:564-572.
3. Richer S, Stiles W, Statkute L, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). *Optometry*. 2004;75:216-230.
4. Age-Related Eye Disease Study Research Group. 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: AREDS Report No. 8. *Arch Ophthalmol*. 2001;11:1417-1436.
5. Yang SP, Morita I, Murota SI. Eicosapentaenoic acid attenuates vascular endothelial growth factor-induced proliferation via inhibiting Flk-1 receptor expression in bovine carotid artery endothelial cells. *J Cell Physiol*. 1998;176:342-349.
6. Von Knetzen A, Callsen D, Brune B. Superoxide attenuates macrophage apoptosis by NF-kappa B and AP-1 activation that promotes cyclooxygenase-2 expression. *J Immunol*. 1999;163:2858-2866.
7. Morita I, Zhang YW, Murota SI. Eicosapentaenoic acid protects endothelial cell function injured by hypoxia/reoxygenation. *Ann N Y Acad Sci*. 2001;947:394-397.
8. Age-Related Eye Disease Study Research Group. The effect of five-year zinc supplementation on serum zinc, serum cholesterol and hematocrit in persons randomly assigned to treatment group in the age-related eye disease study: AREDS Report No. 7. *J Nutr*. 2002;132:697-702.
9. Cusick M, SanGiovanni JP, Chew EY, et al for the AREDS Research Group. The relationship of omega(n)-3 long-chain polyunsaturated fatty acid (LCPUFA) intake and regular aspirin (ASA) use with prevalent neovascular age-related macular degeneration. Presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology, Fort Lauderdale, Fla., May 2005.
10. Coleman H, Chew E. Nutritional supplementation in age-related macular degeneration. *Curr Opin Ophthalmol*. 2007;18:220-223.
11. Bone RA, Landrum JT, Tarsis SL. Preliminary identification of the human macular pigment. *Vision Res*. 1985;25:1531-1535.
12. Chew EY, AREDS Study Group. Age-related eye disease study 2 (AREDS 2): A multi-center, randomized trial of lutein, zeaxanthin, and omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] and eicosapentaenoic acid [EPA]) in age-related macular degeneration. Version 4.0 Study protocol; Dec 2006. Available at: https://web.emmes.com/study/areds2/resources/areds2_protocol.pdf. Accessed: May 17, 2007.
13. Meyer CH, Sekundo W. Nutritional supplementation to prevent cataract formation. *Dev Ophthalmol*. 2005;38:103-119.
14. Chiu CJ, Taylor A. Nutritional antioxidants and age-related cataract and maculopathy. *Exp Eye Res*. 2007;84:229-245.
15. Seddon JM. Multivitamin-multimineral supplements and eye disease: age-related macular degeneration and cataract. *Am J Clin Nutr*. 2007;85:304-307S.