Much awaited AREDS 2 results show lutein and zeaxanthin supplementation slow AMD progression only in subjects with low dietary intakes

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Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly and the primary cause in industrialized countries. With an increase in life expectancy, age-related eye diseases such as AMD and cataract are more prevalent and adequate treatment options are required to maintain quality of life. AMD affects the macula, a region 5-6 mm in diameter in the posterior pole of the retina that is responsible for sharp central vision. Dry AMD accounts for 90% of the cases and can advance slowly to advanced dry AMD or wet AMD (also known as choroidal neovascularization or exudative AMD). There are treatment options for wet AMD which delay AMD progression but none for dry AMD. Nutritional interventions are part of the efforts for preventing progression of dry AMD.

The Age-related eye disease study (AREDS) showed that supplementation with a combination of vitamin C (500 mg), vitamin E (400 mg), β-carotene (15 mg), zinc (80 mg) and copper (2 mg) significantly reduced the progression to advanced AMD. The AREDS formulation also significantly improved visual acuity. AREDS 2 was initiated in 2006 at 82 clinical sites across the country with an objective to evaluate whether the original formulation could be improved by adding lutein and zeaxanthin or omega-3 fatty acids or both. Lutein and zeaxanthin are oxygenated carotenoids that preferentially accumulate in the macula to form macular pigment. As macular pigment, these carotenoids have been shown to protect the retina from damaging short wavelength blue light and oxidative stress. The concentration of DHA is the highest in the rod outer segments of the retina, about 30-35% of total fatty acids. Also, there are several observational studies that provide evidence for a beneficial association between lutein and zeaxanthin and omega-3 fatty acids and AMD risk. Another objective was to study the effect of eliminating β-carotene as literature shows increased incidence of lung cancer and mortality in high risk groups such as smokers and asbestos works. AREDS 2 also evaluated the effect of reducing zinc dosage to a level that is reported to be the maximum level absorbed. Subjects aged 50 to 85 years at a high risk of progression to advanced AMD were randomized as shown in the table below.

Table 1: Randomization of subjects in AREDS 2 study

Placebo	Lutein (10 mg) + Zeaxanthin (2 mg)	DHA (350 mg) + EPA (650 mg)	Lutein (10 mg) + Zeaxanthin (2 mg) & DHA (350 mg) + EPA (650 mg)
All subjects were randomized again to receive one of the four original AREDS formulations (as shown below). Current smoker or former smokers (quit in the past year) were randomized to no β-carotene groups.			
Formulation 1	**Formulation 2**	**Formulation 3**	**Formulation 4**
Vitamin C (500 mg)	Vitamin C (500 mg)	Vitamin C (500 mg)	Vitamin C (500 mg)
Vitamin E (400 IU)	Vitamin E (400 IU)	Vitamin E (400 IU)	Vitamin E (400 IU)
β-carotene (15 mg)	β-carotene (0 mg)	β-carotene (0 mg)	β-carotene (15 mg)
Zinc oxide (80 mg)	Zinc oxide (80 mg)	Zinc oxide (25 mg)	Zinc oxide (25 mg)
Cupric oxide (2 mg)	Cupric oxide (2 mg)	Cupric oxide (2 mg)	Cupric oxide (2 mg)

Supplementation with lutein + zeaxanthin, DHA + EPA or both in addition to the original AREDS formulation showed no statistically significant effects on progression to advanced AMD and visual acuity. However, subgroup analyses showed a significant protective effect for subjects who were in the lowest quintile of dietary lutein + zeaxanthin intake. AMD progression was reduced by 26% in this group. Data also showed increased incidence of lung cancers in subjects who had a smoking history and who received AREDS with β-carotene but not in those who received lutein + zeaxanthin. The findings suggest β-carotene could be substituted with lutein + zeaxanthin without compromising on the protective effects of the original AREDS formulation. The dosage of zinc required to achieve a significant protective effect remains unclear.

The overall null findings were partly attributed to the study population who were highly educated and well nourished. Also, the serum lutein + zeaxanthin and DHA + EPA concentrations in the AREDS 2 cohort was significantly higher than the general population aged $\geq$60 years. Also, baseline macular pigment optical density, which is a measure of lutein and zeaxanthin in the retina, was shown to be unusually high in AREDS 2 subjects enrolled at the Utah site relative to age-matched controls. Further investigation on whether lutein and zeaxanthin and omega-3 fatty acids benefit those with low intake of these nutrients is warranted. In conclusion, even though no overall effects were observed, data from subgroups analyses showing reduced AMD progression in subjects with low lutein and zeaxanthin intakes is of importance.

References

The Age-related Eye Disease Study 2 (AREDS 2) Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: The age-related eye disease study 2 (areds2) randomized clinical trial. JAMA. 2013;309(19):2005-15.