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LAST II: Differential temporal responses of macular pigment optical density in patients with atrophic age-related macular degeneration to dietary supplementation with xanthophylls

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Abstract

BACKGROUND: Age-related macular degeneration (ARMD) is the leading cause of vision loss in aging Western societies. The objective of the Lutein Antioxidant Supplementation Trial (LAST) was to determine whether specific dietary interventions increased macular pigment optical density (MPOD) and visual function in patients with atrophic ARMD. The current objective of LAST II is to discern those specific characteristics that increase MPOD, i.e., that might differentiate a responder from a nonresponder.

METHODS: The LAST study was a prospective, 12-month, randomized, double-masked, placebo-controlled trial conducted at an urban midwestern Veterans Administation Hospital from August 1999 to May 2001. Ninety patients with atrophic ARMD entered the study and were assigned randomly to 1 of 3 groups. Patients in group 1 received 10 mg lutein; in group 2, 10 mg lutein in combination with vitamins, minerals, and antioxidants; and in group 3, maltodextrin placebo. Changes in macular MPOD over time were evaluated. Characteristics potentially influencing MPOD included age, weight (body mass index), initial baseline values of macular pigment, and combining xanthophylls with other nutrients.

RESULTS: MPOD increased with supplementation and declined slightly without supplementation (regression slopes not equal to zero in supplemented groups, $P < 0.02$). The highest increases in MPOD over time occurred in patients with lower baseline values of MPOD. Statistically significant increases in MPOD density were observed in the lutein group for patients with baseline MPOD $\leq$0.3 optical density units and up to 0.2 optical density units in the lutein plus antioxidant group. Further analysis found that none of the subjects' eyes in the lowest quartile of baseline MPOD were in the lowest quartile for change in MPOD.

CONCLUSION: Noteworthy is the observation that those individuals with lowest MPOD, and in greatest need of supplementation, were also most likely to benefit from either the lutein or the lutein plus antioxidant supplementation. For those individuals who responded to supplementation, their macular pigment optical density had not ceased to increase at 12 months' duration of supplementation. The inference is that if a deficiency in macular pigment optical density is accurately diagnosed, effective interventions should be able to re-establish this prophylactic barrier.

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Age-related macular degeneration (ARMD) is the leading cause of untreated vision loss in aging Western societies. It accounts for 45% of all visual disability in the United States and is increasing not only in Western but in Asiatic societies, possibly reflecting consequences of contemporary dietary changes.[1-4] In addition to age, other risk factors

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include both behavioral characteristics and physiological characteristics, smoking representing the former and gender, cardiovascular health, and genetics the latter.[5-10] Studies using animal models have found that oxidative and photo-oxidative stress can induce apoptosis.[11,12] Carotenoids (lutein and zeaxanthin) have been found recently to protect against both apoptosis and mitochondrial loss of photoreceptors in rats.[13] The first Age-Related Eye Disease Study (AREDS) demonstrated the ability of antioxidants and zinc to slow progression of ARMD and loss of visual acuity in selected cases.[14]

Epidemiologic studies suggest that diets rich in antioxidants and the xanthophyll macular pigments, lutein and zeaxanthin, are inversely correlated with the prevalence of the disease.[5,15] Smaller studies indicate the macular pigments lutein and zeaxanthin, both alone and in combination with omega-3 fatty acids, appear to be able to reduce the prevalence and may slow the progression of macular degeneration.[16-22] The xanthophylls are versatile low/high-$\mathbf{P}_{O_2}$ antioxidants, strongly absorb blue light, and can influence fluidity of cellular membranes.[23-25] Some balance of these characteristics is inferred to govern their influence on ARMD. The direct clinical effects of intervention are the topics of the massive AREDS II study being undertaken by the National Eye Institute (NEI).

These still tentative observations, nonetheless, have led investigators to quantify the levels of macular pigment, and to track the influence on it with respect to dietary intervention or supplementation. Numerous methods have been described for measuring the levels of macular pigment in vivo.[23,26,27] They include reflectance, scattering, absorbance, and absorbance re-emission methods. Some methods measure the mean levels of total xanthophylls over the macula, whereas others provide information about their spatial distribution. Some definitive confirmation of the variation in levels of macular pigments has been seen in small-scale studies by High Pressure Liquid Chromatography (HPLC) of analysis of human retinas obtained from eye banks.[17] The inverse correlation of xanthophyll level with ARMD is suggestive of a mechanistic relation.

If increased levels of macular pigment can provide some protection from the multiple causes of ARMD, then it is important to ascertain effective means for enhancing their levels, especially for populations found to be at greater risk of the disease.[28,29] The LAST study provided an opportunity for understanding the influence of intervention on both macular pigment and visual function.[30]

LAST II, in contrast, is concerned with differential temporal response to lutein and the factors that might affect the structural replenishment of macular pigment. Such factors include age, weight (body mass index [BMI]), initial baseline values of macular pigment, and the inclusion of a mixture of additional carotenoids/antioxidants.

Materials and methods

Subjects and study design

The LAST was a prospective, 12-month, randomized, double-masked, placebo-controlled trial conducted at an urban midwestern Veterans Administration Hospital from August 1999 to May 2001. The Institutional Review Board of Hines Department of Veterans Affairs Medical Center approved the study protocol in June 1999. Written informed consent was obtained from each subject before participating in the study.

Patients with atrophic ARMD were referred by ophthalmologists at 2 Chicago-area veterans' medical facilities. Eligibility included diagnosis of atrophic ARMD (ICD9 362.51) by stereo bio-ophthalmoscopy, and at least 1 vision-degrading ARMD-associated visual abnormality associated with ARMD in 1 or both eyes such as depressed contrast sensitivity, abnormal photostress glare recovery, or Amsler grid deficits. Subjects were excluded if they had undergone recent (within 6 months) cataract or retinal surgery, were taking photosensitizing drugs, or did not meet ophthalmic/visual entrance criteria. One hundred nine subjects were registered with 19 excluded because they were fundus positive but had no psychophysical abnormalities (n = 9), voluntarily withdrew during baseline workup (n = 6), received ARMD laser treatment (n = 2), or had preretinal membrane (n = 1) or Alzheimer's disease (n = 1).[29]

Procedures

A total of 90 subjects participated in the initial screening during which demographic data (gender; age; years with ARMD diagnosis; cigarette, alcohol, caffeine use; BMI), nutritional status (multivitamin use, Harvard School of Public Health Food Frequency Intake Questionnaires), ocular data (iris color, lens opacity classification system [LOCS] 3 cataract grade, AREDS disease stage, macular pigment optical density [MPOD]), and visual data (visual acuity, contrast sensitivity function [CSF], glare recovery, Amsler grid defect count) were collected.[29]

Subjects who participated in the study were randomly assigned to 1 of 3 groups. Subjects in group 1 (L) received 10 mg lutein per day; subjects in group 2 (L/A) received 10 mg lutein per day plus a broad spectrum of antioxidants in a preparation including vitamins, minerals, amino acids, and bioflavonoids; subjects in group 3 received a maltodextrin placebo. The 10-mg dose was extrapolated from spinach pilot case series data as previously described[30,31]; the non-esterified (free alcohol) Floraglo® lutein is chemically identical to that found in spinach. Subjects were encouraged not to alter their diets and were provided an integrated instruction sheet/questionnaire/Amsler grid to monitor changes in vision over time.[32] Subjects returned for follow-up visits at 4, 8, and 12 months, during which time MPOD and visual measures were repeated.