

Clinical & Refractive Optometry is pleased to present this continuing education (CE) article by Dr. Stuart P. Richer entitled **The Age-Related Eye Disease Study Found an Antioxidant/Mineral Supplement Decreases the Progression of Age-Related Macular Degeneration, While Emerging Science Suggests Benefits of Spinach and Lutein Supplementation.** In order to obtain a 1-hour Council of Optometric Practitioner Education (COPE) approved CE credit, please refer to page 159 for complete instructions.

The Age-Related Eye Disease Study Found an Antioxidant/Mineral Supplement Decreases the Progression of Age-Related Macular Degeneration, While Emerging Science Suggests Benefits of Spinach and Lutein Supplementation

Stuart P. Richer, OD, PhD, FAAO

ABSTRACT

In 2001, the Age-Related Eye Disease Study (AREDS), a US National Institute of Health, National Eye Institute clinical trial followed over 3000 age-related macular degeneration (AMD) patients for 6.3 years. Scientists reported that progression to advanced AMD was delayed in patients with intermediate (Category 3) or advanced (Category 4) disease who received high doses of antioxidants (vitamin C, vitamin E, and beta carotene) plus zinc. This article suggests prescribing this dietary ocular supplement for delaying progression in advanced AMD patients, based on the established science of AREDS. We further explore recent findings about the “emerging science” of lutein supplementation for macular health and enhanced visual function. Emerging scientific results from epidemiological studies, an autopsy study, a pilot study, and a case control study (in peer review) of 90 subjects suggests that supplementation with high doses of the carotenoid lutein may improve visual function in patients with early or even late stages of this disease.

BACKGROUND

Lutein, zeaxanthin, and lycopene are three of more than 15 major carotenoids in human blood and tissues, but unlike beta carotene, do not contribute to vitamin A supply.¹ Lutein

is found in kale, spinach, and other dark green, leafy vegetables. Zeaxanthin can be obtained from corn, oranges, and red peppers. Lycopene is present in cooked tomato products. Lastly, dietary sources of beta carotene include squash, cantaloupes, and apricots. Over the last 20 years, the effect of beta carotene on cancer and heart disease has been extensively studied in the US. Beta carotene was more readily available than lutein or zeaxanthin at the time of the Age-Related Eye Disease Study (AREDS) that investigated age-related macular degeneration (AMD), thus this carotenoid form was evaluated.²

Lutein and zeaxanthin are efficient antioxidants that quench molecular oxygen formed in photo-oxidation. According to the oxidative retinal pigment epithelial (RPE) stress theory, the retina has a high metabolic rate and high oxygen levels that throw off reactive oxygen species. Lutein in the anterior retina filters blue light, acts as an antioxidant, and provides structural support to photoreceptors in the posterior retina.

AMD has been described as a waste management disease of the RPE. While some RPE cells are lost as part of the aging process, the macular region contains a protective yellow macular pigment (macula lutea) derived from dietary lutein and zeaxanthin, and seniors who maintain their macula pigment will have visual sensitivity equivalent to that of younger patients. There is ample in vitro and in vivo evidence that the amount of macular pigment is inversely associated with incidence of AMD, an irreversible process that is the major cause of blindness in the elderly.³ Zeaxanthin is emerging as another important protective factor, perhaps more protective than lutein.⁴

Selenium-dependent glutathione peroxidase, super oxide dismutase, catalase, glutathione reductase, and macular pigment are endogenous substances that protect against oxidative stress and AMD, while exogenous protection is provided by alpha-tocopherol (vitamin E), ascorbate (vitamin C), selenium, zinc, and carotenoids, including lutein.

INTRODUCTION

The AREDS AMD study excluded people with Category 1 AMD (no or few drusen). Participants included 3640 patients with Category 2 early AMD (multiple small drusen, or single intermediate drusen), Category 3

S.P. Richer — Chief, Optometry Section, DVA Medical Center; Associate Professor, Family and Preventive Medicine, Chicago Medical School, North Chicago, Illinois

Correspondence to: Dr. Stuart P. Richer, Eye Clinic 112e DVA Medical Center, 3001 Green Bay Road, North Chicago, IL 60064; E-mail: Stuart.Richer1@Med.VA.Gov

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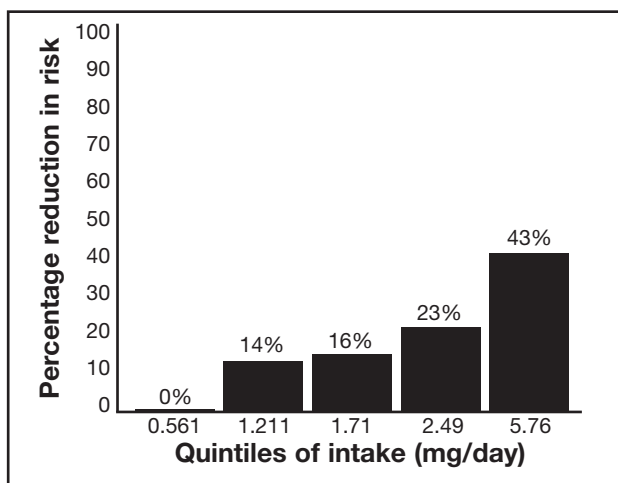


Fig. 1 Lutein and zeaxanthin serum level quintiles (mg/day) and risk of progression to advanced age-related macular degeneration.

intermediate AMD (extensive intermediate drusen or at least 1 large druse), or Category 4 advanced AMD in the non-study eye (central geographic atrophy or choroidal neovascularization). Patients were randomized to one of four daily supplements: antioxidants (500 mg vitamin C, 400 IU vitamin E, and 15 mg beta carotene), zinc (80 mg zinc oxide and 2 mg cupric oxide), antioxidants and zinc, or placebo. After 6.3 years, among patients with Category 3 or Category 4 AMD, compared to patients who took placebo, those who took antioxidants plus zinc had a 25% lower risk of progressing to advanced AMD, and a 19% lower risk of losing 15 or more letters of vision.² This large clinical trial provides scientific evidence of how patients with Category 3 or 4 AMD who take supplements with antioxidants and zinc benefit from a delayed progression to advanced AMD.

The “emerging science” of the effect of lutein on AMD includes epidemiological findings,^{5,6} an autopsy study,⁷ a pilot study of 14 cases,⁸ and a study (in peer review) of 90 subjects.⁹ These investigations suggest that lutein might improve visual outcomes and slow progression to advanced AMD. In the Eye Disease Case Control (EDCC) study, Seddon et al showed that patients in the highest lutein quintile, taking 5.8 mg/day, had a 43% lower risk of advanced exudative AMD (Fig. 1).⁵ The NHANES III study found that 6 mg/day of lutein was associated with a reduced risk of pigment abnormalities in the retina.⁶ A study of autopsy donor retinas showed that the risk for AMD dramatically increased with low levels of lutein in the retina.⁷

A diet high in lutein may also slow cataract progression and increase macular pigment. Several studies suggest spinach to be protective against the development of cataracts. Macula pigment optical density (MPOD) is

20% lower in women and is also lower in individuals with light-colored irises, and in smokers. During recent ARVO meetings, we presented studies demonstrating weak correlations between contrast sensitivity or glare recovery (GR) and MPOD.

Gale et al recently reported that the risk of developing AMD can be halved with high intake of dietary zeaxanthin.⁴ On a recent visit to China, I observed that a berry highly concentrated in zeaxanthin is readily available (Wolfberry). In that country, cataract is the most common eye abnormality, followed by glaucoma. AMD is rare. Is it possible that dietary zeaxanthin plays a role in reducing the prevalence and incidence of AMD in China?

“AMD WORK-UP” PROTOCOL

While it is usually easy to detect advanced stages of AMD such as choroidal sclerosis and frank neovascularization or scarring, it is often much more difficult to detect earlier stages of AMD. In fact, there is no consensus of test(s) to diagnose and categorize early AMD. Thus in 1999, we published an “AMD work-up” protocol based upon baseline and serial measurements of several visual psychophysical parameters.¹⁰ This work-up is analogous to a follow-up protocol used to treat glaucoma patients. It includes determination of Amsler grid abnormalities, Snellen visual acuity, and contrast sensitivity function (CSF). The later involves using a chart or device (Fig. 2) to detect abnormalities in the overall quality of vision at several spatial frequencies. For example, it is common for a CSF abnormality to appear before the doctor measures any decrease in visual acuity. Contrast sensitivity instruments can cost from \$300 to \$1000. Next, I evaluate GR to a photo stressed condition. I allow the patient to adapt to a 5000 K photographic light box for 1 minute, and then I have them read 1 line greater than their maximum near low contrast/low luminance visual acuity. I use a stopwatch to record how long it takes for patients to re-establish their visual acuity after exposure to glare. The low luminance SKILL card (Fig. 3) works well in this regard, and it can also be used to discern low luminance/low contrast visual acuity. Remember, AMD patients often have problems with light adaptation, within a narrow range of lighting conditions. Finally, patients are asked to fill in an activity of daily vision survey (ADVS) concerning consumption of dark green leafy vegetables and omega-3 rich fish, intake of supplements, and ability to perform activities such as driving at night. Performing AMD visual tests, a natural evolutionary skill for optometrists and their staff, is the sole means to ensure that this field of study evolves from testimonials to science.

PILOT STUDY OF 14 AMD PATIENTS

Using the AMD protocol, we performed a pilot study of 14 male veterans (aged 61 to 79). They had a baseline daily intake of 0.28 to 1.18 portions (where a portion

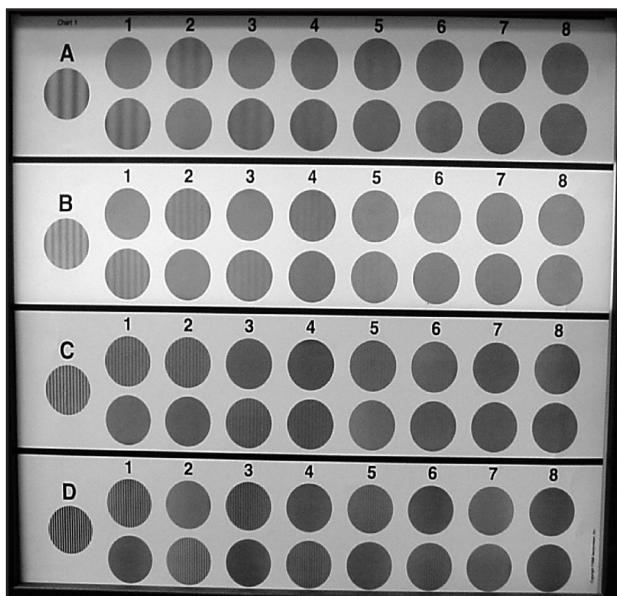


Fig. 2 Contrast sensitivity function (CSF) test of 4 different spatial frequencies of variable contrast used to assess baseline and serial change in the quality of vision of AMD patients; courtesy VECTOR-VISION Inc.



Fig. 3 SKILL CARD (High Luminance Side), Smith Ketterwell Institute, Low Luminance test card for evaluating near visual acuity, low contrast/low luminance vision and glare recovery in conjunction with a standard 5000 K photographic light box and stopwatch.

Table I Effect of 4 ounces of spinach supplementation (or lutein – 3 patients) on alternate days for 12 months in 14 male veterans.⁸

Visual Test	1	2	3	4	5	6	7	Patient 8	9	10	11	12	13	14	Positive Effect
Amsler	+	0	+	na	na	na	na	+	+	+	na	+	na	+	87 %
VA	+	+	+	+	0	0	+	0	+	+	+	+	0	+	71 %
CSF	+	+	+	+	+	+	+	+	+	+	0	+	+	+	92 %
SKILL	+	0	0	+	+	0	0	+	0	+	+	+	+	+	65 %
GR	+	nd	0	+	+	+	0	+	0	+	+	+	0	+	69 %
ADVS	+	+	+	0	0	0	+	+	nd	nd	+	nd	0	nd	60 %

ADVS = activities daily vision scale, Amsler = Amsler grid, CSF = contrast sensitivity function, GR = glare recovery, na = not applicable, nd = not determined, SKILL = test for visual acuity at levels of low light and contrast, VA = visual acuity

equals 4 oz or half a cup) of dark green leafy vegetables. The subjects ate 1 additional portion of sautéed spinach 4 times a week, for up to 1 year.⁸ The 12-month findings, which are summarized in Table I, show that most patients exhibited a high degree of improvement in the visual parameters that we have mentioned. Improved contrast sensitivity, Amsler grid scotomas and metamorphopsias, Snellen visual acuity, GR, SKILL readings, and ADVS improved in 92%, 87%, 71%, 69%, 65%, and 60% of subjects, respectively. Yet there was no significant correlation between retinal appearance and visual outcome, and only a weak effect (60%) between patient symptoms and changes in visual function.

The AMD work-up results for one representative pilot study patient are illustrated in Figure 4. Baseline test results were: visual acuity of 20/30 in the right eye and 20/50 in the left eye, abnormal contrast sensitivity, and distorted Amsler grid. After eating a half a cup of spinach

every other day for 3 months, the patient's contrast sensitivity function shifted upwards (broadly improved) and his low light level acuity response improved. Visual acuity improved to 20/15 in the right eye and to 20/25 in the left eye, and the Amsler grid test revealed absence of distortion in the right eye.

LUTEIN ANTIOXIDANT SUPPLEMENTATION TRIAL

The lutein antioxidant supplementation trial (LAST), a prospective, placebo-controlled, double-masked, crossover, 1-year study, enrolled 90 male veterans with atrophic AMD.⁹ LAST was a multidisciplinary collaboration involving an ophthalmologist, an intern, a statistician, and a nurse. The 90 patients were randomized to 3 groups receiving the following daily supplements: 10 mg lutein (29), 10 mg lutein plus antioxidants (30), or placebo (31).

The investigators obtained demographic, visual/psychophysical, ocular, and nutritional data. In addition to

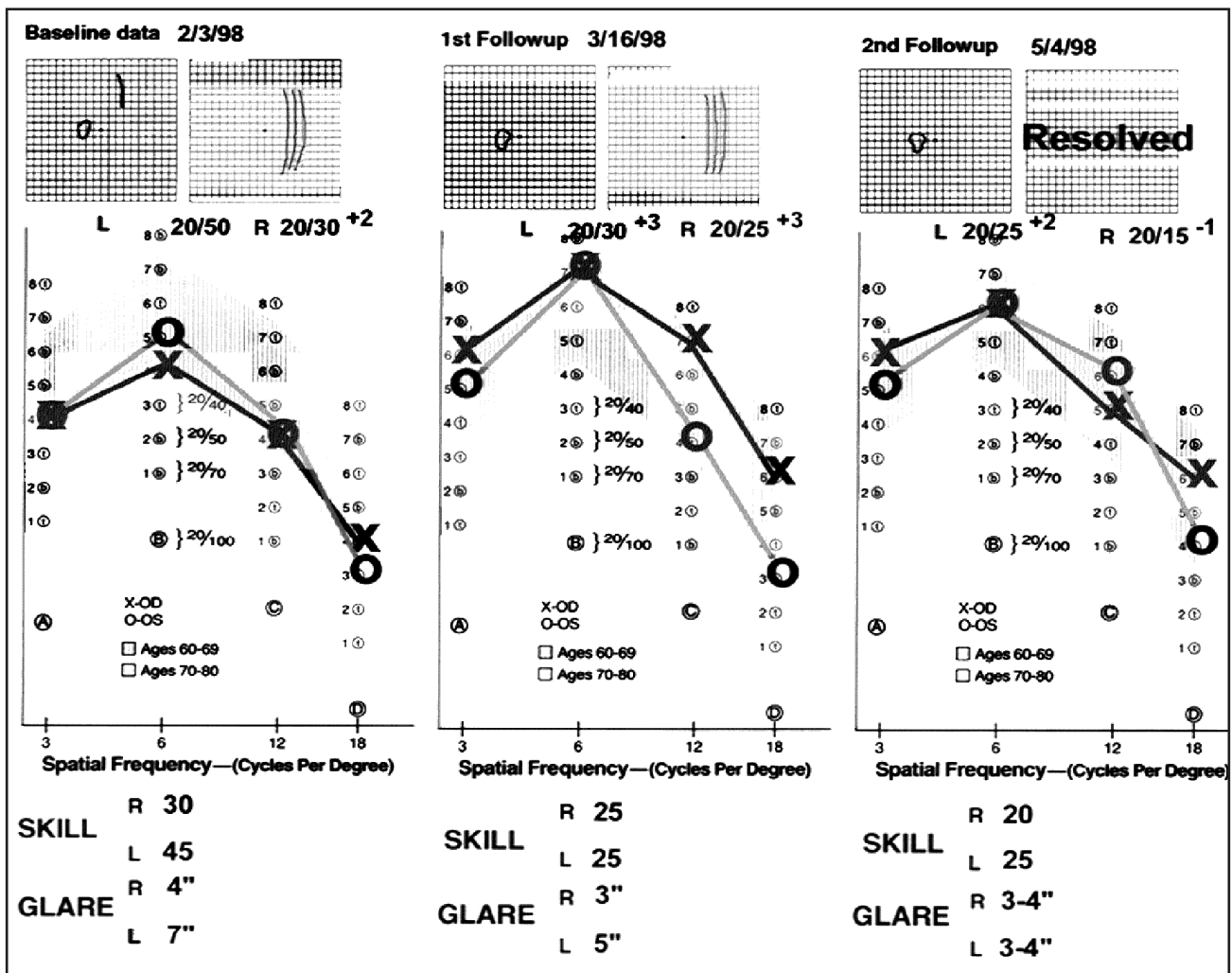


Fig. 4 AMD work-up form.¹⁰

the standard AMD work-up tests described earlier, subjects were evaluated for MPOD using a heterochromic flicker photometer, a procedure that takes about 1 hour in an elderly patient. There are only about a dozen of these \$25,000 instruments in use in the US. Follow-up measurements were taken every 4 months for 1 year. About 25 patients in each group completed the study.

Patients had similar baseline average age and history of AMD, smoking, and alcohol consumption. The subjects in the lutein plus antioxidant group, however, included more overweight or obese patients (body mass index [BMI] approximately 30 or higher) who had lower baseline MPOD, more cataract, and slightly lower scores on the contrast sensitivity test, consistent with the science. The 3 groups were well matched in terms of Amsler grid defects.

At 12 months, subjects taking lutein or lutein and antioxidants showed a 37% to 43% increase in MPOD ($P < 0.05$), compared to subjects taking a maltodextrin placebo. In addition, unlike the placebo group, in which there was no change, subjects in the intervention groups showed significant improvements in GR (it normalized at about 1 minute), contrast sensitivity, and, in some cases, Amsler grid defects. These patients reported that their vision was better. The effect appeared to be independent of the AMD disease stage. This suggests that it may be beneficial to place low vision patients on antioxidants with lutein to enhance visual function. The group receiving lutein and antioxidants seemed to have the greatest benefits by CSF. A few of our clinic low-vision patients have remarked on noticeable improvement in vision, despite initial poor visual function and advanced disease.

The LAST limitations were the investigation of primarily males, small sample size, and a short study duration. This study, sponsored by Kemin Foods International (DesMoine, IA) and Nutraceutical Sciences Inc (Boynton Beach, FL) was presented at ARVO, and is in peer review. Note that women have higher percentage of body fat, so lutein tends to be absorbed within their fat cells, and much of it may theoretically not get to the retina. The National Institute of Health is currently performing dosing studies on patients of both genders.

CLINICAL APPLICATIONS

PreserVision (Bausch & Lomb), contains the identical AREDS research supplement, and can be recommended for patients with intermediate or advanced AMD. As the “emerging science” concerning the benefits of lutein is very strong as well, I suggest that patients eat a half-cup of spinach every other day, or more if they are willing. We advise our patients, except those on a blood thinner such as warfarin (Coumadin), that if they eat half a cup of spinach every other day, they should decrease their risk of developing both cataract and macular degeneration. Cardiac patients with AMD prescribed the blood thinner Coumadin should not be advised to increase their consumption of spinach. A lutein supplement such as OcuVite with lutein is beneficial for those patients and for smokers.

THE IMPORTANCE OF OMEGA-3 IN COLD-WATER FISH

Recent reports based on the prospective Nurses Health Study of 42,743 women and 29,746 men over age 50 showed that greater than 4 servings a week of cold-water fish, high in omega-3-fatty acids (such as tuna, sardines, salmon, and mackerel) was associated with a significantly lower risk of AMD (odds ratio 0.65; CI 0.46-0.91).¹¹ To ensure that your patients obtain the recommended lutein, antioxidants, and omega-3 fatty acids, you could suggest something as simple as eating spinach and sardines every other day.

SUNGLASSES, ESPECIALLY FOR YOUNG PEOPLE

Patients should be reminded that sunglasses are protective, particularly for youngsters. The Beaver Dam Eye Study on sunlight and 5-year incidence of AMD suggests a slight, non-significant protective effect with the use of hats and sunglasses. People with red or blond hair were slightly more at risk (odds ratio 1.33; CI 0.97-1.83).¹²

Several studies have linked smoking with increased risk of AMD, so patients should be encouraged to quit smoking. Beta carotene has been linked to increased lung cancer in smokers. However, even smokers can benefit from antioxidant supplements with lutein (but without beta carotene).

CONCLUSION

AREDS science and “emerging science” are giving us insights into ways to prevent or avoid advanced AMD while “potentially” improving patients visual function with lutein. For patients with Category 1 or Category 2 AMD, you could suggest that they add spinach and sardines to their diet and take a supplement such as OcuVite with lutein (Bausch & Lomb). For patients with Category 3 or Category 4 AMD, you can recommend that they make the same additions to their diet and take PreserVision, the supplement recommended by AREDS scientists for these patients. □

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