A Prospective Study of Neuro-Cognitive Enhancement with Carotenoids in Elderly Adult Males with Early Age Related Macular Degeneration

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Authors' contributions

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ABSTRACT

Background: Diets rich in carotenoids may reduce cognitive impairment. Little is known about dietary zeaxanthin.
Objective: Evaluate zeaxanthin carotenoid supplementation against change in cognitive status.

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Methods: American Psychological Association (APA) certified cognitive evaluation from the Zeaxanthin and Vision Function Study (USFDA Investigative New DrugIND#78,973), a 1 year prospective randomized controlled trial (RCT) of elderly males with mild age related macular degeneration. Neurocognitive testing Repeatable Battery for the Assessment of Neuropsychological Status Update RBANS and Trail Making A & B. Subjects evaluated at baseline and 1 year after dietary isomer RR zeaxanthin (8 mg/d) alone or combined with lutein (9 mg/d) using one way ANOVA, (P<0.05) and T testing.
Results: n=50 subjects completed both study visits. Delayed memory in the zeaxanthin group improved from RBANS score of 91.8 (SD 16) to 99.4 (SD 12), *P* = 0.04.
Conclusions: Zeaxanthin, typically minimally present in the US diet, may nonetheless be important in the context of emerging relationships in primates between dietary xanthophyll carotenoids and cognitive function. Additional larger scale RCTs is indicated to investigate the clinical utility of this carotenoid in nutritional neuroscience.

Keywords: Age related macular degeneration; carotenoids; macular pigment; cognition.

1. OBJECTIVES

The ZVF primary objectives were to evaluate the visual function properties of zeaxanthin independent of lutein, and to assess the added benefit of dietary RR zeaxanthin to traditional lutein supplementation, in elderly male veterans with AMD [1]. Accordingly, for this segment of the study, the objectives were as follows:

1) Evaluate the effect of carotenoid zeaxanthin on cognitive status.
2) Evaluate the effect of 8 mg zeaxanthin combined with 9 mg lutein on cognitive status.

2. PURPOSE AND BACKGROUND

Age-related macular degeneration (AMD) and cognitive impairment are both neurodegenerative disorders associated with aging and have been hypothesized to share common pathogenic pathways [2]. In a large population based study, Wong et al showed a weak association between cognitive function and early ARM. That is, persons with severe cognitive impairment based on Word Fluency Test scores were more likely to have early AMD (odds ratio (OR: 1.6, 95% confidence interval [CI]: 1.1-2.2) and its components, soft drusen (OR: 1.6; 95% CI: 1.1-2.3) as well as pigmentary abnormalities (OR: 1.5; 95% CI: 0.9-2.5) than those without severe impairment [3]. In a later second large scale trial, persons with low Digit Symbol Substitution Test (DSST) (lowest quartile of scores, ≦30) were more likely to have early AMD (odds ratio, 1.38; 95%confidence interval, 1.03-1.85) [4]. The authors conclude that in older populations, cognitive impairment may share common age-related pathogenesis and risk factors with early AMD.

There is a growing body of literature to support the use of dietary carotenoids i.e. lutein and zeaxanthin in the intervention of AMD [5,1]. Research has linked vision loss greater than 20/40 with cognitive impairment [6]. In healthy older adults, macular pigment optical density (MPOD) was only related to visual-spatial and constructional abilities. More recently, for subjects with mild cognitive impairment (MCI), MPOD was shown to be broadly related to cognition including the composite score on the mini-mental state examination, visual-spatial and constructional abilities, language ability, attention and total scale on the Repeatable Battery for the Assessment of Neuropsychological Status [7]. MPOD is related to cognitive function in primates and older adults, and a biomarker of L and Z embedded in all neural tissue [8,9].

Older adults consuming the highest amounts of green leafy vegetables and cruciferous vegetables (both rich sources of lutein) have slower cognitive decline than those consuming the lowest amounts [10,11]. Supplementation with lutein has been shown to improve cognitive function in older women [12]. As well, there is increasing support for the idea that oxidative stress may play an important role in the pathogenesis of more severe cognitive impairment, specifically Alzheimer's disease (AD), the most common form of cognitive impairment.

Historical evolving evidence has suggested oxidative stress is highly implicated in diseases associated with aging, and lesions typically associated with attacks by free radicals have

been found in the brains of persons with AD. The free radicals in the brain that cause oxidative stress, high vascularity and metabolism along with an abundance of fat, provide fodder for free radical attack and protection by endogenous antioxidants [13]. However, early research with the specific antioxidants A and E, thought related to beta amyloid toxicity in AD brains, were found *not associated with* cognitive decline in non-demented subjects [14].

Nonetheless, more recent studies demonstrate that dietary antioxidants may indeed help with slowing the pathogenesis and thereby the progression of cognitive impairment. Observed delays in decline of ADL status, severe dementia, institutionalization and death support this position [13]. Other large scale cross sectional studies [15] suggest that while it is unclear whether low levels of plasma carotenoids precede or are the consequence of cognitive impairment, low carotenoid levels may play a role in cognitive impairment. Plasma analysis of a broad spectrum of antioxidants including carotenoids in elderly groups with unimpaired cognition, mild cognitive impairment (MCI) and Alzheimer's Disease (AD), showed lower levels of peripheral levels and activities of antioxidants in the MCI and AD groups as compared to healthy controls [16]. Therefore, it has been hypothesized that diets rich in antioxidants or supplementation may reduce the risk of cognitive impairment. Recently in the Georgia Centenarian Study, serum lutein, zeaxanthin, and β-carotene concentrations were most consistently related to better cognition ($P < 0.05$) in the whole population as well as centenarians. Only serum lutein was significantly related to better cognition in octogenarians [17].

Obviously, a lifetime of healthy, nutritionally rich foods would be preferable to late life supplementation. Yet, studies have statistically shown significant improvements with verbal fluency and memory scores following lutein and n3 fatty acid supplementation [12], and given that supplementation yields notoriously low negative side effects, this therapy avenue has warranted continued exploration. Accordingly, this study would purport to examine protective factors in the form of dietary supplements that are found in neural tissues and their effect on both AMD and cognitive functions. While both zeaxanthin and lutein are found throughout body tissues, the highest concentration exists in central neural regions, namely the retina, as well as frontal and occipital cortical regions of the brain [8,9].

3. STUDY DESIGN

The present study was conducted as a portion of a larger, one-year, prospective randomized, double blind, intention to treat, lutein (faux-placebo) controlled study of patients with early and moderate AMD, as determined by a retinal specialist using the AREDS 1 simplified scale. [1] No patients with advanced AMD were included. The sample included 60 patients, equally assigned to one of two dietary supplement treatment carotenoid pigment arms, or the traditional 9 mg non–esterified lutein (Kemin Health, Des Moines IA) supplement control group. The groups were broken down as follows: 8mg dietary RR zeaxanthin (Chrysantis, Ball Horticulture, Inc, Chicago, IL) (n=25); 8 mg zeaxanthin + 9 mg lutein (n=25) and the faux placebo 10 mg lutein control Group (n=10).

Subjects were patients in the Optometry/ Ophthalmology Clinic at the North Chicago VAMC with early AMD retinopathy participating in the Zeaxanthin and Vision Function RCT (The ZVF Study Group (FDA IND #78,973) [1]. Those with high risk NEI AREDS retinopathy or who had taken lutein or zeaxanthin supplements or had cataract or retinal surgery within the last 6 months were excluded. Those subjects taking photosensitizing drugs, did not meet ophthalmic/visual entrance criteria, had active comorbidities such as dementia (AD and non-AD type), schizophrenia, severe diabetes, glaucoma, uveitis or optic neuritis or were taking retinotoxic medications were all excluded.

4. METHODS

Age range of patients was 54 to 93 (mean of 75.1, SD = 10.0). Education ranged from 6 years of formal education to 20 years (mean of 13.4, SD = 2.6).After subjects were deemed eligible and informed consent was obtained, several assessments were completed and subsequently published, including:

1. Demographic and Symptom Assessment
2. Ocular Physical Assessment
3. Macular Function and Visual Measurements
4. Neuropsychological Assessment

Macular pigment is a well known surrogate marker of plasma levels – more so as it represents end organ tissue accumulation of carotenoids following competition within the duodenum for absorption as well as lipoprotein

segregation within the liver. The present article focuses only on the Neuropsychological Assessment portion of the study at baseline and final study visit. Neurocognitive testing consisted of Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Trail Making Test A & B. RBANS is a brief and comprehensive cognitive assessment tool with age stratified norms, which provides a more global assessment of neuropsychological functioning for adults age 20 and older. Specifically, neurocognitive domains evaluated include immediate and delayed memory, attention, language and visuospatial/ constructional abilities. Trail Making Test A & B is a portion of the larger Halstead Reitan Neuropsychological Battery and measures simple and divided attention respectively. This test also taps speed of information processing, sequencing and visual scanning abilities. Norms from Tombaugh [18] were employed for the Trail Making Test, and norms published with the RBANS were used to interpret those scores.

RBANS and Trail Making Test A & B were administered at baseline and one year, at the conclusion of ZVF, by an APA certified neuropsychologist (KG-H) and her team.

5. STATISTICS

Data were determined to be normally distributed using the Kolmogorov-Smirnoff and Shapiro-Wilk tests. Analysis of variance (ANOVA) was used to assess for between group differences and the test of Scheffe was used to assess specific comparisons. Bartlett's Test was also used to test ANOVA's equal variances assumption. Differential scores were taken (baseline pre-test - 1 year post-test) and placed in a correlation matrix. Within the group, changes over time were assessed using a two sample, T test using an equal variances assumption. For all tests an alpha level of 0.05 was considered statistically significant. All calculations were made using STATA™ version 10.1 (College Station, Texas, USA).

6. RESULTS

In ZVF, 90% of subjects completed ≥ 2 visits with an initial Age Related Eye Disease Study (AREDS report #18) retinopathy score of 1.4 (1.0 SD) /4.0 (mild macular degeneration), pill intake compliance of 96% and no adverse effects. [1]All testing was administered by the ZVF study neuropsychologist or trained and supervised technicians. Of 60 patients recruited, 60 completed the initial assessment, and 50 completed the second assessment. Data from deceased subjects (n = 2), those who dropped out (n = 7) or those who refused retesting (n = 1) were not analyzed. Therefore, the control group was comprised of 7 subjects of the original 10, 21 of 25 zeaxanthin only, and 22 of 25 in the lutein + zeaxanthin group.

In Table 1 appear the mean (SD) descriptive statistics (age, education), neurocognitive baseline and final RBANS and Trail Making A, B status. There was initial unequal variance for the RBANS variables 'Attention" and "Trail Making Factors B" which failed to sustain statistical significance, by study end.

As there was no true placebo in the ZVF design, one way analysis of variance (ANOVA) was performed on the entire data set to determine an effect from carotenoid supplementation. The RBANS mean sample index and Z scores indicated that, with the exception of immediate memory, the scores for simple and divided attention, delayed memory, visuospatial/ constructional abilities and language were all in the average range. Immediate memory fell within the low average range, in comparison with age and educationally matched normative samples:

- Immediate Memory ANOVA yielded $F_{(2, 49)}$ =1.58 with p=0.22.
- Visuospatial / constructional ANOVA yielded $F_{(2, 49)}$ = 0.731 with p=0.49.
- Language ANOVA yielded $F_{(2, 49)}$ =0.052 with p=0.95.
- Attention ANOVA yielded $F_{(2, 49)}$= 1.35 with p=0.87.
- Delayed Memory ANOVA yielded $F_{(2, 49)}$ = 0.067 with p=0.96.
- Total RBANS Score ANOVA yielded $F_{(2, 49)}$ = 0.383 with p=0.68.
- Trails A ANOVA yielded $F_{(2, 49)}$ = 1.429 with p=0.25.
- Trails B ANOVA yielded $F_{(2, 49)}$ =0.039 with p=0.96.

In Table 2, changes in neurocognitive status over time, for each of the 3 intervention groups is presented with a T test P< 0.05 considered significant. Individual and Total RBANS parameters as well as Trails A and B were all non-significant with the exception of zeaxanthin, RBANS delayed memory. Delayed memory in

Table 1. Mean (sd)ZVF population descriptive statistics (age, education) and neurocognitive baseline and final RBANS and Trail Making A, B scores. Initial baseline unequal variance for the variables "Attention" and "Trail Making Factors B" failed to sustain statistical significance, by study end

Variable	Baseline			Baseline Bartlett's test for equal variance between groups	Final			Final Bartlett's test for equal variance between groups
	N	Mean	(sd)		N	Mean	(sd)	
Age (yrs)	60	75.1	10.0	NS				NS
Education (yrs)	60	13.4	2.6	NS				NS
Immediate memory	60	88.3	15.3	NS	50	93.9	14.0	NS
Trails making factors b	60	-0.8	1.7	0.05	50	-0.9	2.3	NS
Visual spatial construction	60	98.4	19.7	NS	50	91.0	17.6	NS
Language	60	97.0	9.9	NS	50	99.1	8.6	NS
Attention	60	93.2	15.5	0.02	50	96.5	14.0	NS
Delayed memory	60	92.5	14.7	NS	50	95.4	16.0	NS
Total	60	91.6	13.3	NS	50	93.1	13.5	NS
Trails making factors a	60	0.1	0.9	NS	50	-0.1	1.3	NS

the zeaxanthin group improved from a RBANS score of 91.8 (SD 16) to 99.4 (SD 12), one way ANOVA, P = 0.04.

7. DISCUSSION

No significant differences were found between the groups except for "Delayed Memory", suggesting no broad multi factorial effect was seen by supplementing with zeaxanthin or by adding zeaxanthin to lutein. A larger sample size may have been able to show an effect size. Notably, subjects did however maintain their cognitive function during the duration of the study, lending at least modest support for the hypothesis that xanthophyll carotenoids can slow the progression of oxidative stress by containing free radicals and preserving neural tissue, over the 1 year ZVF study period, in elderly adult male veterans.

The strengths of this study are randomization, double masking and sensitive instruments. The weaknesses were no true placebo and non – generalizable to other populations such as the young, females and those without AMD. Differences with other studies were subtle, and may have been enhanced by subject selection and placement in groups with graded levels of dementia (i.e., unimpaired, mild moderate and severe), that may have highlighted subtle effect(s). Subjects may have also been 'pre-screened for dementia' or other comorbid conditions adversely affecting cognitive performance.

The presence of a true 'control group' receiving a placebo instead of one of three treatment groups may have been useful to underscore any difference that might have been correlated with supplement use. As such, study design or subject selection procedures may have been a factor in masking additional benefit(s). Some studies actually stratify subjects' education-level [14], which is a known protective factor in the development of cognitive impairment. Since ZVF veterans manifested a broad range of education levels between 6 and 20 years, but overall a higher than average mean level at 13.2 years, this may have had a veiling effect on outcome.

Quite recently, serum markers of both oxidation and inflammation have been found to predate the onset of AD [19,20]. It follows that dietary modification / supplementation with carotenoids may take more than 1 year to mount an effect size measurable by our selected instruments.

Table 2. Change in Neurocognitive status over time, for 3 intervention groups: faux placebo lutein (left column); zeaxanthin (central column) and zeaxanthin + lutein (right column). 1 way ANOVA, *P*<0.05 considered significant

	n=	Lutein mean (SD)	*P* value	n =	Zeaxanthin mean (SD)	*P* value	n =	L + Zmean (SD)	*P* value
Immediate Memory	Baseline = 10 Final = 7	84.7 (16.5) 91.7 (17.5)	NS	Baseline = 25 Final = 21	89.8 (16.0) 96.5 (10.4)	NS	Baseline = 25 Final = 22	88.3 (14.5) 92.0 (16.1)	NS
Visual Spatial Construction	Baseline = 10 Final = 7	102.6 (19.1) 99.1 (19.2)	NS	Baseline = 25 Final = 21	99.0 (18.0) 93.6 (15.9)	NS	Baseline = 25 Final = 22	96.1 (22.0) 85.9 (17.8)	NS
Language	Baseline = 10 Final = 7	91.8 (10.9) 98.0 (5.2)	NS	Baseline = 25 Final = 21	98.6 (9.5) 98.0 (9.4)	NS	Baseline = 25 Final = 22	97.4 (9.6) 100.5 (8.9)	NS
Attention	Baseline = 10 Final = 7	85.7 (18.2) 97.9 (17.9)	NS	Baseline = 25 Final = 21	90.2 (15.9) 94.5 (14.2)	NS	Baseline = 25 Final = 22	99.3 (11.8) 98.0 (12.8)	NS
Delayed Memory	Baseline = 10 Final = 7	93.1 (19.2) 97.9 (20.7)	NS	Baseline = 25 Final = 21	91.8 (12.3) 99.4 (11.8)	0.04	Baseline = 25 Final = 22	93.0 (15.5) 90.7 (17.0)	NS
RBAN TOTAL	Baseline = 10 Final = 7	89.0 (16.8) 96.0 (17.9)	NS	Baseline = 25 Final = 21	91.4 (11.6) 93.7 (11.4)	NS	Baseline = 25 Final = 22	93.0 (13.8) 91.6 (14.3)	NS
Trails Making A	Baseline = 10 Final = 7	-0.50 (1.2) -0.99 (1.2)	NS	Baseline = 25 Final = 21	0.10 (0.8) -0.18 (1.5)	NS	Baseline = 25 Final = 22	0.4 (0.9) 0.2 (1.0)	NS
Trails Making B	Baseline = 10 Final = 7	-1.2 (1.7) -1.3 (1.8)	NS	Baseline = 25 Final = 21	-0.74 (1.7) -0.65 (1.4)	NS	Baseline = 25 Final = 22	-0.65 (1.8) -0.99 (3.2)	NS

Future studies may also do well to pair serum markers with cognitive screening tools completed by patients or their surrogates, functional visual assessment measures and new objective structural measures of the human lens and retina. This would yield data that could illuminate any relationship between plasma levels, cognitive performance, objective ocular tissue biomarkers and patient/family observations regarding functional cognitive capacity. Such a global data set would enable researchers to evaluate cognitive performance and ocular functional/structural improvements, enhancing the ecological validity of evaluating the eye and brain together.

4. CONCLUSION

Cognitive decline and visual decline remain major comorbidities among the aging population, with incidence increasing exponentially from 65 years of age to 85 years of age [21]. With the significant increase in both the number and longevity of older persons, it becomes necessary to identify universal lifestyle choices and treatment options that might stabilize or reduce the effects of aging on both visual and cognitive disability. Dietary xanthophyll carotenoids will surely play a role.

INFORMED CONSENT AND ETHICAL APPROVAL

The ZVF study (FDA IND # 78,973) obtained and secured informed consent, protection of privacy, and other human rights through the Institutional Review Board and Human Subjects Committees at Hines, VA (Chicago, IL). "All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 "Declaration of Helsinki."

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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