A Double-Blind, Placebo-Controlled Study on the Effects of Lutein and Zeaxanthin on Photostress Recovery, Glare Disability, and Chromatic Contrast

Billy R. Hammond,[1] Laura M. Fletcher,[1] Franz Roos,[2] Jonas Wittwer,[2] and Wolfgang Schalch[2]

[1]Vision Sciences and Human Biofactors Laboratories, Department of Psychology, University of Georgia, Athens, Georgia, United States
[2]DSM Nutritional Products Ltd., Wurmisweg, Kaiseraugst, Switzerland

Correspondence: Billy R. Hammond, Vision Sciences and Human Biofactors Laboratories, Department of Psychology, University of Georgia, 125 Baldwin Street, Athens, GA 30602-3013, USA; bhammond@uga.edu.

Submitted: August 28, 2014
Accepted: November 11, 2014

Citation: Hammond BR, Fletcher LM, Roos F, Wittwer J, Schalch W. A double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on photostress recovery, glare disability, and chromatic contrast. *Invest Ophthalmol Vis Sci*. 2014;55:8583–8589. DOI:10.1167/iovs.14-15573

Purpose. Past studies have shown that higher macular pigment optical density (MPOD) and lutein (L) and zeaxanthin (Z) supplementation are related to improvements in glare disability, photostress recovery, and chromatic contrast. This study assessed those links using a randomized, double-blind, placebo-controlled design.

Methods. The visual effects of 1 year of supplementing L (10 mg/d) and Z (2 mg/d) were investigated. One hundred fifteen young, healthy subjects were recruited and randomized into the study (58 received placebo, 57 L+Z). Several dependent measures were collected at baseline and then once every 3 months: serum L and Z measured by HPLC chromatography; MPOD measured using customized heterochromatic flicker photometry; photostress recovery assessed by measuring the time needed to recover visual acquisition of a grating target after 30 seconds of an intense xenon white flash exposure; glare disability evaluated as the energy in a surrounding annulus necessary to veil a central grating target; and chromatic contrast assessed by measuring thresholds for a yellow grating target superposed on a 460-nm background.

Results. Macular pigment optical density increased significantly versus placebo at all eccentricities (10, 30, 60, and 105 minutes from the center of the macula). Serum L and Z also increased significantly by the first follow-up visit (at 3 months), and remained elevated throughout the intervention period of 1 year. Chromatic contrast and photostress recovery time improved significantly versus placebo. Glare disability was correlated with macular pigment density throughout the study period but did not increase significantly in the treated group.

Conclusions. Daily supplementation with L+Z resulted in significant increase in serum levels and MPOD and improvements in chromatic contrast and recovery from photostress. These results are consistent with past studies showing that increasing MPOD leads to improved visual performance. (ClinicalTrials.gov number, NCT00909090.)

Keywords: lutein, zeaxanthin, macular pigment, disability glare

Carotenoids are plant-derived pigments that serve a wide variety of roles in human biology.[1] For instance, because carotenoids absorb visible light and are incorporated into ocular tissues, they can influence the optical characteristics of the human eye. In fact, many of the standard methods of measuring lutein (L), zeaxanthin (Z), and meso-zeaxanthin (MZ) in the retina are based on behavioral tests of visual function; hence, psychophysicists have known for many decades that L and Z within the retina influence vision as a linear function of amount.[2] A related question is whether, as mechanisms of natural selection would predict, these functional effects are ecologically meaningful.[3] Lutein and Z concentrate (over 1000 times the amount in serum) in the inner layers of the macular region of the eye (there, along with MZ, they are referred to as macular pigment, MP). Macular pigment selectively absorbs the lower third of the visible spectrum (400–500 nm, peak absorbance = 460 nm). By forming an internal yellow filter that screens cones and central rods, a number of ecologically significant effects on vision can be expected to occur. Those most supported by the empirical evidence to date[4–14] are reducing the effects of glare disability (GD) and discomfort, speeding photostress recovery (PR), extending visual range, and improving chromatic contrast (CC).

Glare refers generally to a condition in which individuals are exposed to a light source, either direct or indirect, that is in excess of their adaptive state. Such light can cause both discomfort and disability (a reduction in visual performance). A number of studies have shown that yellow intraocular filters (or L+Z supplementation) improve GD (see Ref. 15 for recent review). Very short intense light exposures can result in a temporary loss of sight (photostress) that is caused by a combination of photopigment bleaching and adaptation. Measuring the time necessary to recover sight of a visual target following an intense exposure is termed photostress recovery, and this measure has also been related to MP density and L+Z supplementation.[11]

Another variable explored in a previous correlational study is the effect of MP upon CC.[14,15] In 1972, Luria[16] demonstrated this effect by showing that the threshold for a yellow increment flash on a blue background was reduced when viewed through a blue-absorbing filter. Wolffsohn et al.[17] confirmed this effect using contrast measures. The degree of contrast enhancement varied among studies of filters with different spectral characteristics. For optimum enhancement, some research supported blocking wavelengths from approximately 400 to 480 nm (matching the absorbance spectrum of MP). The contrast-enhancing effects that were measured with blue-filtering lenses arose because the filters reduced the luminance of the background relative to the target, which increased contrast and therefore increased the detectability of the central target. These simple laboratory situations are actually a good reflection of many visual situations outdoors. The preponderance of Rayleigh-scattered light (seen as "blue haze" and blue sky light) creates a natural situation in which many targets are viewed on short-wave (blue) backgrounds (sky light peaks at the same absorbance peak as MP, 460 nm).

A contrast-enhancing effect of MP likely has wide applications. Often adjoining objects in nature appear similar in color, but actually a spectral analysis would show that the two are quite different.[18] The question of the optimal characteristics of a filter for enhancing contrast was originally discussed by Gordon Walls.[19] He noted that there is a ubiquity of yellow filters in nature (e.g., the carotenoids in the oil droplets of birds) and that the specific and strategic nature of this filtering was quite important: "By cutting out the different amounts of blue in different but alike-looking green mixtures, the greens are made to look unlike; and almost any other contrasts can be sacrificed by the animal if only those between greens, so numerous in nature, can be enhanced" (p. 196).

In a previous study performed by Stringham and Hammond,[11] the effect of L and Z supplementation on GD, PS, and CC was investigated. Forty young, healthy adults received daily L+Z (10 + 2 mg/d) for 6 months while MP, GD, and PR were measured. At the baseline time point, MP optical density (OD) at 30′ eccentricity ranged from 0.08 to 1.04, and was strongly correlated with improved visual performance in the two glare tasks. After 6 months of L+Z supplementation, average MP density (at 30′ eccentricity) had increased from 0.41 to 0.57, and was shown to significantly reduce the deleterious effects of glare for both the visual performance tasks assessed. Thus, it was concluded that MP was strongly related to improvements in GD and PR in a manner strongly consistent with its spectral absorption and spatial profile (spatial and spectral conditions were varied as a control).

In this study we repeated this basic approach, but we added CC as one of the additional dependent measures of visual performance, extended the intervention to a year, included serum analysis, and included a placebo group in a randomized study design.

Methods

Study Description

The present study utilized a prospective, randomized, double-blind parallel design (ClinicalTrials.gov identifier: NCT00909090). Subjects were randomized to receive either a supplement or placebo. The supplement was a red-coated tablet containing the active ingredients 10 mg lutein (FloraGLO Lutein; Kemin Foods L.C., Des Moines, IA, USA) and 2 mg zeaxanthin (OPTISHARP Zeaxanthin; DSM Nutritional Products Ltd., Kaiseraugst, Switzerland) or matching placebo. The study subjects were instructed to take one tablet with breakfast every day for a total duration of 1 year. The actual subject visit dates were delayed by approximately 10% on average versus the planned schedule of 0, 3, 6, 9, and 12 months, and the timing between visits was not always equal; hence, we depict the total study duration in the figures up to 400 days. One hundred fifteen subjects (recruited from the University of Georgia student population) met the study inclusion criteria and were selected for randomization. The randomization was done by a neutral second party, Wolfgang Köpcke at the Institute for Biometry and Clinical Research, University of Münster, Germany. The inclusion/exclusion criteria are provided in Hammond et al.[20] As shown in Figure 1, plasma L and Z for the placebo group did not change during the course of the study, suggesting that the ad libitum diet also did not change. This study was approved by University of Georgia institutional review board, and the experimental procedures were conducted in accordance with Good Clinical Practice Guidelines and the ethical principles of the Declaration of Helsinki.

Equipment and Procedures

For details regarding the reliability and stimulus characteristics for all of the variables, see the extended treatment in Hammond et al.[20] The apparatus and procedure used to measure macular pigment optical density (MPOD) have also been described in detail previously.[20,21] This method of measuring macular pigment has been extensively validated.[2] A macular densitometer (Macular Metrics, Inc., Rehoboth, MA, USA) was employed. The protocol was the same as that previously published.[20,22] A schematic of the optical setup of the apparatus is given in Wooten et al.[21] (see Fig. 3 therein). Lutein and Z in the serum were measured using reverse-phase high performance liquid chromatography (HPLC), and that measurement is also detailed in Hammond et al.[20]

Three efficacy parameters were measured (PR, GD, and CC), and all three parameters were assessed on the same apparatus, modified for each parameter. The apparatus was a Maxwellian view optical system providing up to three channels. A schematic of the setup of the apparatus is given in Wooten et al.[21] (see Fig. 1 therein). Consistent Maxwellian delivery of the stimulus to the eye was maintained by a dental impression bite bar and forehead rest assembly. A monitor with an infrared camera was used to monitor pupil position and ensure that subjects were both aligned and viewing the stimuli during intense exposures.

Based on the assumption that the mechanisms for accumulating MP evolved as a result of outdoor activities, we strove to design the stimuli in a manner that was as ecologically valid as possible. Thus, as shown in Figure 1 of Hammond et al.,[20] we used a xenon source that closely matched the spectral distribution of sunlight (an even better match can be made to the solar spectrum provided in Fig. 1 of Hammond et al.[23]). For the GD measurement, subjects adjusted the intensity of an annulus (centered at 11.5° eccentricity) until it veiled a 1° circular grating (4 cyc/deg) target. Photostress recovery was assessed by exposing the subjects to a bright (5.5 log trolands) circular disc (5°) of xenon light for 5 seconds. Based on calculations by Margrain et al.,[24] this bleaches approximately 50% of the central photopigment. Recovery was measured as the time needed to see a dim flashing target (200-ms cycle) that begins shuttering after the cessation of the photostress. Chromatic contrast was determined by having subjects adjust a circular blue (460 nm) surround until it caused the disappearance of a circular (1°) yellow (570 nm) grating target. The entire series of visual measurements took approximately 1 hour to complete.

Fasting samples (10 mL whole blood) were collected on the morning of a study visit by a licensed phlebotomist for

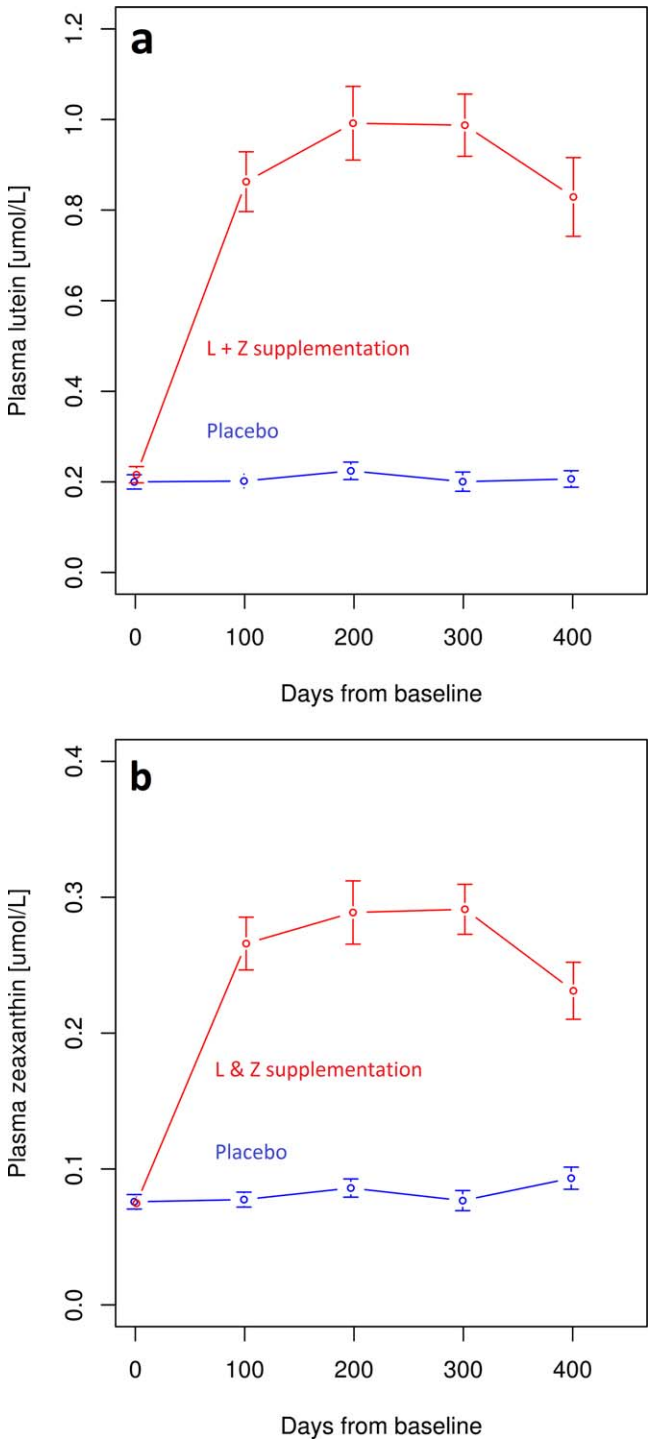

Figure 1. Significant increase in lutein and zeaxanthin plasma levels upon supplementation. Upon supplementation with lutein and zeaxanthin, the plasma levels of lutein (**a**) and the plasma levels of zeaxanthin (**b**) increased very significantly while they remained constant in the placebo group. The means are presented for each average visit time from baseline. The *error bars* represent the empirical standard error of the mean at the visit.

quantification of carotenoids, retinol, and tocopherol. The samples, collected in 10-mL lithium heparin-coated vacutainers (BD, Franklin Lakes, NJ, USA) were separated by centrifugation at 1500*g* for 20 minutes at 4°C. After separation, the plasma was distributed into 1.5-mL light-protected Eppendorf vials, 1 mL per vial. The samples were stored at –80°C until express shipment (in insulated boxes on dry ice) to DSM Nutritional Products, Inc., in Kaiseraugst, Switzerland, for analysis. Blood samples were prepared and analyzed for L and Z determination as described by Hartmann et al.[25]

Extensive calibration was conducted in this study, since the intervention lasted an entire year and it was critical that the stimuli were stable, effectively, over several years. Hence, both radiometric and photometric calibrations were regularly performed. Prior to each experimental sitting, a dedicated radiometer was used to ensure that total light output remained constant (S370 Optometer; UDT Instruments, Hawthorne, CA, USA). The neutral-density wedge was calibrated using a second radiometer (model 370; Graseby Optronics, Orlando, FL, USA). Photometric calibrations were done using a telescopic spectral radiometer (model PR650; PhotoResearch, Inc., Chatsworth, CA, USA) with the stimuli projected onto a white reflectance standard calibrated to the instrument. Spatial alignment of the channels was checked every session by increasing the intensity of the light source and checking the precise location of the projected image against a fixed point on a wall, the position of which relative to the equipment never changed (the equipment was bolted to the floor). To assess the daily and long-term laboratory performance of the HPLC plasma analytics, dedicated control plasma was used. This control was composed of pooled human plasma that was characterized internally and then used as a quality control measure to ascertain the daily and long-term repeatability of the HPLC plasma analytics. All of the analytical methods were regularly checked through participation in international ring trials organized by the National Institutes of Standards and Technology (USA) and the Society for Vitamins and Biofactors (France). The control samples were analyzed at least four times a day during the study.

Statistical Analyses

A power analysis based on previous published studies on the relationship between L and Z intake and resultant significant changes in MPOD determined that >80% probability of detecting a change at the 95% significance level would be achieved if each group consisted of 50 subjects. For all data of the final analyses presented in this publication, we used the "intention to treat" (ITT) data set (defined as all randomized subjects who returned for at least one subsequent follow-up visit) according to International Conference on Harmonization (ICH) guidance E9, "Statistical Principles for Clinical Trials," 1998, section 5.2.3 (Primary analysis is to be conducted on full data set). A linear mixed model regression[26,27] was performed, which has the advantage of being able to take into account all available data points for all subjects, including incomplete subject data. The time–treatment interaction was considered the most relevant output since it reflects a gradual effect of the treatment versus the placebo. All statistical analyses and visualizations were performed in the open-source statistical software package R version 2.15.2 (2012-10-26) (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/, in the public domain). The mixed models were performed using the function "lme" in the corresponding R package nlme_3.1-105.

Results

Of the 115 randomized subjects, mostly university students, 109 returned for at least one follow-up visit (ITT set: 53 subjects in the L+Z group and 56 subjects in the placebo group). Thirty-four subjects withdrew over the course of the study, usually because they left the university (17 subjects per group; these subjects did not differ systematically from those who remained in the trial). Of the 460 planned follow-up

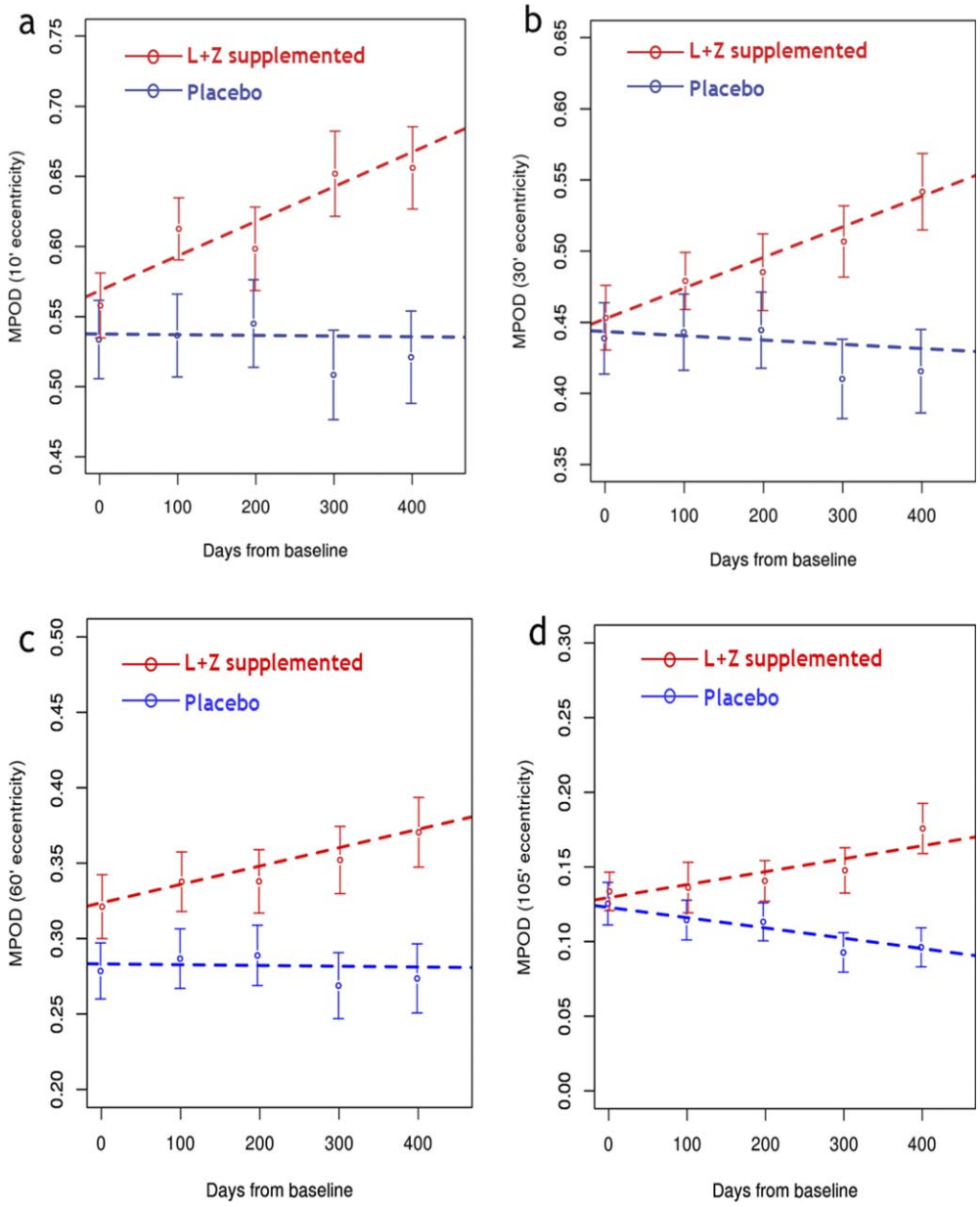

FIGURE 2. Significant MPOD increases at different eccentricities upon supplementation (ITT set). Macular pigment optical density increased significantly in the lutein- and zeaxanthin-supplemented group at 10′, 30′, 60′, and 105′ eccentricities. *Dashed lines* represent the regression lines; *error bars* represent the standard error of the mean.

measurements, 365 were actually obtained for the primary parameter, MPOD. This corresponds to 91 complete subject data sets. The baseline characteristics of the ITT population are shown in Table 1.

Figures 1a and 1b show the statistically significant increases in plasma L and Z that were obtained over the course of the study period in the L+Z-supplemented group versus placebo ($P < 0.001$ for both L and Z). These results, when considered with our pill counts, suggest that subjects were reasonably compliant. Serum lycopene and total carotene did not change significantly over the study duration for either group. Serum tocopherol levels did not change significantly in the placebo group but increased significantly in the supplementation group versus the placebo group ($P = 0.012$, intercept 24.2 units, slope 0.21 units versus placebo/mo). Serum retinol also increased significantly over the study duration by 0.015 units per month ($P = 0.0013$) in the entire study population, without any significant difference between the placebo and supplement groups ($P = 0.34$).

The increases in serum LZ were adequate to raise MP density at all of the retinal locations that we measured, and these data are shown in Figure 2. The absolute baseline and the increase from baseline are smallest in the outer eccentricities (60′ and 105′ shown in Figs. 2c, 2d), and highest close to the fovea (10′ and 30′ shown in Figs. 2a, 2b). In the L+Z supplementation group, for example, MPOD at 10′ increased by 0.101 after 400 days of supplementation (final MPOD of approximately 0.66; see Fig. 2a).

As shown in Table 2, there was a significant correlation between MPOD levels over time and visual performance (irrespective of group assignment). These significant relations, which were seen for MPOD measured at 10 and 30 minutes

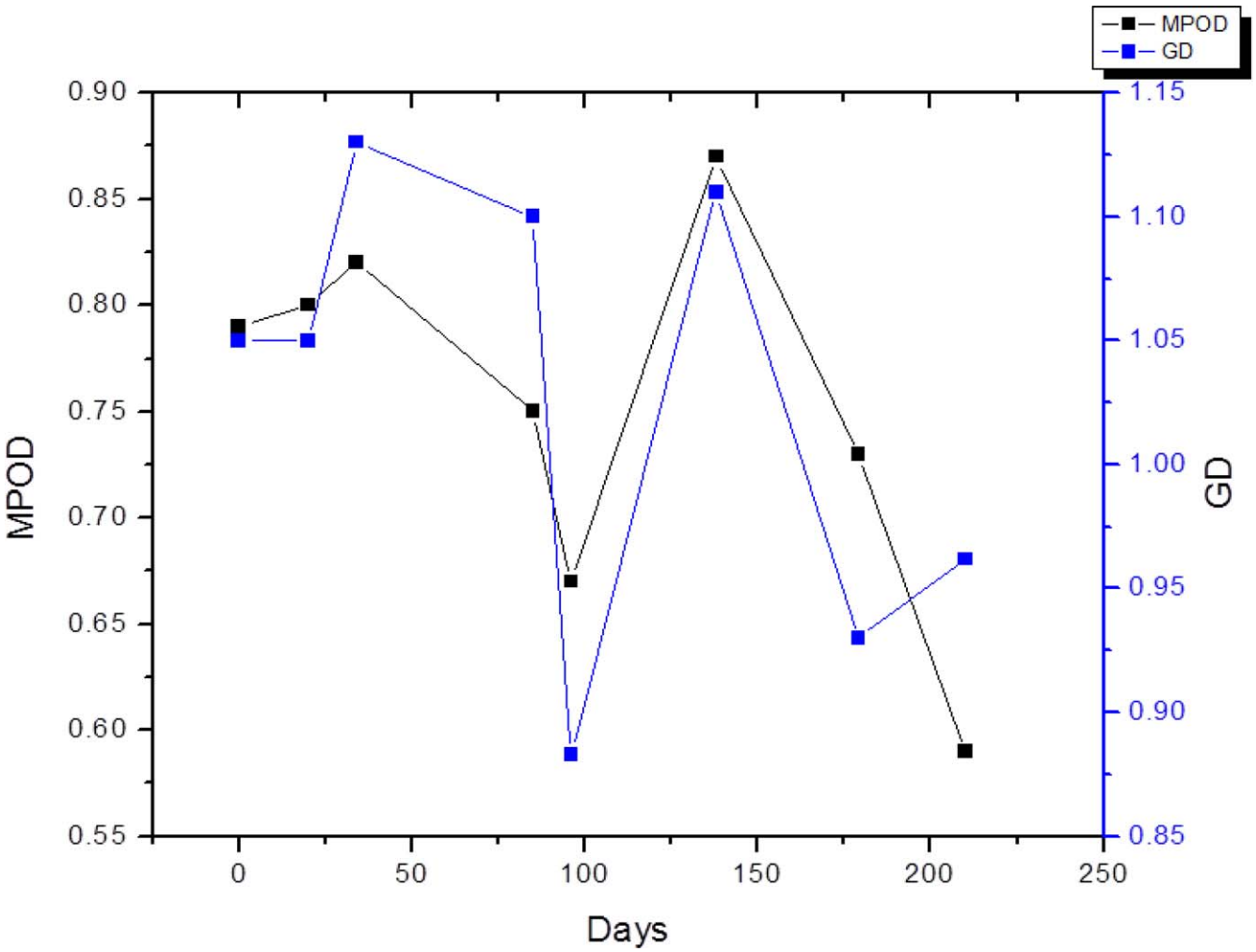

FIGURE 3. Relationship of MPOD and variance in glare disability. The relation between MPOD (*black line*) and variance in glare disability (GD; *blue line*; expressed as log relative energy) for one subject who was tested repeatedly during the study period and was not taking a supplement or placebo. Note the close correspondence in the two curves.

(the latter is shown in Table 2) but not at more eccentric retinal locations (the exception was MPOD at 60′ for CC), can be used as a general predictor for visual function.

Table 3 shows the visual changes when analyzed according to allocation of treatment or placebo. For all three variables, there was no significant change in the placebo group. In contrast, both PR and CC improved significantly in the intervention group versus the placebo group. Glare disability also decreased versus the placebo group, but this change was not statistically significant.

No serious adverse events occurred throughout the intervention period. Twenty adverse events occurred during the entire study period. However, no adverse events occurred that were directly attributable to the study intervention.

DISCUSSION

The overall analysis demonstrates that supplementation of L and Z increases MPOD, and that higher MPOD results in contrast enhancement and faster recovery from photostress. These results extend and confirm the earlier conclusion reported by Stringham and Hammond.[11] In that earlier study, plasma carotenoid data were not collected; a placebo control was not included; CC was not assessed; and the duration of the study was only 6 months. Like that earlier study, the present intervention, using the same supplementation regimen, also found substantial improvements in visual function (measured in nearly precisely the same manner as in the earlier study). There were a few notable differences. Stringham and Hammond[11] found a 5-second improvement in PR measured over 6 months; the current study found a nearly 9-second improvement measured over 1 year. This suggests an increasing benefit on PR with duration of use. Stringham and Hammond[11] also reported an improvement in GD, noting an average improvement from a baseline energy of 2.7 to 2.9 μW/cm^2 (~7%). The current study found an average improvement from approximately 1.66 to 1.8 μW/cm^2 (~8%). (Note that slightly different conditions were used in the current experiment in order to reduce the overall energy needed to induce glare conditions.) Although these changes may seem small from a percentage standpoint, note that the energy values are expressed in logarithmic units (meaning, if translated into linear units, that a 0.10 log change reflects an approximately 23% change). Increasing MP density allowed subjects to tolerate significantly more energy before losing sight of a visual target. The amount of change in CC thresholds is similarly large (approximately 20% based on a linear percentage). For comparison, achromatic luminance contrast thresholds are often much less than 1%. The fact that

Investigative Ophthalmology & Visual Science

Table 1. Baseline Characteristics of Intention to Treat Population Set, $n = 109$

	Placebo, $n = 56$, Mean	Placebo, $n = 56$, SD	Min	Max	Treatment, $n = 53$, Mean	Treatment, $n = 53$, SD	Min	Max	*t*-Test, *P* Value
Sex, M/F	22/34	-			22/31	-			0.96*
Age, y	22.7	3.32	18.4	30.6	23.7	4.61	18.6	40.6	0.20
Weight, kg	66.3	10.7	50	100	68.1	11.9	45.5	108	0.39
Height, cm	170	8.11	152	189	172	8.93	152	191	0.21
BMI	22.8	2.66	19.3	29.9	22.9	2.45	19.6	30	0.96
Iris darkness score	2.81	1.27	1	4	2.9	1.31	1	5	0.74
Contrast energy, $\mu W/cm^2$	1.1	0.43	0	1.81	1.01	0.34	0	1.67	0.26
Photostress rec time, s	32.7‡	19.6	1.03	2.24	36§	18.7	0.588	2.19	0.38
Glare energy, $\mu W/cm^2$	1.76	0.306	4.8	80.3	1.68	0.308	7.25	82.5	0.14
Total zeaxanthin, µmol/L	0.076	0.04	0.009	0.236	0.0748	0.034	0.028	0.199	0.88
Total lutein, µmol/L	0.2	0.118	0.046	0.707	0.216	0.13	0.067	0.837	0.51
MPOD, 10′	0.53†	0.21	0.07	0.91	0.56	0.17	0.15	0.95	0.50
MPOD, 30′	0.44†	0.19	0.1	0.85	0.45	0.17	0.11	0.95	0.67
MPOD, 60′	0.28†	0.14	0.04	0.65	0.32	0.15	0	0.66	0.13
MPOD, 105′	0.13‡	0.11	0	0.37	0.13	0.09	0	0.34	0.67
Total lycopene, µmol/L	0.98	0.41	0.238	2.04	0.99	0.43	0.348	2.31	0.92
Total tocopherol, µmol/L	24.1	5.56	13.7	37.7	24.3	6.79	16.1	47.8	0.85
Retinol, µmol/L	1.69	0.41	0.87	2.51	1.76	0.48	0.97	3.33	0.40
Total carotene, µmol/L‖	0.44	0.34	0	1.44	0.57	0.50	0.067	2.22	0.13

BMI, body mass index; rec, recovery.
* A χ^2 test was used to check the sex balance.
† Values based on $n = 55$.
‡ Values based on $n = 54$.
§ Values based on $n = 51$.
‖ Total carotene represents the sum of the concentrations of alpha- and beta-carotene.

increasing MP creates this much of an internal change in CC within the eye would translate to very significant improvements in, for example, the perception of distant objects (e.g., see the modeling by Wooten and Hammond).[28]

Macular pigment density was significantly correlated with GD for both groups and at all the time points that were measured (this is illustrated for one subject in Fig. 3). Unlike what was found in other studies, however, L+Z supplementation did not lead to statistically significant improvements in GD in this sample. This may be due to the fact that MPOD did not increase as much as it did in our previous study (Stringham and Hammond[11]). It could also be due simply to noise within the measurement. Glare disability is one of the more difficult measures since subjects must increase the intensity of light entering their eye until they are, essentially, blinded (i.e., they lose sight of the grating target). This is unlike the photostress measurement, in which the intensity of the exposure is not under the subject's control. Measuring "disability" is likely sufficiently aversive to incur additional noise in the measurement.

This result suggests that in order for supplementation to change visual function (optically), it must result in increased MPOD. While there was biological variability (e.g., MP density for some of the placebo group substantially increased and decreased), average MPOD increased very significantly in the treatment group versus the placebo group.

Such an observation makes sense based on the mechanism: Most of the effect is likely based simply on filtering short-wave light. For example, convolving differing levels of MP density with the xenon spectrum, and then subtracting the areas under the curves for levels approximating the change seen in Figure 2, lead to a difference across the visible spectrum of approximately 12%; the average change in PR was approximately 17%. Additional effects on PR may be due to a local metabolic effect such as influences on photopigment regeneration.

The mechanisms to accumulate retinal LZ did not evolve to improve problems that are largely associated with modern life, like refractive error. Most of the activity of hunters and gatherers, like agrarian groups, involved seeing objects at a distance, mostly outside, and primarily during the daytime

Table 2. MPOD (30′) as a Predictor of Visual Function (Placebo and Treatment Groups Considered Together)

Variable	Slope	SE of Slope	*P* Value
Photostress recovery	−18.9	6.0	0.002*
Glare disability	0.19	0.09	0.03*
Chromatic contrast	0.48	0.11	<0.0001*

The slope reflects differences in seconds (PR) or energy (GD and CC) associated with one unit difference in MPOD. A mixed model was applied to all subjects at all visits simultaneously to determine the association between MPOD and photostress recovery time.
* $P < 0.05$.

Table 3. Changes in Macular Pigment and Visual Function Compared to Placebo

Variable	Slope, Change per Day*	SE of Slope	*P* Value
MPOD 10′	0.00025	0.00006	<0.0001†
MPOD 30′	0.00025	0.00005	<0.0001†
MPOD 60′	0.00013	0.00005	0.006†
MPOD 105′	0.00016	0.00004	0.0004†
Photostress recovery	−0.019	0.008	0.013†
Glare disability	0.00018	0.00014	0.21
Chromatic contrast	0.00037	0.00017	0.030†

* Daily change in treatment group versus daily change in placebo group.
† $P < 0.05$.

under natural sunlight. Concomitantly, the pigments tend to influence visual function in a way that appears linked to the conditions under which they evolved, for example, intense glaring light from sources that are similar to the sun. Filtering short-wave light, in particular, has ecological significance since it is largely short-wave light that tends to degrade vision through the atmosphere. During viewing of objects at a distance, most of the luminance differences are minimized. By differentially filtering chromatic borders (chromatic enhancement) and creating a luminance edge within the eye, the ability to detect objects at a distance is similarly enhanced.[28–30]

There have been at least eight prior randomized controlled trials that have investigated the effects of L, Z, or MZ supplementation on visual function in normal healthy subjects.[4–9,11,13] All have found significant improvement in visual function resulting from xanthophyll supplementation. The effects of MP on visual function are likely significant from a public health perspective given the dietary origin of the macular pigment and the relatively low intake of LZ in the Western diet, especially in children.[31] A relatively modest gain in MP density resulting from dietary changes or supplementation could translate to meaningful improvements in visual function.

Acknowledgments

Supported by DSM Nutritional Products Ltd. and Kemin Foods L.C.

Disclosure: **B.R. Hammond**, DSM Nutritional Products Ltd. (R), Kemin Foods (R); **L.M. Fletcher**, None; **F. Roos**, DSM Nutritional Products Ltd. (E); **J. Wittwer**, DSM Nutritional Products Ltd. (E); **W. Schalch**, DSM Nutritional Products Ltd. (E, C), P

References

1. Hammond BR, Renzi L. Carotenoids. *Adv Nutrition*. 2013;4:474–476.
2. Hammond BR, Wooten BR, Smollon B. Assessment of the validity of in vivo methods of measuring human macular pigment optical density. *Optom Vis Sci*. 2005;82:387–404.
3. Hammond BR, Fletcher LM. Influence of the dietary carotenoids lutein and zeaxanthin on visual performance: application to baseball. *Am J Clin Nutr*. 2012;96:1207S–1213S.
4. Kvansakul J, Rodriguez-Carmona M, Edgar DF, et al. Supplementation with the carotenoids lutein or zeaxanthin improves human visual performance. *Ophthalmic Physiol Opt*. 2006;26:362–371.
5. Loughman J, Nolan JM, Howard AN, Connolly E, Meagher K, Beatty S. The impact of macular pigment augmentation on visual performance using different carotenoid formulations. *Invest Ophthalmol Vis Sci*. 2012;53:7871–7880.
6. Nolan JM, Loughman J, Akkali MC, et al. The impact of macular pigment augmentation on visual performance in normal subjects: COMPASS. *Vision Res*. 2011;51:459–469.
7. Olmedilla B, Granado F, Blanco I, Vaquero M. Lutein, but not alpha-tocopherol, supplementation improves visual function in patients with age-related cataracts: a 2-y double-blind, placebo-controlled pilot study. *Nutrition*. 2003;19:21–24.
8. 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.
9. Richer SP, Stiles W, Graham-Hoffman K, et al. Randomized, double-blind, placebo-controlled study of zeaxanthin and visual function in patients with atrophic age-related macular degeneration: the Zeaxanthin and Visual Function Study (ZVF) FDA IND #78, 973. *Optometry*. 2011;82:667–680.
10. Stringham J, Hammond BR. The glare hypothesis of macular pigment function. *Optom Vis Sci*. 2007;84:859–864.
11. Stringham J, Hammond BR. Macular pigment and visual performance under glare conditions. *Optom Vis Sci*. 2008;85:82–88.
12. Stringham JM, Garcia PV, Smith PA, McLin LN, Foutch BK. Macular pigment and visual performance in glare: benefits for photostress recovery, disability glare, and visual discomfort. *Invest Ophthalmol Vis Sci*. 2011;52:7406–7415.
13. Yao Y, Qiu QH, Wu XW, Cai ZY, Xu S, Liang XQ. Lutein supplementation improves visual performance in Chinese drivers: 1-year randomized, double-blind, placebo-controlled study. *Nutrition*. 2013;29:958–964.
14. Renzi L, Hammond BR. The effect of macular pigment on heterochromatic luminance contrast. *Exp Eye Res*. 2010;91:896–900.
15. Thibos LN. Calculation of the influence of lateral chromatic aberration on image quality across the visual field. *J Opt Soc Am A*. 1987;4:1673–1680.
16. Luria SM. Vision with chromatic filters. *Am J Optom Arch Am Acad Optom*. 1972;49:818–829.
17. Wolffsohn JS, Cochrane AL, Khoo H, Yoshimitsu Y, Wu S. Contrast is enhanced by yellow lenses because of selective reduction of short-wavelength light. *Optom Vis Sci*. 2000;77:73–81.
18. Mollon JD, Regan BC. The spectral distribution of primate cones and of the macular pigment: matched to properties of the world? *J Opt Technol*. 1999;66:847–852.
19. Walls GL. *The Vertebrate Eye and Its Adaptive Radiation*. New York: Hafner; 1942:191–205.
20. Hammond BR, Fletcher L, Elliott J. Glare disability, photostress recovery, and chromatic contrast: relation to serum and retinal lutein and zeaxanthin. *Invest Ophthalmol Vis Sci*. 2013;54:476–481.
21. Wooten BR, Hammond BR Jr, Land RI, Snodderly DM. A practical method for measuring macular pigment optical density. *Invest Ophthalmol Vis Sci*. 1999;40:2481–2489.
22. Snodderly DM, Mares JA, Wooten BR, Oxton L, Gruber M, Ficek T. Macular pigment measurement by heterochromatic flicker photometry in older subjects: the carotenoids and age-related eye disease study. *Invest Ophthalmol Vis Sci*. 2004;45:531–538.
23. Hammond BR, Johnson BA, George ER. Oxidative photodegradation of ocular tissues: beneficial effects of filtering and exogenous antioxidants. *Exp Eye Res*. 2014;129:135–150.
24. Margrain TH, Thomson D. Sources of variability in the clinical photostress test. *Ophthalmic Physiol Opt*. 2002;22:61–67.
25. Hartmann D, Thürmann PA, Spitzer V, Schalch W, Manner B, Cohn W. Plasma kinetics of zeaxanthin and 3′-dehydro-lutein after multiple oral doses of synthetic zeaxanthin. *Am J Clin Nutr*. 2004;79:410–417.
26. Pinheiro JC, Bates DM. *Mixed-Effects Models in S and S-PLUS*. New York: Springer Verlag; 2000:146–174.
27. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analysis*. Hoboken, NJ: John Wiley and Sons; 2011:189–240.
28. Wooten BR, Hammond BR. Macular pigment: influences on visual acuity and visibility. *Prog Retin Eye Res*. 2002;21:225–240.
29. Hammond BR, Wooten BR, Engles M, Wong JC. The influence of filtering by the macular carotenoids on contrast sensitivity measured under simulated blue haze conditions. *Vision Res*. 2012;63:58–62.
30. Fletcher L, Engles M, Hammond BR. Visibility through atmospheric haze and its relation to macular pigment. *Optom Vis Sci*. 2014;91:1089–1096.
31. Johnson EJ, Maras JE, Rasmussen HM, Tucker KL. Intake of lutein and zeaxanthin differ with age, sex, and ethnicity. *J Am Diet Assoc*. 2010;110:1357–1362.