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Research article

Serum and retinal responses to three different doses of macular carotenoids over 12 weeks of supplementation

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ABSTRACT

The macular carotenoids lutein (L), zeaxanthin (Z), and mesozeaxanthin (MZ) have been shown to have neuroprotective and visual performance benefits once deposited in retinal tissues. The purpose of this 12-week trial was to determine biweekly the absorption kinetics, efficiency of retinal deposition, and effects on the spatial profile of macular pigment for three levels of L + Z + MZ supplement.

This study was a double-blind, placebo-controlled 12-week trial. Twenty-eight healthy subjects, aged 18–25 yrs participated. Subjects were randomly assigned to one of four daily supplementation groups: placebo (safflower oil; n = 5), 7.44 mg total macular carotenoid (n = 7), 13.13 mg total macular carotenoid (n = 8), and 27.03 (n = 8) mg total macular carotenoid. Ratios of the three carotenoids were virtually identical for the three levels of supplement (83% L, 10% Z, 7% MZ). At baseline and every two weeks thereafter over the 12-week study period, a fasting blood draw was conducted and, via heterochromatic flicker photometry, spatial profiles of macular pigment optical density (MPOD) were determined.

Compared to placebo, serum concentrations of both L and total Z, for each of the supplement levels, were found to increase significantly from baseline after two weeks of daily ingestion ($p < 0.001$). Likewise, MPOD increased significantly in all treatment groups ($p < 0.001$) compared to placebo. Serum responses (L, Z, and L + Z) were linearly related to dose ($p < 0.001$ for all), but not to retinal response. L: Z serum response ratios decreased exponentially with increases in dose ($p = 0.008$). The ratio of MPOD change: total serum response was found to be highest for the 13.13 mg level of supplement ($p = 0.021$), followed by 27.03- and 7.44-mg doses. The very center of the spatial profile of MPOD increased in a fashion commensurate with dose level.

Although L serum responses increased with dose, the slope of increase was shallower than for Z. Given the higher levels of L in the supplements, this is suggestive of a compressed response with relatively high doses of L. Although all three doses significantly augmented MPOD, the 13.13 mg/day L + Z supplement level was the most efficient in doing so. The data regarding efficiency may inform recommendations regarding macular carotenoid supplementation for age-related macular degeneration. Lastly (although not statistically significant), the shift toward a more pronounced central peak in the spatial profile of MPOD in all treatment groups suggests that central retinal deposition of Z and MZ was efficient and can be seen after a short period of supplementation, especially with higher (e.g. 27.03 mg) daily doses of macular carotenoids.

ISRCTN trial registration number: ISRCTN54990825.

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1. Introduction

Lutein (L) and zeaxanthin (Z) are diet-derived, yellow-orange colored carotenoids obtained primarily from leafy-green vegetables (Sommerburg et al., 1998). L and Z are not synthesized by the body, and therefore must be obtained via dietary means; those who have diets rich in leafy greens, or supplement with sufficient L and Z tend to maintain and accumulate higher blood and tissue concentrations (Ciulla et al., 2001; Bone et al., 2003). One of the conspicuous features of L and Z is their specific accumulation in the macular retina (Snodderly et al., 1984b), where they can reach extremely high

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concentrations (e.g. Hammond et al., 1997); it is not uncommon to see concentrations in the fovea that exceed 10,000 times that seen in the blood (Bone et al., 1993). Once deposited in the retina, some of the L is converted to a stereoisomeric form of zeaxanthin, called mesozeaxanthin (MZ; Neuringer et al., 2004). Although rare, MZ has been shown to exist in nature, and indeed in the human food chain – its presence has been recently verified in salmon, trout, and sardine skin, and also trout flesh (Nolan et al., 2014). Importantly, MZ has been shown to be readily deposited in the retina when taken in supplement form (Loughman et al., 2012). The accumulation of these three carotenoids in the macula yields a yellowish coloration, classically known to ophthalmologists as the "macula lutea" ("yellow spot"; first noted by Buzzi, 1782). Today, this collective pigmentation is commonly referred to as macular pigment (MP; Wald, 1945), with concentrations typically expressed in terms of optical density (MPOD).

Xanthophyll carotenoids such as L, Z, and MZ are especially potent antioxidants (Krinsky et al., 2003). Via a process called triplet excitation transfer (Ruban et al., 2002), L, Z, and MZ can regenerate to repeatedly "quench" the energy of singlet oxygen. This makes them capable of long-term accumulation in target tissues such as the retina, where they can provide protection against oxidative stress. Another critical function of the macular carotenoids involves their optical properties within the eye. As noted above, one of the primary tissue targets for these carotenoids is the retina, where they accumulate (as MP) in very high densities in the fovea (Snodderly et al., 1984b). Specifically, L, Z, and MZ are deposited in retinal layers anterior to the lipid-rich photoreceptor outer segments, which are vulnerable to oxidation by radiant energy (Wiegand et al., 1983). The central, pre-receptoral location of macular pigment is therefore advantageous in at least three ways: 1) It enables the yellow-orange MP to filter high-energy short-wavelength (blue) light (Snodderly et al., 1984a) before it can cause damage via lipid peroxidation of the photoreceptor outer segments, 2) Its central location in the fovea preferentially protects the cones serving high-performance central vision (whose densities in humans can reach 400,000/mm^2 and perhaps even higher (Curcio et al., 1990), and 3) The filtration of short-wave (blue) light can yield visual performance benefits, such as improvements in contrast sensitivity (Loughman et al., 2012; Kvansakul et al., 2006; Stringham et al., 2011; Yao et al., 2013; Sasamoto et al., 2011), parameters of visual performance in glare (Stringham et al., 2011; Hammond et al., 2013), chromatic contrast (Hammond et al., 2013) and outdoor vision through atmospheric haze (Fletcher et al., 2014). Importantly, the long-term protection conferred to the retina by the impressive antioxidant and filtering capability of MP translates to a significantly reduced risk of developing diseases that are brought on by cumulative tissue damage, including age-related macular degeneration (AMD; e.g. Seddon et al., 1994), the leading cause of blindness in the Western world (Klaver et al., 1998).

Given the many benefits of a diet rich in L and Z, and relatively high tissue densities of L, Z, and MZ, a pressing question going forward involves the response kinetics of people to different levels of carotenoid ingestion. The development of reliable dose/response curves for these carotenoids would enable us to better understand dietary need and its relationship to health and performance benefits. Additionally, the fact that carotenoids are often affected by competitive absorption with each other (Wang et al., 2010) suggests that the relationship between dietary intake of a mixture of carotenoids and absorption profile could be vastly different. Previous studies have determined that supplementation with the macular carotenoids generally yields significant increases in serum concentrations and MPOD in healthy subjects over study periods ranging from 8 weeks (Connolly et al., 2010) to 1 year (Nolan et al., 2011). The purpose of this study was to determine, with relatively fine resolution, relationships among dose, relative and temporal kinetics of serum absorption for L vs. the collective zeaxanthin isomers (Z + MZ), and subsequent MPOD response. To this end, we conducted a fasting blood draw and assessed spatial profiles of MPOD in subjects consuming three different levels of a macular carotenoid supplement vs. placebo, at baseline and every two weeks thereafter for 12 weeks.

2. Materials and methods

This study was reviewed and approved by the University of Georgia Institutional Review Board. Informed consent was obtained for each subject, and the study adhered to the tenets of the Declaration of Helsinki. Thirty-two University of Georgia students, aged 18–25 yrs, enrolled in the study. Twenty-eight completed the entire 12-week trial. Subjects were randomly assigned to one of four daily supplement groups: placebo (n = 5), 7.44 mg L + total Z (n = 7), 13.13 mg L + total Z (n = 8), or 27.03 L + total Z (n = 8). Pills were provided by Omniactive Health Technologies, Inc., and were brown-colored, soft gelatin capsules, with L and Z suspended in safflower oil. Independent analysis of 100 pills in each dose category indicated that the 7.44 mg group supplement contained 6.18 mg L/0.73 mg Z/0.53 mg MZ, the 13.13 mg group supplement contained 10.86 mg L/1.33 mg Z/0.94 mg MZ, and the 27.03 mg group supplement contained 22.33 mg L/2.70 mg Z/2 mg MZ. Placebos contained no L or Z, but only safflower oil. All reported values were within ±5% variability. Subjects were instructed to ingest one pill with a meal (preferably lunch or dinner) every day. Compliance was ensured with weekly phone calls and pill counts.

To ensure subjects met inclusion criteria for participation, biometric data (e.g. height, weight, body fat percentage), as well as health habits data (e.g. whether or not a smoker) were obtained at the screening/intake visit. Subjects were excluded from participation in the study if they were determined to have a BMI higher than 27, if they currently smoked, or currently took supplements containing any of the carotenoids involved in the study. Subjects were instructed to maintain their current diet; those that were planning on changing their diet (for whatever reason) were excluded from consideration for the trial. In consideration of MPOD testing, all subjects had uncorrected or contact lens-corrected visual acuity of 20/20 or better in the test (right) eye, and had no current or previous history of ocular pathology. After being familiarized with the study, subjects were instructed to visit the laboratory every 2 weeks, in order to participate in vision testing and phlebotomy. Phlebotomy was conducted after fasting for at least 10 h, and subjects were given some food (e.g. a bagel or a breakfast bar) and water immediately after the blood draw. Macular pigment measurement occurred shortly thereafter.

2.1. Measurement of macular pigment optical density (MPOD)

The spatial profile of MPOD was assessed with a non-invasive, perceptual task called customized heterochromatic flicker photometry (cHFP; Stringham et al., 2008). A densitometer (Macular Metrics Corp., Rehoboth, MA) described by Wooten et al. (1999) was used for this purpose. The densitometer, detailed measurement procedures, and the principle of HFP have been fully described in earlier publications (Wooten et al., 2005). Briefly, subjects are presented with two superimposed lights that are temporally alternated in square-wave counterphase. This gives the subject an impression of a flickering disc of light. The peak (550 nm) of the spectral composition of one of the lights is chosen to bypass the absorption of MP, and the other (460 nm) is strongly absorbed by MP. The subject's task is to adjust the relative radiance of the two

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