Study Title: Macular Pigment and Visual Performance in Glaucoma Patients

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Purpose of the Study

The purpose of the present study is to determine cross-sectional relationships between macular pigment optical density (MPOD) and visual performance in glaucoma. Also, to determine the effect of lutein, zeaxanthin, and mesozeaxanthin supplementation on MPOD and visual performance in glaucoma patients.

Background & Significance

Neurodegeneration of the optic nerve and associated ganglion cell death in glaucoma leads to several well-characterized losses in visual function, most notably progressive peripheral visual field loss (see, e.g., Weinreb et al. 2014). Several recent studies (Amanullah et al. 2017; Siah et al. 2017; Wang et al. 2017; Bambo et al. 2016) have characterized significant visual function deficits in glaucoma patients that may be more sensitive indicators of disease than classical visual field loss, including compromised CS, increased disability glare (DG) and protracted dark adaptation (DA).

Given the available evidence, it appears that visual function, if assessed carefully, is a reliable indicator of ocular health and / or disease state. It follows that an improvement in visual function would be indicative of an improvement in ocular health. Although improvement of visual function is not typically seen in ocular disease, there is recent evidence to suggest that visual performance and associated progression of ocular disease may actually be modifiable via nutritional strategies and dietary modification (in age-related macular degeneration [AMD]; Nolan et al. 2017). Because much of the structural damage in glaucoma is associated with increased ocular inflammation (see, e.g., Vohra et al. 2013), local anti-inflammatory action may extend or improve good visual performance, and perhaps even hold the progression of the disease at bay. Given their exceptional anti-inflammatory activity and potential for rich deposition in the retina, the macular carotenoids lutein (L), zeaxanthin (Z), and mesozeaxanthin (MZ) may hold promise for this strategy. Indeed, a recent cross-sectional study (Siah et al. 2017) of the relationship between macular carotenoid level and visual performance in glaucoma patients found that those patients with low levels were significantly more likely to experience problems with glare – and were also more likely to have greater ganglion cell loss.

L and 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 concentrations – values as high as 1.50 log optical density near the foveal center are not uncommon (e.g., Hammond et al. 1997); it is also 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-orange 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, in the absence of excessive oxidative or inflammatory stress (e.g. smoking, or systemic disease such as diabetes), they are resistant to turnover, and can provide continuous protection against oxidation and inflammation.

Another critical function of the macular carotenoids involves their optical properties within the eye. Visual discomfort in glare (Stringham et al. 2004; Wenzel et al. 2006; Stringham & Snodderly, 2013), disability glare (Stringham & Hammond, 2007; 2008; Stringham et al., 2011; Hammond et al., 2013; Stringham et al. 2016), and photostress recovery time (Stringham & Hammond, 2007; 2008; Stringham et al., 2011; Hammond et al., 2013; Stringham et al. 2016) are all significantly improved with higher MPOD status. CS has also been found in several laboratories (for both normal and clinical populations) to be related to / enhanced by augmentation of MPOD (Kvansakul et al. 2006; Stringham et al. 2011; Sasamoto et al. 2011; Loughman et al. 2012; Yao et al. 2013; Nolan et al. 2017; Stringham et al. 2017). Dark adaptation speed, absolute scotopic thresholds, and mesopic contrast sensitivity have also been found to be impacted positively by MPOD (Hammond et al. 1998; Nolan et al. 2011; Patryas et al. 2013; Stringham et al. 2015).

A high concentration of macular carotenoids (i.e. high MPOD) is therefore advantageous in at least three ways: 1) Protection from oxidation and inflammation, 2) Filtration of potentially actinic high-energy short-wavelength light, and 3) Improvement of visual performance (via pre-receptoral screening of short-wave light and neurophysiological enhancement). 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).

At baseline, our proposed study has the potential to determine cross-sectional relationships between MPOD, visual performance, and disease severity in glaucoma. Given the recent data from Siah et al. (2017), significant relationships are plausible – and if we determine these kinds of relationships, standard of care for glaucoma patients could be changed to include improved patient education regarding nutrition. Additionally, visual function testing (to include CS, DA, and DG testing) may be instituted for glaucoma suspects and established glaucoma patients. If we are able to show an acute effect of improvement in visual performance, disease parameters, or even simply increases in MPOD in glaucoma patients upon supplementation with macular carotenoids, it could lead to larger trials that may yield extremely important data with regard to management of glaucoma. Given the predicted exponential increase in worldwide glaucoma prevalence (76 million in 2020 to 111.8 million in 2040; Tham et al. [2014]), strategies that may delay the onset of visual disturbance or prolong good visual function would be hugely significant.

Study Design & Procedures

The proposed study design is a randomized, double-masked, placebo-controlled one-year intervention in glaucoma patients with moderate to advanced disease. The total period of performance for this study (to allow for recruitment, experimental visits, analysis, and final report) would be 24 months.

General evaluation:

The following is a list of assessments to be conducted at each patient visit.

1. Measurement of MPOD. Equipment: The Heidelberg Spectralis with MPOD module will be used to obtain an MPOD spatial density profile; no dilation required. Patient time: 15 minutes.

2. CS testing. Equipment: M&S Technologies Smart System. Sine-wave gratings with frequencies of 1.5, 3, 6, 12, and 18 cycles / degree will be used to generate a contrast sensitivity function. Patient time: 15 minutes.
3. DG testing. Equipment: M&S Technologies Smart System with integrated glare testing system. Glare testing will be similar to the CS test, but only 6 cycles / degree will be assessed. Patient time: 10 minutes.
4. DA assessment. Equipment: MacuLogix Adapt Dx. Patients' speed of rod-mediated dark adaptation will be measured at 12^0 retinal eccentricity. This technology allows for rapid (< 10 minutes) assessment. Patient time: 10 minutes.
5. Visual Function Questionnaire (NEI VFQ-25). Patient time: 10 minutes.
6. Point-spread function; optical quality of the eye. Equipment: HD Analyzer. Patient time: 1 minute.
7. Visual field assessment. Equipment: SAP 24-2; SAP 10-2. Patient time (total): 15 minutes.
8. Review of medical history;

The results of the above assessments will be convolved with patients' clinical exam data to form the study's comprehensive database.

Selection of Subjects

All participants must have signed the consent form. A power analysis based on previous retinal response and corresponding visual performance data from AMD patients revealed that 30 patients each in both placebo and treatment groups would be required to detect effects, if present. Assuming some attrition, we plan to recruit a total of 60 patients, half of which would be randomly assigned to receive a macular carotenoid supplement, containing 10 mg L, 2 mg Z, and 10 mg MZ (to be consumed once daily with a meal). In terms of macular carotenoid content, 22 mg total is roughly equivalent to 2 large bowls of spinach. The other half would receive an identical pill, containing only sunflower oil (as with the active supplement, patients would be instructed to take one pill daily, with a meal). Baseline measures (see below) for patients consenting to enroll in the study would be determined shortly after enrollment, prior to the onset of supplementation.

Inclusion criteria:

1. Subjects must be between the ages of 18 and 75 years old;
2. Both males and females will be included.
3. Be able and willing to provide signed informed consent and follow study instructions

Exclusion criteria:

1. Subjects will be excluded if they present with any systemic or ocular conditions that in the opinion of the Principal Investigator may prevent them from completing the tests.

Scheduled Visits

Patients will be assessed at baseline, 3 months and 6 months (final visit).

Unscheduled visits

An unscheduled visit may be any visit to the Investigator other than the specific visits requested in the protocol as possibly required for the subject's ophthalmic condition. The Investigator will perform all procedures necessary to evaluate the study participant at these visits and record any adverse events in the source document.

Subject Recruitment and Compensation

Subject recruitment will be done at the Duke University Eye Center clinics. The study will also utilize D.E.D.U.C.E (Duke Enterprise Data Unified Content Explorer) an on-line research tool providing Duke investigators with access to clinical information collected as a by-product of patient care. The study will apply for a waiver of consent to identify potential subjects for the study. The PI will introduce potential eligible subjects to the study during their visit to the eye clinics, and if they are determined eligible a delegated key personnel will obtain consent from the subject. If the subject is not available for immediate consenting the PI will obtain the patient's permission to be contacted by telephone at a later date. A telephone script will then be used for the conversation. In addition, once the subject has the consent signed we will request access to their medical records through a medical records release form to obtain the participant's general medical history, previous use of systemic medications, previous use of ophthalmological medications, previous ocular examinations, previous ocular procedures, and results of other medical tests.

There will be no additional costs as a result of being in this study. Both macular carotenoid supplement and placebo will be provided by the manufacturer (MacuHealth LP, Birmingham, MI). Patients should be able to complete each visit within 90 minutes, and will be compensated a total of $100 for study completion. This compensation is for expenses related to subject participation (parking, gas, and time) and will be provided by funding from the Department of Ophthalmology.

Consent Process

We will use protected health information to screen for possible/eligible subjects. No PHI will leave Duke. A member of the eye care team will approach the potential participant to introduce the study. Knowledgeable key personnel will explain the study to the potential subjects and the Principal Investigator will be available during the consenting process to answer any questions the potential subjects may have about the study. The consenting process will occur in a private room and no study related activities will begin until the subject's consent is obtained. Only delegated key personnel can consent potential subjects.

A waiver of consent and HIPAA authorization will be filed with the Duke IRB to allow us to review PHI and health information to screen potential participants.

A telephone script will be submitted to schedule potential subjects in Maestro Care for study screening prior to full consent, and in case subjects are interested in participating and they cannot discuss the study in person when they are initially seen, after the PI introduces the study and key personnel to them.

Subject's Capacity to Give Legally Effective Consent

Adult subjects able and willing to participate will sign the consent forms. If the vision of the potential subject is severely impaired enough to affect reading the consent document, the person obtaining consent, a study team member or a witness will read aloud and a witness will be required to sign the consent.

Risk/Benefit Assessment

Risks

Risks from participating in the study are low. The primary risks for all participants are some discomforts, which are similar to those encountered in any complete eye examination. Participants will undergo non-invasive procedures used for diagnostic purposes. All medical instruments are FDA approved. The software for OCT Angiography and Macular pigment optical density analysis are currently undergoing FDA review and are not currently approved.

Lutein, zeaxanthin, mesozeaxanthin are over-the-counter nutritional supplements from natural sources. Lutein, zeaxanthin, mesozeaxanthin are likely safe when taken by mouth appropriately. There are no known risks or drug interactions associated with macular carotenoids as part of the diet. They are likely safe when used in the amounts found in food for pregnancy and breast-feeding

There is, however, the potential risk of loss of confidentiality. Every effort will be made to keep the information confidential; however, this cannot be guaranteed. Some of the questions that will be asked as part of this study may make the patients feel uncomfortable. Patient may stop their participation in this study at any time.

Unknown/unforeseeable risks

In addition to the risks and discomforts listed here, there may be other risks that are currently not known. Subjects will be informed if any other potential risk becomes known through the duration of the study. Also, the risks and discomforts may occur more often or be more severe than have been seen before and written in this form.

Benefits:

Although our proposed study is somewhat exploratory in nature, the ideas are based on strong science and are fundamentally sound. There are many areas in which positive results may emerge; if this is determined to be the case, patient care and outcomes could benefit greatly.

Costs to the Subject

All procedures described here, including both visits and drugs, will be free of charge to patients. There is no additional cost for the subject if they participate in the study. Study related activities/procedures will be paid by the study.

Data Analysis & Statistical Considerations

Baseline data will be analyzed with Pearson product-moment correlations, multiple regression, and (if clinically relevant group demarcation can be established, ANOVA). Intervention data will be analyzed primarily by repeated-measures ANOVA.

With our location in the Duke Eye Center, we foresee no issues in terms of patient recruitment or convenience for patient visits. Additionally, we have access to all of the experimental equipment (listed above) and other resources required to conduct the study.

All statistical analyses will be performed by Dr. Medeiros and associates using commercially available statistical and mathematics software Stata (version 15; StataCorp LP, College Station, TX, USA), MATLAB (Mathworks, Inc.), and MPLUS (Muthen & Muthen). An alpha level will be generally set at 0.05, unless there is a need to correct for multiple comparison testing which will then be performed by procedures such as false discovery rate.

Data & Safety Monitoring

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), and all reportable adverse events (AEs) will be submitted per the DUHS IRB policies.

All examinations will be performed by appropriately trained personnel. If any incidental findings are discovered during testing, the patient will be verbally informed and referred to a physician of the appropriate specialty, and eligibility to the study will be reassessed.

Privacy, Data Storage & Confidentiality

Subjects will be assigned a unique code number for this study. The computers to be used are encrypted and protected by layers of passwords. All electronically data will be stored on a secure, backup server under Dr. Medeiros name on the V:drive named "Performance Lab". Copy of source documents, study related paper files will be in stored in locked file cabinets at the Visual Performance Laboratory. The laboratory is locked when not in use and access is by key entry.

Published data will not be traceable to any specific individual. The study results will be retained for at least six years or after the study is completed. At that time, either the research information will be destroyed or identifying information will be removed. Any research information in the medical record will be kept indefinitely.

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