Augmented Macular Pigment Supplement and Pericentral Visual Function: A Randomized Controlled Trial

NCT #: Not yet assigned

Date: 17 December 2020

Lumega-Z PLUS Randomized Controlled Trial
Research Protocol

Section 1: Purpose:

The purpose of this study is to prospectively analyze changes in macular pigment ocular density and dermal carotenoid levels as they relate to perimetry in patients prescribed Lumega-Z, a medical food in combination with dorzolamide.

Section 2: Background and Significance:

Macular pigments (MP) are a group of fat-soluble carotenoid polyenes that concentrate in the human macula and give it its characteristic yellow color.[1] They are well studied compounds that optimize visual function and protect the macula from high energy visible light, inflammation, and oxidative damage.[2]

Large historic randomized controlled trials have demonstrated that oral supplementation of lutein (L) and zeaxanthin (Z) are associated with macular protection and improvements in contrast sensitivity.[3–5] Recent investigations have demonstrated that the addition of the third macular pigment, meso-zeaxanthin (MZ) increases the bioavailability of both L and Z, and leads to higher MPOD than L and Z without MZ.[6,7]

Lumega-Z (LM) is a commercially available medical food that includes L, Z, and MZ, among other vitamins and minerals. Although this and other similar formulations have been shown to reduce risk of ARMD progression, the mechanisms of macular protection portend a benefit in other neurodegenerative processes as well. Indeed, high fidelity investigation of the effects of macular pigment supplements on memory has demonstrated measurable cognitive improvement.[8]

Glaucomatous neuron loss is a complex process with multiple contributing factors, and is not yet fully understood.[9] Events that likely promote RGC apoptosis[10] include disruption of neurotrophic factor axonal transport,[11] glutamate mediated excitotoxicity,[12] oxidative damage,[13] and autoimmune processes.[14,15] The physical and chemical properties of the macular pigments suggest they act to attenuate the effects exerted by at least some of these mechanisms. The long polyene backbone of these carotenoids, for example, allows them to efficiently and sustainably dissipate energy from reactive oxygen species.[2,16]

Two of the macular pigments, L and Z, are commonly found in the human diet, and blood levels respond directly to changes in dietary or supplemental intake.[17–19] Pressure mediated reflection spectroscopy has been shown to reliably measure dermal carotenoid levels, which correlate with plasma levels. This method can be used to non-invasively monitor carotenoid levels in glaucoma patients.[20–22]

Dorzolamide is a topical carbonic anhydrase inhibitor (CAI) commonly used to treat glaucoma by inhibiting the production of aqueous humor to reduce intraocular pressure (IOP).[23] Incidentally, the targeted inhibition of carbonic anhydrase in the ocular circulation may have other effects on retinal and visual physiology, including increased retinal blood flow, improved perimetric light sensitivity, contrast sensitivity, and perimetric short wavelength sensitivity.[24–26] The vasodilation caused by topical CAI's suggest they may enhance delivery of the macular pigments to the retina, and so may have a synergistic benefit when paired with LM or other macular pigment-containing oral supplement.

Briefly, LM has demonstrated favorable effects on two objective measures of visual function: macular pigment optical density and contrast sensitivity, and an addition of a topical CAI may enhance delivery of the pigments to the macula. Anecdotal experience of the investigators suggests there may be an additional benefit in a subset of nutritionally vulnerable glaucoma patients. We therefore hypothesize that this subset of patients who experience improvement in visual field function after LM supplementation may be nutritionally or physiologically deficient of the macular pigments. This study will therefore prospectively examine the effects of LM supplementation in combination with a CAI on visual field function, MPOD, and CS in the context of a spectrophotometric analysis of dermal carotenoid levels in glaucoma patients compared to untreated controls.

Section 3: Location, Facility and Equipment to Be Used:

LOCATION
311 Camden St, Ste 306, San Antonio, TX 78215

FACILITY
The medical office of Dr. William Sponsel

EQUIPMENT
1. Slit Lamp (Haag-Streit, Bern, Germany)

2. Veggie Meter (Longevity Link, Salt Lake City, Utah, USA)

3. MapcatSF (Guardion Health Sciences, San Diego, California, USA)

4. Vector Vision (Vector Vision Ocular Health, Greenville, Ohio, USA)

5. Humphrey Matrix Model 715 FDT Perimeter (Carl Zeiss Meditech, Jena, Germany)

6. Humphrey Field Analyzer Model 740i (Carl Zeiss Meditech, Jena, Germany)

Section 4: Subjects and Informed Consent:

All subjects will be recruited from the medical practice of Dr. William E Sponsel. No advertising shall be employed. Eligible patients will be verbally informed of the study. If they express interest a detailed description of the study will be presented, including the written informed consent (attached) If they elect to participate, written informed consent will be obtained prior to any data collection. Consent documents will be available in both English and Spanish. Translation into Spanish will be performed by investigators fluent in the language. All study records will be anonymized and maintained on an encrypted and password protected computer under the control of the PI. Only aggregated mean results will be published in the scientific press.

PARTICIPANTS

This prospective double-masked, randomized, placebo-controlled study will consist of 20 subjects age >18 with the diagnosis of Glaucoma (ICD-10: H40. *). Only patients under the care of the investigating surgeon (WES) will be considered. Subjects will be identified at the time they are deemed to be candidates for Lumega-Z supplementation (adequate IOP control with RNFL or visual field glaucomatous progression). After verifying no history of AREDS formula oral supplement use, patients will be approached by the co-investigator (GTS) in the principal investigator's ophthalmology clinic and asked if they are interested in participating in this study. An Excel (Microsoft, Redmond, WA)

spreadsheet with deidentified data will be kept in clinic on-site on a password-protected computer in order to store and analyze data. GTS is a full-time employee at the investigating practice and has HIPPAA-compliant access to patients and patient records independent of this study.

INFORMED CONSENT

Before study participation, participants will have a consultation with a representative investigator at the clinical practice of WES (311 Camden St Ste. 306, San Antonio, TX, 78215) in which they will be informed of the risks, benefits, and alternatives of participating in the study. They will be assured that their decision to participate or not will have no bearing on their personal or medical treatment by the investigators. Subjects will be given a printed copy of their signed informed consent. Completed informed consent forms will be scanned and stored on their patient profile of a password protected and encrypted electronic medical record. After they are scanned onto the electronic medical record, the hard copies will be shredded. Participants will be given a copy of the signed informed consent forms.

Inclusion Criteria

-Age ≥ 18 years

-Glaucoma diagnosis (H40. *) with abnormal visual field as measured by 30-2 Humphrey Perimetry (mean deviation < -2.00)

-Adequate IOP control (IOP > 7 mmHg and < 22 mmHg) by medical or surgical means measured by Goldman Applanation Tonometry for at least 3 months

-Visual field progression - decrease (more negative) in MD by 1.00 dB or more when compared to prior HVF)

-Refractive error ≤ 10 diopters and astigmatism ≤ 3 diopters

Exclusion Criteria

-BCVA worse than 20/200

-Pt Is unable to tolerate MPOD, CS, dermal carotenoid measurement-taking procedures

-Patient reports taking LM supplement ≤ 2 times per week or cannot tolerate oral supplement intake

-Patient loses IOP control and requires surgical intervention

-Patient already taking AREDS formula oral supplement

-Patient taking medication or dietary supplements that may interact with LM ingredients

-History of photosensitive epilepsy

-History of penetrating ocular trauma or vitrectomy

-History of ocular or orbital radiation therapy or is currently receiving chemotherapy

-Women who are nursing, pregnant, or are planning pregnancy

-Has a known adverse reaction and/or sensitivity to the study supplement or its ingredients:

Including: N-acetyl-cysteine, acetyl-L-carnitine, L-taurine, quercetin, Co-enzyme Q-10, lutein, meso zeaxanthin, zeaxanthin, astazanthin, lycopene, alpha-lipoic acid.

-Currently enrolled in an investigational drug study or has used an investigational drug within 30 days prior to recruitment.

-Is planning on having ocular surgery at any time throughout the study duration, or had ocular surgery < 3 months before enrollment

-Native lens opacity ≥ grade 3 on ARLNS standard photograph

-Blue light filter intraocular lens

-Sulfa Allergy

Section 5: Subject Compensation:

There will be no patient compensation for participation in this study. Patients will not be reimbursed for travel expenses or other expenses regarding this study. All study procedures will be covered and the patients will incur no additional expenses when participating in this study.

Section 6: Duration:

Patient recruitment, data collection, data analysis, and abstract/manuscript writing will take 6-12 months.

Section 7: Research Design (Description of the Experiment, Data Collection and Analysis):

1. **Study Design**

This is a prospective double-masked, randomized controlled study which compares pre-Lumega-Z supplementation MPOD, CS, dermal carotenoid levels, and visual field status to post-supplement measurements of the same. Participants will be randomized to twelve weeks of LM + dorzolamide or twelve weeks of placebo. All packaging of LM and dorzolamide and their placebos will be identical and distributed by a third party. Both subjects and the investigators examining patients will be masked to placebo and experimental groups.

2. Supplement and CAI Dosing and Distribution

LumegaZ is a commercially available medical food (see ingredient table) which is consumed daily in a 1.5 Tbsp (0.75 FL OZ) dose. Subjects will be offered a 3 month supply (or placebo) for the duration of the study. Dosing instructions are included on the packaging.

The CAI which will be used in this study is Dorzolamide 2% ophthalmic solution used as follows: one drop in the affected (or both) eye three times per day. Dosing instructions are included on the packaging.

LumegaZ and CAI (or placebo) will be delivered directly to patients' homes in a single shipment in packaging identical to the standard LM supplement. Lot number will be recorded and used to determine whether subjects were in the placebo or supplement group after data gathering is complete.

Ingredient	Amount		Ingredient	Amount
Vitamin C	500mg		Copper	2 mg
Vitamin D3	2000 IU		Manganese	2 mg
Vitamin E	200 IU		Chromium	120 mcg
Thiamin	1.5mg		Molybdenum	75 mcg
Riboflavin	1.7mg		N-acetyl-cysteine	500 mg
Vitamin B3	20 mg		Acetyl-L-Carnitine	500 mg
Vitamin B6	10 mg		L-Taurine	500 mg
Folate	800mcg		Quercetin	100 mg
Vitamin B12	1000 mcg		CoQ10	50 mg
Biotin	100 mcg		Lutein	15 mg
Panothenoic Acid	10 mg		Meso-zeaxanthin	3 mg
Calcium	250 mg		Astaxanthin	1000 mcg
Magnesium	100 mg		Lycopene	500 mcg
Zinc	25 mg		Alpha-lipoic acid	200mg
Selenium	70 mcg			

3. Randomization

After recruitment, subjects will be registered as a study participant and randomized by computer generated randomization table generated prior to subject recruitment to be in the placebo or intervention group by a Guardion Health Sciences representative without access to patient data. The Guardion representative will receive the subject name and delivery address only, which is the same information they receive for every patient prescribed this medical food.

The clinically active investigators and subjects will be masked to group assignment for the duration of the study. The placebo will be distributed directly to participants'' homes in packaging identical to the standard LM product in a single shipment.

Dermal carotenoid measurement will be randomized by coinflip to the right or left index finger of each subject at the initial visit. The same finger will be used at every follow-up visit.

MPOD is measured in one eye only, as there is very high correlation in values measured between eyes.[27] At the initial visit, the measured eye will be randomized by coin flip. The same eye will be measured at every follow up visit.

4. Data Collection for dermal carotenoids, MPOD, and CS

All participants will have dermal carotenoid levels, MPOD, and CS measured at every visit up to 3 months after starting LM. The baseline measurements will be taken on the day of enrollment, then follow-up measurements will be taken 1 month, 2 months, and 3 months after initiation of topical dorzolamide + LM oral supplementation.

a. Dermal Carotenoid Levels with Veggie Meter®

After finger randomization, the Veggie Meter® will be light- and dark- calibrated before every measurement. Smoking status, age, height, weight, handedness, and finger used will be documented at the time of data acquisition. Participants will be seated and insert the randomized index finger into the device, placed on a table at the level of the patients' heart. After a short wait of 3-10 seconds to allow for finger-tip compression by the device, optical data acquisition will begin (no blood sample is collected). After the ~5 seconds required to acquire data, the finger will be removed for ≥ 10 seconds to allow for recirculation of the tested finger. The measurement will be repeated 2 more times (for a total of 3 measurements per visit) and a carotenoid score will be reported and recorded as the average of the 3 values.

b. Macular Pigment Optical Density with Heterochromatic Flicker Photometry

This data will be acquired as follows: After eye randomization the patient will be fitted into the device. They will be instructed to look at the center of a flashing circle and adjust the device to correct for their refractive error. A human operator will follow an independently developed algorithm (attached) to determine MPOD ± standard deviation, which will be calculated by the Mapcat device and recorded at each visit.

c. Contrast Sensitivity with VectorVision

Participants will be asked to identify the location of a sine-wave gradient in a series of images by selecting the circle with the gradient as top, bottom, or neither. This will be repeated for all 4 different spatial frequencies and plotted on a contrast sensitivity curve.

5. Perimetry

All participants will have a baseline Humphrey Visual Field 10-2 taken no more than 1 month before starting LM supplementation. Follow-up HVF 10-2 testing will also be completed at 3 months after LM initiation.

6. Power Analysis

The primary outcome measure in this study is dermal carotenoid levels, so power analysis with mean baseline score reported in the population is 335 ± 13.7, and conservative expected increase in carotenoid score to 360 with an alpha of 0.05 and a beta of 0.90 given a calculated n of 12 subjects. We will therefore recruit 20 subjects to participate in this study – 10 intervention and 10 controls.

7. Data Analysis

Pre-supplement dermal carotenoid scores, HVF 10-2 MD and pericentral sensitivity, MPOD, and CS parameters will be compared within subjects at the 1-month (except perimetry), 2-month (except perimetry), and 3-month time points using a two-way Repeated-measures ANOVA with post-hoc t-testing for evaluation of significant differences.

All investigators will contribute to data analysis.

Section 8: Risk Analysis:

LM is a medical food with well-studied ingredients established to be safe, and are effective at preventing progression of mild-moderate age-related macular degeneration. A 10-year follow-up on the AREDS study cohort found zero MP-related adverse events in 4757 participants.[28]

Dorzolamide is a very common topical antiglaucoma medication. It is reasonably well tolerated, but adverse reactions may occur. These include ocular allergy, burning, stinging, and bitter taste. Burning and stinging may occur in as many as 40% of patients but this does not typically warrant discontinuation of the drug.[29] Preservative free formulations of dorzolamide can be used in cases of ocular allergy, and patients who cannot otherwise tolerate the stinging/burning will be excluded from the study.

MPOD tests involve looking at a flickering light. It is conceivable that in a predisposed individual, focusing on such a stimulus may trigger a seizure.[30] There are no reports in the literature of a Mapcat device triggering an epileptic seizure. As an added precaution, patients who are recruited for the study will be screened for a history of photosensitive seizures.

Dermal carotenoid measurement involves the application of moderate pressure on the index finger. This may cause pain in vulnerable patients, for example those with a history of arthritis or gout affecting the distal interphalangeal joint of the second digit. A physical exam by an investigating physician will identify patients who may be vulnerable to such pain and they will be informed that they can be removed from the study if they cannot tolerate the finger pressure.

Contrast sensitivity and involves identifying which of a set of circles has stripes. There are no known risks associated with conducting this test.

It is feasible that patients in the placebo group will be subject to increased risk of glaucomatous progression because they will not start on the topical carbonic anhydrase inhibitor, which has been shown to reduce IOP. Only patients with adequately controlled IOP will be included in the study, so topical CAI would otherwise not be indicated for their treatment regimen. Therefore, placebo patients will still be receiving the standard of care for their glaucoma. Any patients with unexpected findings (such as elevated IOP) at any of the study visits requiring additional intervention will receive it.

COVID-19 Statement

The investigators acknowledge the current COVID-19 pandemic and associated risks. While the majority of COVID-19 infections are asymptomatic or mild severity, there is a risk of severe respiratory illness which can result in hospitalization, admission to the intensive care unit, intubation, chronic respiratory, cardiac, or neurologic sequalae, and death (risk varies widely and increases with age, although a global estimate is ~3%).[31]

Robust COVID-19 risk mitigation protocols are already in place at the investigating practice, which include the use of symptom and temperature screening, social distancing, intensive room and

device cleaning with germicidal substances, thorough personal hygiene, use of personal protective equipment (PPE), and contact tracing and testing protocols to monitor exposed individuals. PPE includes N95 or equivalent facemasks, isolation gowns, gloves, eye protection, and plexiglass slit lamp face shields. Patients are also required to wear face masks at all times while in the clinic and are required to practice hand hygiene upon arrival. No patients with known or suspected COVID-19 infection are permitted in the clinic. These protocols are informed by, and exceed the requirements set forth by the US Centers for Disease Control.[32]

Section 9: Confidentiality:

All records shall be anonymized and maintained on a password-protected encrypted computer under the control of the PI. Only aggregated, mean results will be published in the scientific press.

Section 10: Literature Cited:

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