Macular Pigment: its importance for use in clinical practice

Professor Stephen Beatty
Director

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- MacularMetrics
- sightrisk
- Neutricia
- Novartis
- Zeiss
- ECR Vault
Introduction

• Background

• Research-based evidence

• Summary
BACKGROUND
The Macula
Nutrition and the Eye: Macular Pigment
Carotenoid Distribution at the Macula

Image: The Macular Pigment. II. Spatial Distribution in Primate Retinas. 
*Snodderly et al. 1984 IOVS*

Image: Stereochemistry of the Human Macular Carotenoids
*Bone et al. 1993 IOVS*
Chemical Structure of Macular Carotenoids

- **Zeaxanthin**
- **Meso-zeaxanthin**
- **Lutein**
Sources of Macular Carotenoids
How many Macular Carotenoids do we actually eat?
Sources of Macular Carotenoids

A field turns from orange to green as harvesters pick marigold flowers in Mexico
Dietary Supplements (EUR)
Functions of Macular Pigment

Why Macular Pigment is important
1. Visual Performance and Protection in AMD eyes
2. Visual Performance in non-diseased eyes
Age-related Macular Degeneration
Electromagnetic Irradiation & Visible Light

- Gamma Rays
- X-rays
- Ultraviolet
- Infrared
- Radio Waves

- Radar
- TV
- FM
- AM

Visible Light:
- 400 nm
- 500 nm
- 600 nm
- 700 nm
Pathogenesis of AMD: Oxidative Stress

Free Radical Production caused by Oxygen Metabolism
Pathogenesis of AMD

Free Radical Production caused by Cumulative Blue Light Damage

Blue light damage and the retina
The “Protective” Hypothesis
The “Vision” Hypothesis

Short-wavelength (blue) light filtration by macular pigment:
1. Promotes visual comfort by reducing glare and dazzle
2. Enhances detail by the absorption of ‘blue haze’
3. The enhancement of contrast
Conversion of Incident Light into a Visual Stimulus

![Diagram showing spatial density and visual eccentricity](image)

- **Spatial Density (cells/mm²)**
  - Temporal
  - Nasal

- **Visual Eccentricity (deg)**
  - 60
  - 40
  - 20
  - 0
  - 20
  - 40
  - 60
  - 80

- **Retinal Eccentricity (mm)**
  - 25

- **Cones**
- **Rods**

**Macular Pigment**
Measuring Vision

- Visual acuity
- Contrast sensitivity
- Glare
Visual Acuity

1  20/200
2  20/100
3  20/70
4  20/50
5  20/40
6  20/30
7  20/25
8  20/20
Contrast Sensitivity

Fourier Decomposition of a 2D image (into “high” & “low” spatial frequencies)

(a) Original  (b) High Frequencies  (c) Low Frequencies
Light Scatter

Why is the Sky Blue?

Sunlight made of all colors

The Scattering of Blue Light by Gas Molecules in the Atmosphere

DURING THE DAY

Blue light scattered towards us from all directions.
Light Scatter and Glare

Glare Hypothesis of Macular Pigment:

- Macular Pigment reduces glare disability and discomfort and speeds photostress by absorbing intraocular scatter.
Glare

- Glare disability - daytime
Glare

- Glare disability – night time
Glare

- Glare discomfort
RESEARCH BASED EVIDENCE
AREDS 1: Proof of Concept

Age-Related Eye Disease Study 1
Influence of high-dose micronutrients on age-related eye diseases

Participants
• 3,640 patients aged 55 - 80 years (AMD)
• 1,117 controls

Study Design
• Multi-centred, randomised, double-blind, placebo-controlled clinical trial
• Vitamin C 500mg, Vitamin E 400 IU, beta-carotene 15mg, zinc 80mg, copper 2mg (no macular carotenoids)
• Follow-up at least 5 years

Funding
Funded by the National Eye Institute (NEI)
Age-Related Eye Disease Study (AREDS) Treatment Assignment

Randomized Participants
N=4757

- Placebo
  N=1,483

- Antioxidant
  N=1,482

- Zinc
  N=904

- Antioxidant & Zinc
  N=888
Rates to Advanced AMD

AMD Categories 3 and 4 by Treatment Group

- Placebo
- Antioxidants
- Zinc
- Antioxidants + Zinc

Estimated Probability:
0% 10% 20% 30% 40%

Years: 0 1 2 3 4 5 6 7

- 20% Risk Reduction
  P vs. A+Z – p<0.01
  P vs. Z – p<0.01

- 28% Risk Reduction
AREDS 1: Criticism

In theory, ideal supplementation should not have included beta-carotene, and should include L and Z
Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration: The Age-Related Eye Disease Study 2 (AREDS2) Randomized Clinical Trial

The Age-Related Eye Disease Study 2 (AREDS2) Research Group

A ge-related macular degeneration (AMD), the leading cause of blindness in the developed world, accounts for more than 50% of all blindness in the United States. In 2004, it was estimated that 5 million individuals had intermediate AMD, defined as bilateral drusen, and approximately 2 million had advanced AMD, either neovascular AMD or geographic atrophy. Although intracocular drugs that inhibit vascular endothelial growth factor are currently available for treatment of neovascular AMD, no effective therapies are proven for atrophic AMD. Without more effective ways of slowing progression, the number of persons with advanced AMD is expected to double over the next 20 years, resulting in increasing socioeconomic burden.

The Age-Related Eye Disease Study (AREDS) demonstrated that daily oral supplementation with antioxidants vitamin C and E, beta carotene, and zinc has been shown to reduce the risk of progression to advanced age-related macular degeneration (AMD). Observational data suggests that increased dietary intake of lutein + zeaxanthin (carotenoids, omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid (EPA)), or both may further reduce this risk.

OBJECTIVES To determine whether adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating beta carotene, lowering zinc doses, or both in the AREDS formulation.

Design, Setting, and Participants The Age-Related Eye Disease Study 2 (AREDS2), a multicenter, randomized, double-masked, placebo-controlled phase 3 study, included 4,003 participants who were assigned to one of the following groups: placebo, lutein + zeaxanthin, 10 mg/2 mg; omega-3 long-chain polyunsaturated fatty acids, 1 g/day; or the combination.

Main Outcomes and Measures Development of advanced AMD. The unit of analysis used was by eye.

Results Median follow-up was 5 years, with 1,980 study eyes (408 participants) progressing to advanced AMD. Kaplan-Meier probabilities of progression to advanced AMD by years were: 11% (681 eyes [104 participants]) for placebo, 70% (66 eyes [36 participants]) for lutein + zeaxanthin, 31% (163 eyes [70 participants]) for DHA + EPA, 10% (18 eyes [12 participants]) for DHA + EPA, and 30% (47 eyes [22 participants]) for lutein + zeaxanthin + DHA + EPA. Comparison with placebo in the primary analyses demonstrated a statistically significant reduction in progression to advanced AMD (hazard ratio [HR]: 0.90 [95% CI, 0.78–1.04], P = 0.21). There was no evidence of benefit for beta carotene elimination or lowering doses of sodium zinc on progression to advanced AMD. More lung cancers were noted in the beta carotene versus no beta carotene group (2.0% vs 1.0%, P = 0.36), mostly in former smokers.

Conclusions and Relevance Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analysis did not further reduce risk of progression to advanced AMD. However, because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.
AREDS2: Design and Outcome Measures

Multi-centred, randomised, control trial.

**Study design**
Median of five years follow-up

**Primary outcome measure**
Progression to advanced AMD

**Secondary outcome measures**
1. Visual acuity (15-letter loss)
2. Lens opacity
3. Vision change in advanced AMD patients
4. The effect on AMD of eliminating beta-carotene from the original AREDS formula
5. The effect on AMD of eliminating zinc from the original AREDS formula
6. The effect on vision of eliminating beta-carotene from the original AREDS formula
7. The effect on vision of eliminating zinc from the original AREDS formula
Primary Randomization

Randomized Participants

Control*  Lutein/Zeaxanthin  DHA/EPA  L/Z + DHA/EPA

*No placebo group because AREDS treatment considered standard care

AREDS-I Type Supplements
Hazard Ratio Tree

Favors Treatment

Not Statistically Significant

Favors Placebo

95% CI

Hazard Ratio

Favors Treatment

Favors Placebo

Hazard Ratio (95% CI)

0.6 0.8 1 1.2 1.4 1.6
Probability of Progression to AAMD

- Placebo - AREDS: 31%
- L/Z: 31%
- DHA/EPA: 30%
- L/Z & DHA/EPA: 29%
Progression to Advanced AMD by Primary and Secondary Randomization Main Effects

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard Ratio (HR)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>L/Z vs. No L/Z</td>
<td>0.90</td>
<td>0.04</td>
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<tr>
<td>DHA/EPA vs. No DHA/EPA</td>
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<td></td>
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<tr>
<td>Low Zinc vs. High Zinc</td>
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<td></td>
</tr>
<tr>
<td>Beta-Carotene Yes vs. No</td>
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</tbody>
</table>

10% additional reduction in the risk of progression to AAMD with lutein/zeaxanthin
HR: 0.74   P<0.01
26% additional reduction in the risk of progression to AAMD with lutein/zeaxanthin for lowest quintile
AREDS2 Formulation

- Vitamin C (500 mg)
- Vitamin E (400 IU)
- Beta Carotene (15 mg)
- Lutein (10 mg)/Zeaxanthin (2 mg)
- Zinc (80 mg zinc oxide)
- Copper (2 mg cupric oxide)
- Omega-3 fatty acids (DHA/EPA)
Clinical Data

Data from Macular Pigment Research Group, Vision Research Centre, Waterford, Ireland
Peer-reviewed publications
Supplementation with All Three Macular Carotenoids: Response, Stability, and Safety

Eithne E. Connolly,1,2 Stephen Beatty,1,2 James Loughman,2,3,4 Alan N. Howard,5,6 Michael S. Lotu,2 and John M. Nolan1,2

Purpose. This study was designed to investigate serum and macular response to and safety of supplementation with meso-zeaxanthin (MZ), lutein (L), and zeaxanthin (Z), the carotenoids that constitute macular pigment (MP).

Methods. Forty-four healthy subjects were recruited into this randomized, placebo-controlled, clinical trial. Subjects consumed one tablet per day containing 10.6 mg MZ, 5.9 mg L, and 1.2 mg Z (intervention, I group) or placebo (P group). The spatial profile of MP optical density (MPOD) was measured with customized heterochromatic flicker photometry (cHFP), and serum concentrations of L and Z were quantified by using high-performance liquid chromatography (HPLC). Subjects were assessed at baseline and at 3 and 6 months. Clinical pathology analysis was performed at baseline and 6 months.

Results. Serum concentrations of L and Z increased significantly in the I group (P = 0.001 and 0.003, respectively) and remained stable in the P group (P > 0.05). There was a significant increase in central MPOD in the I group (0.25°: P = 0.001; 0.5°: P = 0.001), with no significant change in the P group (P > 0.05). Clinical pathology analysis confirmed that all variables remained within the normal reference range, with the exception of total cholesterol and low-density lipoprotein (LDL), which exhibited baseline values outside the accepted normal reference range before supplementation.

The macula houses a yellow pigment, attributable to the carotenoids meso-zeaxanthin (MZ), lutein (L), and zeaxanthin (Z). Indeed, this pigment lends its name to the macula lutea (Latin for yellow), and has been more recently referred to as macular pigment (MP). Interestingly, of the more than 700 carotenoids identified in nature, these three dietary carotenoids selectively accumulate at the macula,1,3 indicating an exquisite degree of biological selectivity in this retinal tissue.

An average Western diet contains 1.3 to 3 mg/d of L and Z combined,4 with substantially more L than Z (represented by an estimated ratio of ~7:1). It has been reported that approximately 78% of dietary L and Z is sourced from vegetables, with L found in highest concentrations in dark green, leafy vegetables.5 It appears that humans ingest relatively low levels of MZ, although it should be noted that there has been no satisfactory published investigation of MZ concentrations in the foods of a typical diet. Interestingly, despite its absence or low concentrations in a normal diet, MZ accounts for about one third of total MP at the macula, consistent with the hypothesis that retinal MZ is produced primarily by isomerization of retinal L at the macula.6

Age-related macular degeneration (AMD) is a degenerative condition of the macula, and its late form is the most common cause of blindness in the developed world.
Augmentation of Macular Pigment Following Supplementation with All Three Macular Carotenoids: An Exploratory Study

Eithne E. Connolly1,2, Stephen Beatty1,2, David I. Thurnham3, James Loughman4, Alan N. Howard5,6, Jim Stack2, and John M. Nolan1,2

1Macular Pigment Research Group, Department of Chemical and Life Sciences, Waterford Institute of Technology, Waterford, Ireland
2Institute of Vision Research, Whitfield Clinic, Waterford, Ireland
3Northern Ireland Center for Food and Health (NICHE), University of Ulster, Coleraine, UK
4Department of Optometry, School of Physics, Dublin Institute of Technology, Dublin, Ireland
5Downing College, University of Cambridge, Cambridge, UK
6Howard Foundation, Cambridge, UK

ABSTRACT

Purpose: At the macula, the carotenoids meso-zeaxanthin (MZ), lutein (L), and zeaxanthin (Z) are collectively referred to as macular pigment (MP). This study was designed to measure serum and macular responses to a macular carotenoid formulation.

Materials and Methods: Ten subjects were recruited into this study (five normal and five with early age-related macular degeneration [AMD]). Subjects were instructed to consume a formula...
Serum response to supplemental macular carotenoids in subjects with and without age-related macular degeneration

Katherine A. McEagher1*, David I. Thurnham2, Stephen Beatty1,3, Alan N. Howard1,5, Eithne Connolly1, Wayne Cummins6 and John M. Nolan1,3

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2Northern Ireland, Centre for Food and Health (MICHE), University of Ulster, Coleraine, UK
3Institute of Vision Research, Whitfield Clinic, Waterford, Republic of Ireland
4Howard Foundation, Cambridge, UK
5Downing College, University of Cambridge, Cambridge, UK
6Department of Chemical and Life Sciences, Pharmaceutical and Molecular Biotechnology Research Centre, Waterford Institute of Technology, Waterford, Republic of Ireland

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Abstract

Macular pigment (MP) is composed of lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ). The present study reports on serum response to

MPRG MACULAR PIGMENT RESEARCH GROUP
Peer-reviewed publications

**Family History**

- Control subjects
- FH of ARM/AMD

**Age**

- Mean MP optical density in each 10-year age group

**Cigarette Smoking**

- Never smoked
- Past smokers

*Risk factors for age-related maculopathy are associated with a relative lack of macular pigment.*

John M Nolan, Jim Stack, Orla O’Donovan, Edward Loane, Stephen Beatty

[Elsevier logo]

EXPERIMENTAL EYE RESEARCH 84 (2007) 61–74
Normal macular pigment profile in 88% of subjects (n=426)

Central dip in macular pigment profile present in 12% of subjects (n=58)

**Retina**

*A Central Dip in the Macular Pigment Spatial Profile Is Associated with Age and Smoking*

*Mark L. Kirby, Stephen Beatty, Edward Loane, Mukunda C. Akkali, Eithne E. Connolly, Jim Stack, and John M. Nolan*
Peer-reviewed publications

Study Design:
• Double-blind
• Randomised
• 30 subjects, 10 in each group
• Study visits: baseline, four and eight weeks
• Three macular carotenoid formulations

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>L (mg)</th>
<th>Z (mg)</th>
<th>MZ (mg)</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>20</td>
<td>2</td>
<td>-</td>
<td>Ultra Lutein™ by Nature’s Plus</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>Macushield ™ by Macuvision Europe</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>3</td>
<td>2</td>
<td>17</td>
<td>High MZ by Industrial Orgánica</td>
</tr>
</tbody>
</table>
Central dip study

Group 1: 20 mg lutein; 2 mg zeaxanthin; Nature’s Plus Ultra Lutein
Group 3: 17 mg Meso-zeaxanthin, 3 mg lutein, 2 mg Z, provided by Industrial Orgánica SA
Central dip study

Group 2: 10 mg Meso-zeaxanthin; 10 mg lutein; 2 mg zeaxanthin Macushield
Macular carotenoid supplementation in subjects with atypical spatial profiles of macular pigment

John M. Nolan a, b, *, Mukunda C. Akkali a, James Loughman c, d, Alan N. Howard e, f, Stephen Beatty a, b

a Macular Pigment Research Group, Department of Chemical and Life Sciences, Waterford Institute of Technology, Waterford, Ireland
b Institute of Vision Research, Whitfield Clinic, Waterford, Ireland
c Macular Pigment Research Group, Optometry Department, Dublin Institute of Technology, Dublin, Ireland
d African Vision Research Institute, University of KwaZulu Natal, Faculty of Health Sciences, Durban, South Africa
e Downing College, University of Cambridge, Cambridge, UK
f The Howard Foundation, Cambridge, UK

Abstract

This study was designed to investigate the impact of macular carotenoid supplementation on the spatial profile of macular pigment (MP) in subjects where the profile does not exhibit the typical central peak (i.e., peaked MP at foveal epicentre). Thirty one healthy subjects with such atypical MP spatial profile were assigned to one of three intervention groups: Group 1: (n = 10), 20 mg/day lutein (L), 2 mg/day zeaxanthin (Z); Group 2: (n = 10), 10 mg/day meso-zeaxanthin (MZ); Group 3: (n = 10), placebo.
The Impact of Macular Pigment Augmentation on Visual Performance Using Different Carotenoid Formulations

James Loughman,1,2 John M. Nolan,3,4 Alan N. Howard,5 Eithne Connolly,3,4 Katie Meagher,3
and Stephen Beatty3,4

Purpose. To investigate changes in macular pigment optical density (MPOD) and visual performance following supplementation with different macular carotenoid formulations.

Methods. Thirty-six subjects (19 male, 17 female; mean ± SD, age 51 ± 13 years) were recruited into this single-masked placebo-controlled study, and were randomly assigned to one of the following three intervention (supplementation) groups: (1) group 1 (20 mg lutein [L] and 2 mg zeaxanthin [Z]); (2) group 2 (10 mg L, 2 mg Z, and 10 mg meso-zeaxanthin [MZ]); and group 3 (placebo). Outcomes measures included visual performance and MPOD response. Data were collected at baseline, at 3 months, and at 6 months.

Results. At 3 and 6 months, a statistically significant increase in MPOD was found at all eccentricities (other than the most peripheral 3° location) in group 2 (P < 0.05 for all), whereas no significant increase in MPOD was demonstrable at any eccentricity for subjects in groups 1 and 3. Statistically significant improvements in visual performance measures including visual acuity and contrast sensitivity with and without glare were observed for group 2 only. Only mesopic
Meso-zeaxanthin Ocular Supplementation Trial
To investigate the impact of three different macular carotenoid formulations on:

1. Macular pigment optical density (MPOD)
2. Visual performance
3. AMD progression

in subjects with early age-related macular degeneration (AMD)
Design
Design

- Single-blind
- Randomised
- 67 subjects with early AMD
- Study visits: baseline, six, 12, 24 and 36 months

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>L (mg)</th>
<th>Z (mg)</th>
<th>MZ (mg)</th>
<th>Name</th>
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<tr>
<td>1</td>
<td>23</td>
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<td>2</td>
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<td>Ultra Lutein™ by Nature’s Plus</td>
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<td>2</td>
<td>24</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>MacuShield by MacuVision Europe</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>3</td>
<td>2</td>
<td>17</td>
<td>High MZ by Industrial Organica</td>
</tr>
</tbody>
</table>

Patients

- Early AMD in at least one eye
- CDVA of ≥ 6/12
- No other ocular pathology
Methods
Measuring Macular Pigment

MPOD was measured using customised heterochromatic flicker photometry: The Densitometer
Measuring Contrast Sensitivity

Contrast sensitivity and glare disability using the Functional Acuity Analyser

Contrast sensitivity using the Thompson letter chart
Retinal Grading

AMD Grading at the Fundus Photograph Reading Centre, University of Wisconsin, Madison, USA.
Results
## Results: MPOD at 36 Months

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline</th>
<th>36 months</th>
<th>Significance P value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MPOD at 0.25° (mean ± SD)</td>
<td>MPOD at 0.25° (mean ± SD)</td>
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<tr>
<td>Ultra Lutein</td>
<td>0.51 ± 0.29</td>
<td>0.72 ± 0.24</td>
<td>0.004</td>
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<tr>
<td>MacuShield</td>
<td>0.51 ± 0.23</td>
<td>0.76 ± 0.23</td>
<td>0.001</td>
</tr>
<tr>
<td>High MZ</td>
<td>0.46 ± 0.21</td>
<td>0.82 ± 0.28</td>
<td>0.000</td>
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<tr>
<td></td>
<td>MPOD at 0.5° (mean ± SD)</td>
<td>MPOD at 0.5° (mean ± SD)</td>
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<tr>
<td>Ultra Lutein</td>
<td>0.40 ± 0.28</td>
<td>0.62 ± 0.26</td>
<td>0.000</td>
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<tr>
<td>MacuShield</td>
<td>0.44 ± 0.19</td>
<td>0.65 ± 0.20</td>
<td>0.000</td>
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<tr>
<td>High MZ</td>
<td>0.35 ± 0.18</td>
<td>0.65 ± 0.23</td>
<td>0.000</td>
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<tr>
<td></td>
<td>MPOD at 1.0° (mean ± SD)</td>
<td>MPOD at 1.0° (mean ± SD)</td>
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<tr>
<td>Ultra Lutein</td>
<td>0.30 ± 0.19</td>
<td>0.45 ± 0.18</td>
<td>0.006</td>
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<tr>
<td>MacuShield</td>
<td>0.29 ± 0.12</td>
<td>0.46 ± 0.14</td>
<td>0.000</td>
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<tr>
<td>High MZ</td>
<td>0.24 ± 0.16</td>
<td>0.49 ± 0.21</td>
<td>0.000</td>
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<tr>
<td></td>
<td>MPOD at 1.75° (mean ± SD)</td>
<td>MPOD at 1.75° (mean ± SD)</td>
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<tr>
<td>Ultra Lutein</td>
<td>0.17 ± 0.11</td>
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<td>0.160</td>
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<td>MacuShield</td>
<td>0.16 ± 0.11</td>
<td>0.28 ± 0.11</td>
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<tr>
<td>High MZ</td>
<td>0.12 ± 0.12</td>
<td>0.35 ± 0.13</td>
<td>0.000</td>
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</table>
Results: MPOD at 36 Months

Ultra Lutein

- MPOD vs Retinal Eccentricity graph showing data points for Baseline and 36 month comparisons.
Results: MPOD at 36 Months

![Graph showing MPOD at 36 Months](image)

- **Baseline**
- **36 month**

-MPOD
- Retinal Eccentricity

**MacuShield**
Results: MPOD at 36 Months

High MZ

MPOD

Retinal Eccentricity

Baseline

36 month
Results: MPOD response
Results: before supplementation
Results: MPOD at 36 months following supplementation
## Results: Visual Acuity at 36 Months

<table>
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<th>Intervention</th>
<th>Baseline</th>
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<th>Significance P value</th>
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<tr>
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<td>CDVA (mean ± SD)</td>
<td>CDVA (mean ± SD)</td>
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<tr>
<td>Ultra Lutein</td>
<td>99.57 ± 6.93</td>
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<td>MacuShield</td>
<td>98.28 ± 7.67</td>
<td>98.00 ± 8.68</td>
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<td>High MZ</td>
<td>97.80 ± 6.33</td>
<td>100.20 ± 5.72</td>
<td>0.266</td>
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## Results: Letter CS at 36 Months

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<th>Significance P value</th>
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<td><strong>Letter CS 1.2cpd (mean ± SD)</strong></td>
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<tr>
<td>Ultra Lutein</td>
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<tr>
<td>MacuShield</td>
<td>1.70 ± 0.22</td>
<td>1.84 ± 0.18</td>
<td>0.008</td>
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<tr>
<td>High MZ</td>
<td>1.79 ± 0.31</td>
<td>1.84 ± 0.19</td>
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<td><strong>Letter CS 2.4cpd (mean ± SD)</strong></td>
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<tr>
<td>Ultra Lutein</td>
<td>1.75 ± 0.28</td>
<td>1.85 ± 0.18</td>
<td>0.250</td>
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<tr>
<td>MacuShield</td>
<td>1.66 ± 0.31</td>
<td>1.78 ± 0.20</td>
<td>0.079</td>
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<tr>
<td>High MZ</td>
<td>1.67 ± 0.31</td>
<td>1.80 ± 0.21</td>
<td>0.072</td>
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<tr>
<td><strong>Letter CS 6cpd (mean ± SD)</strong></td>
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<tr>
<td>Ultra Lutein</td>
<td>1.42 ± 0.29</td>
<td>1.56 ± 0.19</td>
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<tr>
<td>MacuShield</td>
<td>1.29 ± 0.32</td>
<td>1.47 ± 0.27</td>
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<tr>
<td>High MZ</td>
<td>1.25 ± 0.42</td>
<td>1.54 ± 0.26</td>
<td>0.016</td>
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<td><strong>Letter CS 9.6cpd (mean ± SD)</strong></td>
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<tr>
<td>Ultra Lutein</td>
<td>1.14 ± 0.30</td>
<td>1.29 ± 0.27</td>
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<tr>
<td>MacuShield</td>
<td>1.03 ± 0.28</td>
<td>1.25 ± 0.32</td>
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<tr>
<td>High MZ</td>
<td>0.97 ± 0.45</td>
<td>1.32 ± 0.21</td>
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<tr>
<td><strong>Letter CS 15.15cpd (mean ± SD)</strong></td>
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<tr>
<td>Ultra Lutein</td>
<td>0.75 ± 0.32</td>
<td>1.02 ± 0.23</td>
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<tr>
<td>MacuShield</td>
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<tr>
<td>High MZ</td>
<td>0.62 ± 0.46</td>
<td>0.98 ± 0.24</td>
<td>0.007</td>
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</tbody>
</table>
Results: Letter CS at 36 Months

Ultra Lutein

Log Contrast Sensitivity

Spatial Frequency

1.2 cpd  2.4 cpd  6 cpd  9.6 cpd  15.15 cpd

1.80  1.60  1.40  1.20  1.00

Baseline  36 month
Results: Letter CS at 36 Months

MacuShield

Log Contrast Sensitivity

Spatial Frequency

- 1.2 cpd
- 2.4 cpd
- 6 cpd
- 9.6 cpd
- 15.15 cpd

Baseline

36 month
Results: Letter CS at 36 Months

High MZ

Log Contrast Sensitivity vs. Spatial Frequency for Baseline (orange) and 36 month (blue) conditions.
## Results: AMD Morphology on the Age-Related Eye Disease Study (AREDS) 11-step scale

<table>
<thead>
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<th>AMD Grade</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<td>0</td>
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<td>0</td>
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<td>0</td>
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<tr>
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<td>0</td>
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<td>1</td>
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<td>0</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>8</td>
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<tr>
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<td>10</td>
<td>7</td>
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## Results: AMD Morphology

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<th>36 months</th>
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<tr>
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<td>Low risk AREDS (1-3)</td>
<td>High Risk AREDS (4-8)</td>
<td>Advanced AMD AREDS (9-11)</td>
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<tr>
<td>Low risk</td>
<td>Ultra Lutein</td>
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<td>0</td>
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<td></td>
<td>MacuShield</td>
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<tr>
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<td>0</td>
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<td>3</td>
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<tr>
<td>High risk</td>
<td>Ultra Lutein</td>
<td>0</td>
<td>10</td>
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<tr>
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<td>MacuShield</td>
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</table>
Results: Clinical progression (an increase of 2 steps from baseline to 36 months on the Age-Related Eye Disease Study (AREDS) 11-step scale) by Intervention groups

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Ultra Lutein</td>
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<td>MacuShield</td>
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<tr>
<td>High MZ</td>
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<td>15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43</td>
<td>3</td>
<td>46</td>
</tr>
</tbody>
</table>
Conclusions
Conclusions

• In subjects with early AMD
  – augmentation of MP can be achieved with focused macular carotenoid supplementation
  – supplementation with higher doses of MZ leads to bigger and more prolonged improvements in MP
  – supplementation with higher doses of MZ results with greater improvements in contrast sensitivity
  – There is no significant change in AMD grade when patients with early AMD are supplemented with the macular carotenoids L, Z and MZ
SUPPLEMENTATION WITH THREE DIFFERENT MACULAR CAROTENOID FORMULATIONS IN PATIENTS WITH EARLY AGE-RELATED MACULAR DEGENERATION

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EITHNE CONNOLLY, BSc,†† JAMES LOUGHMAN, PhD,§† JIM STACK, PhD,† ALAN HOWARD, PhD,‡
RONALD KLEIN, MD, MPH,** BARBARA E. KLEIN, MD, MPH,** STACY M. MEUER, BSc,**
CHELSEA E. MYERS, MStat,** KWADWO O. AKUFFO, OD,† JOHN M. NOLAN, PhD††

Purpose: To investigate the impact of three different macular carotenoid formulations on macular pigment optical density and visual performance in subjects with early age-related macular degeneration.

Methods: Fifty-two subjects were supplemented and followed for 12 months, 17 of them were in intervention Group 1 (20 mg/day lutein and 2 mg/day zeaxanthin); 21 in Group 2 (10 mg/day meso-zeaxanthin, 10 mg/day lutein, and 2 mg/day zeaxanthin); and 14 in Group 3 (17 mg/day meso-zeaxanthin, 3 mg/day lutein, and 2 mg/day zeaxanthin). The macular pigment optical density was measured using customized heterochromatic flicker photometry, and visual function was assessed using corrected distance visual acuity and by letter contrast sensitivity.

Results: A statistically significant increase in the macular pigment optical density was observed at all measured eccentricities in Group 2 ($P = 0.005$) and in Group 3 ($P < 0.05$), for all, but only at $1.75^\circ$ in Group 1 ($P = 0.018$). Statistically significant ($P < 0.05$) improvements in letter contrast sensitivity were seen at all spatial frequencies (except 1.2 cycles per degree) in Group 3, and at low spatial frequencies in Groups 1 and 2.

Conclusion: Augmentation of the macular pigment optical density across its spatial profile and enhancements in contrast sensitivity were best achieved after supplementation with a formulation containing high doses of meso-zeaxanthin in combination with lutein and zeaxanthin.

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Thank you.

ANY QUESTIONS?