AREDS 2 and U

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DISCLOSURES

• I’M AN ADVISOR TO:
  • KEMIN PHARMA
  • ALCON
  • B AND L
  • ALLERGAN
Age-Related Eye Disease Study (AREDS): Rationale and Significance

PART 2
• JAMA, May 2013

• Lutein (+) Zeaxanthin and Omega 3 fatty acids for age related macular degeneration: AREDS 2

• The QUESTIONS:

• 1. Does adding lutein (+) zeaxanthin, the Omega 3 fatty acids DHA (+) EPA or both to the original AREDS formula decrease the risk of developing advanced AMD?
QUESTION #2

• Does removal of beta-carotene or reduction in the amount of zinc increase the risk of developing AMD?
QUESTION #3

• JAMA, JULY 2013

• Does L/Z supplementation affect the rate of cataract surgery or cataract associated vision loss?
## AREDS: NEI Trial Overview

<table>
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<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Objective</td>
<td>To evaluate the effect of high-dose vitamin supplementation, age-related macular degeneration (AMD) progression and visual acuity.</td>
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<tr>
<td>Design</td>
<td>Double-masked, randomized, placebo-controlled trial</td>
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<tr>
<td>Population</td>
<td>3640 high risk patients (55-80 years)</td>
</tr>
<tr>
<td>Duration</td>
<td>6.3 years supplementation and follow up</td>
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</table>

ARED (Age related eye disease) Study results

Archives of Ophthalmology - October 2001

Categories

1. NO AMD
2. Mild AMD
3. Moderate AMD
4. Advanced AMD
## Daily Dosage: Placebo VS AREDS formula

Supplements were manufactured to have the following minimum contents:

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antioxidants</strong></td>
<td></td>
</tr>
<tr>
<td>Beta-carotene</td>
<td>15 mg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>500 mg</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>400 IU</td>
</tr>
<tr>
<td><strong>Essential Trace Elements</strong></td>
<td></td>
</tr>
<tr>
<td>Copper</td>
<td>2 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>80 mg</td>
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</tbody>
</table>

AREDS Rationale: Beta-Carotene

• Why is it important?
  ▫ Body unable to synthesize¹
  ▫ Antioxidant capability¹

• What dose was studied?
  ▫ 15 mg/day (AREDS)²

• Where can I get it in my diet?
  ▫ Carrots, broccoli, spinach, kale³
  ▫ 15 mg beta-carotene = 1.6 cups of carrots³
  ▫ 15 mg beta-carotene = 47.1 cups of broccoli³

DON’T FORGET THE CONTRAINdications - Beta Carotene and Cancer

The three beta-carotene intervention trials: the Beta Carotene and Retinol Efficacy Trial (CARET), Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), and Physician's Health Study (PHS) have all pointed to a lack of effect of synthetic beta-carotene in decreasing cardiovascular disease or cancer risk in well-nourished populations. The contribution of beta-carotene supplementation to increased risk of lung cancer in smokers has been raised as a significant concern. Risk increase = approx 30% (avg of 3 studies)
Cigarette smoking and retinal carotenoids: implications for age-related macular degeneration.

Subjects were matched with respect to age, sex, dietary patterns and overall pigmentation (i.e., eye, skin and hair color). The smoking group had a mean MP of 0.16 (SD = 0.12) compared to a mean MP of 0.34 (SD = 0.15) for nonsmokers (P < 0.0001). MP density and smoking frequency were inversely related (r = -0.498 P < 0.001) in a dose-response relationship.
AREDS Rationale: Vitamin C

- **Why is it important?**
  - Body unable to synthesize\(^1\)
  - **Antioxidant capability**\(^1\)
- **What dose was studied?**
  - 500 mg/day (AREDS)\(^2\)
- **Where can I get it in my diet?**
  - Citrus fruits and juices\(^3\)
  - 500 mg vitamin C = 4 cups/32 fl oz of orange juice\(^3\)

AREDS Rationale: Vitamin E

• Why is it important?
  ▫ Body unable to synthesize¹
  ▫ **Antioxidant capability¹**

• What dose was studied?
  ▫ 400 IU/day (AREDS)²

• Where can I get it in my diet?
  ▫ Nuts, fortified cereals, sweet potatoes³
  ▫ 400 IU vitamin E = 182.6 sweet potatoes³

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AREDS Rationale: Zinc: Early studies suggested ability to slow progression, but not VA loss in AMD

- Why is it important?
  - Essential trace element

- What dose was studied?
  - 80 mg zinc/day (AREDS)

- Where can I get it in my diet?
  - Red meat, poultry, mixed nuts
  - 80 mg zinc = 55.8 oz of red meat
  - 80 mg zinc = 50.3 oz of nuts

AREDS Rationale: Copper

• Why is it important?
  ▫ Essential trace element\(^1\)
  ▫ Both an anti-oxidant and pro-oxidant\(^2\)
  ▫ Body unable to synthesize\(^2\)
  ▫ High zinc may cause copper deficiency\(^3\)

• What dose was studied?
  ▫ 2 mg/day (AREDS)\(^4\)

• Where can I get it in my diet?
  ▫ Seafood, Liver, Nuts, Legumes\(^2\)
  ▫ 2 mg copper = 1/2 oz of liver\(^5\)
  ▫ 2 mg copper = 5 cups of beans\(^5\)

AREDS 1: THE RESULTS

- 21 published reports
- Those likely to benefit from AREDS formula:
  - extensive intermediate-size drusen
  - at least one large drusen
  - noncentral geographic atrophy
  - advanced AMD
  - vision loss in one eye
ARED Study results
Archives of Ophthalmology - October 2001

1. Patients over 55 years should have DFE to be evaluated for risk of AMD.

2. If extensive intermed. Drusen, at least 1 large druse, non-central geographic atrophy in 1 or both eyes or advanced AMD and no contraindications - TX

3. Vitamin C 500mg, Vitamin E 400IU, Beta carotene 15mg + Zinc 80mg and Copper 2mg (Oxides)

4. 8% decrease of progression from Category 3 to 4 Reduced visual acuity loss by 19% in Category 3 and 4
IMPORTANT TO NOT TAKE AREDS TOO FAR

- DID NOT PREVENT AMD
- DID NOT REVERSE AMD
WHY AREDS 2?

- WHY L/Z?
- WHY OMEGA 3’S?
AREDS 1: Observations

- Lutein/zeaxanthin and omega-3 fatty acid: Intake was independently linked with decreased likelihood of:
  1. Neovascular AMD (Lutein/zeaxanthin, Omega-3s)
  2. Geographic atrophy (Lutein/zeaxanthin, Omega-3s)
  3. Large or extensive intermediate drusen

- Omega-3 fatty acids were of particular benefit in groups at higher risk for neovascular AMD and geographic atrophy

Significance of Lutein and Zeaxanthin

• Several carotenoids are present in human serum, but only lutein and zeaxanthin are present in macula and provide a yellow color known as macular pigment

• This macular pigment protects the macula from the damaging photo-oxidative effects of blue light

• Body cannot synthesize

• 5:1 ratio of lutein to zeaxanthin in the diet

• Powerful Antioxidant
  – Reduces free radical damage in the eye

Lutein Antioxidant Supplementation Trial (L.A.S.T.) and Macular Pigment Optical Density (MPOD)

- 90 patients with AMD (4 females, 86 males):
  - Mean age: 75
  - Mean number of smoking pack years: 7
- Treatment arms:
  - 10 mg FloraGLO® lutein
  - 10 mg FloraGLO® lutein + antioxidants
  - Placebo
- Significant improvements from baseline in visual function⁴
  - Greatest benefit in patients with lowest baseline MPOD²


*FloraGlo is a registered trademark of Kemin Industries, Inc.*
Long-term FloraGLO® Lutein and Zeaxanthin Supplementation Improves MPOD in patients with AMD

LUTEGA STUDY

• 172 subjects (50+, AMD)
• Double-masked, randomized:
  – 10 mg FloraGLO® Lutein / 1 mg Zeaxanthin / 255 mg Omega-3 QD
  – 10 mg FloraGLO® Lutein / 1 mg Zeaxanthin / 255 mg Omega-3 BID
  – Placebo
• 4 evaluations over 12 months

MPOD CHANGES


*FloraGLO is a registered trademark of Kemin Industries, inc.*
Increased MPOD is linked to Positive Effects on Visual Performance

- Glare tolerance\(^1\)
- Glare recovery\(^1\)
- Contrast sensitivity\(^2\)
- Amsler defect and VA improvement\(^3\)
- Chromatic aberration\(^2\)
- Photophobia\(^4\)

Omega-3 Fatty Acids (DHA/EPA)

• Important for proper visual development and retinal function\(^1\)

• Docosahexaenoic acid (DHA) is found in the highest concentration in the retina\(^1\)

• Eicosapentaenoic acid (EPA) is used in DHA biosynthesis\(^1\)

Omega-3 Fatty Acids (DHA/EPA)

• Benefits of DHA/EPA
  – Intake is associated with a decreased risk of progression from bilateral drusen to geographic atrophy

• Low levels of DHA and EPA associated with chronic eye conditions such as:
  – Diabetic retinopathy
  – Age-related macular degeneration (AMD)
  – Retinopathy of prematurity
  – Dry eye disease

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<td>Assess effect of a alternative combination of vitamins and minerals on the progression of AMD and vision loss</td>
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<td>Design</td>
<td>NEI 5 year, multi-center, randomized, double-masked, placebo-controlled trial</td>
</tr>
<tr>
<td>Population</td>
<td>4000 patients at higher risk of developing AMD (Men and women; 50-85 years*)</td>
</tr>
</tbody>
</table>

PROTOCOL

• NO NORMALS
• 1-3 MONTH RUN IN WITH AREDS (+) PLACEBOS
• IF PATIENT COMPLIES WITH DRUG USE AND SHOWS UP-RANDOMIZED TO TX
• ANNUAL EXAM (+) FUNDUS PHOTOS
• ANNUAL BLOOD TESTS FOR ANTI-OXIDANT BLOOD LEVELS
AREDS2: To Evaluate…

Ingredients being studied in AREDS2:

- FloraGLO® lutein (10mg)
- OPTISHARP® zeaxanthin (2mg)
- Omega-3 fatty acids (350 mg DHA, 650 mg EPA)
- With and without β-carotene (15 mg vs 0 mg)
- High vs low zinc levels (80mg vs 25mg)

Patients in the AREDS2 study are assigned to different combinations of ingredients


*FloraGlo is a registered trademark of Kemin Industries, Inc.
* Optisharp is a registered trademark of DSM IP Assets B.V.
AREDS 2 WAS COMPLICATED

• 16 RANDOMIZED GROUPS
• NO NORMALS
• 2 LEVELS OF RANDOMIZATION
• SPECIAL RULES FOR SMOKERS
• CENTRUM SILVER FOR THOSE ON A MV SUPPLEMENT
• STATISTICS LIMITED BY COHORT SIZE AND DURATION OF STUDY
AREDS2 Study Design

Randomized Participants ~4000

- Placebo
- L/Z
- DHA/EPA
- L/Z+DHA/EPA

ATS* Options

- No ATS*
- AREDS2 Vitamin / Mineral Evaluation
- Original ATS*
- ATS*
- No β-C
- Low Zn
- No β-C & Low Zn

- No smoker can be in an arm with beta-carotene
- Background multivitamin supplementation is allowed, but is standardized


*AREDS type supplements.
Lutein (FloraGLO®)

• 10 mg/day

Zeaxanthin (OPTISHARP®)

• 2 mg/day

• 5:1 ratio of lutein to zeaxanthin commonly found in American diet


FloraGLO is a registered trademark of Kemin Industries, Inc.
Optisharp is a registered trademark of DSM IP Assets B.V.
AREDS2: To Evaluate…

Endpoints:

- Progression to advanced AMD
- Progression to moderate vision loss
- Progression of lens opacity
- Effective cognitive function
- Cardiovascular morbidity/mortality
LIES, DAMN LIES AND STATISTICS

• SPINNING THE AREDS 2 DATA
Re-interpretation of results at ARVO 2013 by lead investigator, Emily Chew et al

- Adding omega 3’s to AREDS: **No benefit**
- Adding L/Z to AREDS and evaluating the effect on the total cohort (study population)
  - 1. L/Z reduced advanced AMD by 10%
  - 2. Neovasc. AMD 11%
  - 3. Neovasc AMD 26% in low L/Z diets
  - 4. Cataract progression 30% in low L/Z diets
  - 5. Beta carotene doubles risk of lung cancer in all participants, 0.9% VS 2% W-BC
Consumption of Lutein/Zeaxanthin in the US is LOW

The average American only gets between 1 mg to 2.3mg per day of combined lutein and zeaxanthin in their diet which is below the AREDS2 intake of 10mg.

The Bottom Line on ARMD/AREDS 1

- DON’T BE Northern European
- DON’T GET OLDER
- DON’T SMOKE
- DON’T GIVE SMOKERS ANTIOX
- CONTROL VASCULAR DISEASE RISK FACTORS
- SUPPLEMENTS DON’T REPLACE A BAD LIFESTYLE
ADDITIONAL RECOMMENDATIONS FROM AREDS 2

- NEVER use beta-carotene in ANYBODY
- INCREASE L/Z foods in patients diet-if not, then supplement
- OMEGA 3’s have value, but NOT for AMD
MY RESEARCH INTEREST

• WHY DO STUDIES HAVE TO LAST 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