American Academy of Optometry  
Ocular Nutrition  
Special Interest Group  

Conclusions and Controversies:  
AREDS 2 and future directions to AMD  

October 23, 2013 10:00 am – 12:00  
Room #615-617  

Dennis Ruskin  

- Chair of the Ocular Nutrition SIG  
- Ocular Nutrition Society – Founding Director  
- Clinical Practice – Toronto Ontario  
- Clinical Investigator  
- President of the College of Optometrists of Ontario  

Nutritional Objectives for Today’s Presentation  

• Understanding the challenges of study design pertaining to nutritional research.  
• Review of the evidenced base science to demonstrate whether nutrients do have a role in affecting ocular and systemic health.  
• Review the importance of some specific essential nutrients that are critical for the visual system as well as the human life cycle.  
• Formulating a strategy to help AMD patients  

Nutrition, Chronic Disease, and Evidenced Base Science
Nutrition, Chronic Disease, and Evidenced Base Science

“The randomized controlled trial, which has become the gold standard for establishing the efficacy of pharmacologic agents, is poorly suited to the evaluation of nutritional effects, a fact that I believe many have been reluctant to acknowledge.”

*R. Heany, MD. Am J Clin Nutr 2006

Drugs vs. Nutrients: Limits of RCT as a Research Strategy in Preventative Medicine

- Chronic diseases have long latency and multifactorial causation
- Absence of no exposure group (only different levels of intake)
- Nutrients interact with one another; drugs designed to work alone
- Nutrients act in modest beneficial ways in virtually every body system; drugs act potentially on single targets (RCT designed for single outcomes)


Nutritional supplementation and eye health

- Historically controversial
- Epidemiologic data
- Physicians’ limited knowledge
- Counseling generally not a focus of a busy clinical practice

BUT AREDS caused a shift…

Age-related eye disease study (AREDS)

**Study Question**

Can antioxidant vitamins and minerals slow the progression of AMD and AMD-associated vision loss?

**Study Design**

- NEI-sponsored
- Prospective clinical trial
- Randomized
- Placebo-controlled
- Masked

AREDS I Conclusions

“Reduces the risk of advanced AMD”
- This effect was in 25% of the study population with stage III AMD.
- Slowed progression from stage III to IV.
- Did not prevent AMD.
- Did not reverse AMD.
- Did not halt progression of AMD.

Progression to advanced AMD

AREDS 2 Objective

- To examine if AREDS formula could be more beneficial than the current formula.
- Adding 10 mg of lutein and 2 mg of zeaxanthin, 350 mg DHA/650 mg EPA, or a combination of the two to the AREDS formulation be more beneficial?
- Might adding these nutrients reduce the risk of progression to advanced AMD by an additional 25% as compared to the original AREDS formula?

AREDS 2 Abstract Conclusion

Conclusions and Relevance  Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses 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.

Trial Registration clinicaltrials.gov identifier: NCT00345176

www.jama.com
### AREDS 2 Problems with Study Design

- Very complicated study design using 2 tiers of randomization
- Emily Chew, author stated: “complicated design involving a secondary randomization which may have affected our ability to evaluate the role of lutein + zeaxanthin and DHA + EPA to the AREDS formula.”

### AREDS 2 Confounding Issues

- 30% of the subjects chose not to receive the secondary randomization
- The group of subjects who moved forward with a secondary randomization were composed of a higher percentage of highly educated and female.
- 14% of participants admitted to taking unauthorized additional supplements either alone or in combination: L/Z/DHA/EPA during the trial.
- Approximately only 84% of subjects took > 75% of their pills

### AREDS 2 Problems with Study Design

- Lack of a true control group
- Subjects were offered a choice to take AREDS 1 formula – most subjects opted to take the supplements including centrum silver multivitamin
- Nearly all (except n=19) of the patients in AREDS 2 were actually taking the original AREDS or some modification of that supplement
  - reduced the zinc,
  - No beta-carotene,
  - or both reduced zinc and no beta carotene.

### AREDS 2 Confounding Issues

- Study participants were more well-nourished than the average American population and highly educated, so they were not a representative sample.
- In addition to taking the original AREDS supplement, the group entered the study already consuming supplements or foods rich in lutein, zeaxanthin, and omega-3 fatty acids.

    *MPOD paper by P Bernstein ....* Specifically, our cohort’s prior usage of lutein and zeaxanthin supplements was exceedingly high, suggesting that we enrolled a very nutritionally aware cohort from a region of the country with a high prevalence of nutritional supplement use.”


    Paul S. Bernstein,1 Faisal Ahmed,1 Aihua Liu,1 Susan Allman,1 Xiaoming Sheng,2 Mohsen Sharifzadeh,3 Igor Ermakov,3 and Werner Gellermann3
**Study Flaw?**

**Carotenoid Competition**

- Compared with subjects who took the beta carotene-containing supplement (no lutein/zeaxanthin), those who took the lutein/zeaxanthin-containing supplement (no beta carotene) had an 18% lower risk of progressing.
- Lutein, zeaxanthin and beta carotene are carotenoids and compete with each other for absorption in the body.
- These results could explain, in part why lutein/zeaxanthin had no overall effect in the primary randomization.
- Study designed assumed little interaction between nutrients → Incorrect study assumption about carotenoid competition may explain why L/Z performance to reduce progression of AMD was not observed.


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**AREDS 2 Conclusions**

- Overall, there was a 9-10% additional reduction in risk using lutein and zeaxanthin in addition to an AREDS type supplement.
- When L/Z were substituted for beta-carotene the additional risk reduction was about 18%.
- Patients with the lowest dietary intakes of lutein and zeaxanthin (average 0.7 mg per day or less) showed a 26% additional reduced risk of progression to advanced AMD.
- Average consumption of L/Z ~ 1.5 L/Z in the diet daily.
- The AREDS 2 group which was much more well nourished than the general population.

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**Risk of Beta-carotene**

- Beta-carotene increased lung cancer.
- 91% of lung cancer cases occurred with subjects (former smokers) who used the original AREDS formula.

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**AREDS 2 Omega 3 Controversy**

- Adding omega-3 fatty acids did not further reduce the risk of advanced age-related macular degeneration (AMD).
  - Dose may not be high enough.
  - Ethyl ester formulation was used, not triglyceride formulation.
  - Did not evaluate risk of incident AMD or progression from early to later stages of AMD.
**AREDS 2 Summary**

- How much zinc? ??

**Should we recommend low or high Zinc?**

- Low dose zinc did not diminish efficacy of the formula according to the JAMA AREDS2 paper

**However**

- Emily Chew reported at the Special Session at ARVO 2013: Results from the Age-Related Eye Disease Study 2 (AREDS2) “favored high zinc – (80 mg) zinc oxide” to reduce the progression of advanced AMD
- The NEI has not made any further statements about zinc recommendations.

**New Recommended AREDS 2 Formula**

As recommended from AREDS2 study

- Lutein (10 mg)
- Zeaxanthin (2 mg)
- Vitamin C (400 mg)
- Vitamin E (400 IU)
- Zinc (80 mg of zinc oxide) ???
- Copper (2 mg of cupric oxide)

**Traditional RCT vs. Genetic Clinical trials**

- Human genome has been catalogued
- ~12 million sites of historical mutation along the human genome
- These sites of “variation” are called single nucleotide polymorphisms or SNPs
- A SNP is a site of base pair substitution (adenine-thymine substituted for cytosine-guanine)
- AMD has the strongest genetic contribution of all human multigenetic diseases
Relative impact of genetic risk markers on advanced AMD.

Genes and AMD

- SNPs associated with AMD are located on genes that affect biological pathways of the disease and this has been confirmed in the scientific literature
- Genes affecting pathogenesis of AMD
- Genes involved with complement pathway are: CFH, C2, CFB, C3, and CFI
- ARMS2 gene has been associated with AMD
- ARMS2 gene is involved with energy metabolism within the mitochondria

Gene SNP's that relate to risk of AMD

<table>
<thead>
<tr>
<th>Gene</th>
<th>Full Name</th>
<th>SNPs</th>
<th>OR</th>
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**Macula Risk PGx**

**Test Components**

- **Phenotype**
  - AMD Diagnosis
  - ICD-9
  - Drusen size

- **Genetics**
  - 15 Gene Markers
  - 12 AMD Genes
  - 4 pathways

- **Non-Genetic**
  - Age
  - BMI
  - Smoking status
  - Education

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**CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration**

More than double the benefit of AREDS:

“We estimate that genotype-directed therapy of the study population would have more than doubled the reduction in AMD progression rate compared with treatment with the AREDS formulation.”

A clear role for genetic testing – [Ivana Kim](#) (co-author)

“This data demonstrates that the composition of supplements recommended to AMD patients should be guided by an individual’s genetic risk profile, indicating a clear role for genetic testing in clinical management.”

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**Age Related Eye Disease Study (AREDS)**

**AMD Patients**

- Antioxidants
- Zinc Oxide
- Antioxidants + Zinc Oxide

17% risk reduction
21% risk reduction
25% risk reduction

AREDS Study (2001) Risk reduction in developing advanced disease, as compared to placebo

4750 Patients - Vitamin C, Vitamin E, Beta Carotene, Zinc
Graph showing estimated probabilities of progression as a function of genotype, treatment group, and time (years)

**Suggested Treatments**

<table>
<thead>
<tr>
<th>CFH Risk Alleles</th>
<th>ARMS2 Risk Alleles</th>
<th>Optimal Treatment</th>
<th>Study Frequency</th>
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<td>AREDS</td>
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<td>Zinc Alone</td>
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<td>Antioxidants Alone</td>
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<tr>
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</table>

*no statistical treatment benefit observed

CFH and ARMS2 Genetic Polymorphisms Predict Response to Antioxidants and Zinc in Patients with Age-related Macular Degeneration
Carl C. Awh, MD.

**What will be the new standard of care for Nutrient Recommendations related to AMD?**

1. Recommendation for the AREDS 2 revised formula as the new standard approach offering your patient population → expect 25% general population benefit
2. Recommendation for genetic testing to profile risk → has a 90% AMD prognosis accuracy
3. Recommendation of a Genome Directed Therapy (GDT) when possible → may double (2X) the AREDS 2 efficacy and furthermore protect from harm specific genotypes
4. → Create a personally optimized AREDS vitamin strategy using GDT and include when appropriate other nutrient strategies that are safe and which could better satisfy your patients individual needs.
**Carotenoids, Minerals in AREDS II**

Stuart P Richer, OD, PhD, FAAO  
Director, Ocular Preventive Medicine  
James A Lovell Federal Health Care Facilit  
Associate Professor, Family and Preventive Medicine, Rosalind Franklin University of  
...edicine & Science / Chicago Medical Schc  
North Chicago, Illinois 60064, USA  
Assistant Clinical Professor, UIC Dept of  
Ophthalmology and Visual Science - Chicago  
Stuart.Richer1@VA.GOV  
American Academy of Optometry  
23 October 2013  
Seattle, WA

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**CAROTENOIDS**

- Demographic, lifestyle, and medical characteristics were ascertained on 4519 AREDS participants aged 60 to 80 years at enrollment.
- Highest vs lowest quintiles of intake, after adjustment for total energy intake and non-nutrient-based covariates.
- **Dietary lutein/zeaxanthin intake** was inversely associated
  - Large or extensive intermediate drusen (OR 0.73; 95% CI, 0.56-0.96).
  - Neovascular AMD (OR 0.65; 95% CI 0.45-0.93).
  - Geographic atrophy (OR 0.46; 95% CI, 0.24-0.86)

**L / Zx: AREDS Report # 22**

Arch Ophthalmol. 2007 Sep;125(9):1225-32.
Lutein is 5x more common in the US diet.

Carotenoid ratios, L:Z:M
- Blood: 3:1:0
- Whole retina: 2:1:0.5
- * Fovea: 1:1:1

Zeaxanthin (18% & foveal)

Photomicrograph courtesy of Dr. Joanne Curran-Celentano.

Comparison of Lutein/Zeaxanthin vs. No Lutein/Zeaxanthin

Advanced AMD: HR: 0.90  P= 0.04
10% further reduction in the risk of progression to AAMD with Lutein/Zeaxanthin

Neovascular AMD: HR: 0.89  P= 0.05
11% further reduction in the risk of progression to neovascular AMD with Lutein/Zeaxanthin

No statistically significant reduction of CGA

Hidden - Online Supplement E Figure 1a:
Comparison of the Main Effects of Lutein + Zeaxanthin vs No Lutein + Zeaxanthin on Progression to Advanced AMD, Stratified by Various Groupings of Dietary Intake of Lutein + Zeaxanthin
(A, Tertiles; B, Quartile; C, Decile)

Quintiles 0.7 mg / 1.1 mg / 1.6 mg / 2.2 mg / 3.9 mg L+Z
What JAMA did not say about substituting L + Z

1) The net result of this 34% reduction, is that several hundred thousand Americans will be able to drive and won’t need expensive & invasive intravitreal injections

2) BETTER VISION W CAROTENOIDS

↑ PARAFOVEAL FUNCTION with 8 mg Floraglo ® Lutein supplementation
Foggy weather is **common**
Your Eye Doctor actually testing low contrast visual acuity is **uncommon**.

**Common and Dangerous especially as we age**

**Near Low Contrast Acuity Measurement - Uncommon**

**Evaluating Contrast Sensitivity (uncommon)**
(multiple spatial frequencies of varying contrasts)

[Zeaxanthin in a formulation means](#)
*↑ Visual Acuity + ↑ Foveal Shape Discrimination + possibly better protection against occult foveal membranes*

**MINERALS IN AREDS II (ZINC)**
Percentage of All Individuals (2 yrs & older) Not Meeting 100% of 1989 RDAs in US (1994-96)

14 Nutrients Most Lacking in U.S. Diet

- Zinc = 73.3%
- Calcium = 65.1%
- Magnesium = 61.6%
- Vitamin B6 = 56.2%
- Iron = 39.1%
- Vitamin C = 37.5%
- Folate = 33.2%
- Vitamin B1 = 30.2%
- Vitamin B2 = 30.0%
- Vitamin B3 = 25.9%
- Protein = 20.5%
- Vitamin B12 = 17.2%

Supplemental Zinc had the strongest effect in AREDS 1.

The 80mg dose is high but Zinc Oxide is poorly absorbed.

ZN Safety Conclusion

- Secondary randomization suggests no differences in the progression to AAMD for elimination of β-Carotene or lowering Zinc dose.
- No differences in adverse side-effects (gastrointestinal disorders or others) between “low” and “high” groups.
- Insufficient data to make a recommendation for zinc.

DNA genomic polymorphism tests

+ Newsome/ AREDS 1 ZN++ data is strong

ZN++ Neutralizes Excess Environmental CU++ / FE++

73% of US is ZN++ Deficient

DNA is not destiny; Epigenetics at play

Total Exclusion might have negative Impact on ZN++ homeostasis / Overall Health

DNA is not destiny; Epigenetics at play

73% of US is ZN++ Deficient

ZN++ Neutralizes Excess Environmental CU++ / FE++

- Low risk CFH genotype implies 68% benefit for AREDS formulation.
- High risk CFH genotype implies only 11% benefit (BUT NO HARM).
- Using ZN++ alone or ZN++ & AO did not justify routine genetic testing or change the current standard of care.


- N=995 AREDS 1 Category 3 in 1 eye w peripheral blood-derived DNA test.
- A retro-post hoc analysis of the original AREDS participants.
- An Increase in progression in patients with the CFH with ZN treatment.
- Maximum benefit of ZN treatment with ARMS2 risk genotype.
- Is testing predictive?

**Are genomic studies actionable?**

- Different genetic markers used in the 2 studies.
- Confounders not evaluated:
  - Age /Smoking / Obesity /Omega III / Sunlight etc.
  - 50,000 Twin Study / 6 countries in Science and Translational Medicine
- Do we deviate from NEI recommendations.

**AMD (Future Directions)**

- Excess CU ++
- Excess FE ++
- Excess CA ++
- Excess Sugar, HFCS
- Excess Fried Food in vegetable oil
- Excess N3 fats
- Drug Muggers + Stress & Hormonal changes
- Chronic ASA use
Thank you

The Omega – 3 Controversy

- Kimberly Reed, OD, FAAO

Let’s look a little closer......

- “No benefit with respect to all-cause mortality, heart attack, or stroke with omega-3 supplements”
- Meta-analysis
- 20 studies
- Almost 70,000 subjects
More questions than answers.....

- How sick were the participants?
- What formulation of omega-3’s were taken?
  - EE
  - FBO
  - FFA
  - rTG

rTG form appears to be better than EE

How much is enough?

- For most patients, 2000 mg of omega-3 EPA/DHA is required to surpass the 8% RBC saturation found to be beneficial in reducing C-V mortality
- HS-Omega-3 Index® (OmegaQuant, LLC)
- Shows whether patients are absorbing the omega-3’s from all sources
- AA/EPA, omega score, others
- 8% saturation of red blood cell membranes with omega 3 DHA+EPA

![Fish Oil Preparations](image)

![OMEGA3TEST](image)
Prospective cohort study, 2013
Mozaffarian et al, Annals Int Med 2013;158:515-525, NIH funded

- Conclusion: “Higher circulating individual and total O-3 PUFA levels are associated with lower total mortality, especially CHD death, in older adults
- 2692 U.S adults average age 74, without CHD, stroke, or heart failure at baseline
- Enrolled 1992, assessed through 2008
Mozaffarian et al, cont

- Extreme-quintile hazard ratios:
  - 0.83 (EPA)
  - 0.77 (DPA)
  - 0.80 (DHA)
  - 0.73 (total O-3 PUFA)

Mozaffarian et al, cont

- CHD deaths showed about a 50% lower risk across quintiles
- Individuals in the highest quintile of O-3 lived an average of 2.22 more years after age 65 than those in the lowest quintile

AREDS 2: The ‘experts’ summarize...

What????????

Putting this into the context of AREDS 2

- AREDS 2 found no significant benefit to supplementation with 1000 total mg EPA + DHA in progression to advanced AMD, in EE form
- Compliance was measured by pill count at follow up visits
- Compliance was defined as at least 75% of pills taken
  - 83-87% of patients complied
Rotterdam Study

- 2167 individuals
- Dietary intake, genetic variants
- Incident early AMD
- Significant risk reduction across several genotypes for zinc, beta-carotene, L/Z, and EPA/DHA intake

Reynolds, Rosner, Seddon
Ophthalmology 2013 May 1020-8

- Evaluated 2531 individuals from AREDS
- FFQ plus genotyping
- “increased self-reported dietary intake of omega-3 fatty acids is associated with reduced risk of GA and may modify genetic susceptibility for progression to GA”

What about prostate cancer?

- SELECT trial, 2013: high plasma LCPUFA increases risk of prostate cancer
- ATBC Study, 2003: no association
- Chua, 2013, meta analysis: high DPA reduces total prostate cancer risk, high EPA and DHA might increase high grade prostate tumor risk

What about prostate cancer?

- Chua, 2012, meta analysis: intake of n-3 and n-6 PUFA does not significantly affect the risk of prostate cancer. High intake of ALA may reduce risk of prostate cancer but LCPUFA does not have a significant effect.
One more factor to consider....

• Virtanen JK et al, Diabetes Care October 3 2013
• “Men in the highest vs the lowest serum EPA+DPA+DHA quartile had 33% lower multivariate-adjusted risk for type 2 diabetes” (CI 95%, P-trend 0.01)

What’s the bottom line?

• Intake of good quality, preferably marine-sourced, TG formulated omega-3 fatty acids is most beneficial at or above 2,000 mg per day
• Prostate cancer association is riddled with conflicting data
  – Established risk factors remain high PSA, family history, black race, age, obesity

Vitamin D

What defines vitamin D deficiency?

We are measuring 25-hydroxy vitamin D3 (25-OH-D)
Optimal levels 30-40 + ng/dL
No adverse effects up to 70 ng/dL
Vitamin D deficiency is linked to:

- Heart disease
- Stroke
- Hypertension
- Autoimmune diseases
- Chronic pain
- Osteoarthritis
- Osteoporosis
- Obesity/Overweight
- Complications in autoimmune diseases
- Muscle weakness
- Periodontal disease
- Reduced cognition
- Birth defects
- Reduced immune function
- Depression
- Diabetes
- ......

Mechanisms of D3 in ocular pathways

- Genetic expression modifier
- Insulin-regulating promoter
- Anti-inflammatory mediator
- Immunoregulator
- Glucose regulator
- VEGF expression modifier
- Endothelial cell function improver

Ocular consequences of Insufficiency or deficiency in D3/receptor abnormalities:

- AMD
- Autoimmune related uveitis
  - E.g. Bechet’s disease, Ankylosing spondylitis, lupus
- Vogt-Koyanagi-Harada (VKH) disease development
- Optic neuritis, with or without MS
- Diabetic retinopathy

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<th>Test</th>
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<th>Units</th>
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<tr>
<td>25-hydroxyvitamin D</td>
<td></td>
<td>mmol/L</td>
<td>75-250</td>
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</table>

- Deficient: <25
- Insufficient: 25-74
- Optimal: 75-250
- Excessive: >250

Vitamin D helps regulate serum calcium and phosphorus levels by increasing intestinal absorption of calcium and stimulating tubular reabsorption of calcium.

Your results suggest that you are Vitamin D deficient. Vitamin D deficiency affects numerous functions in the body.

We recommend that you seek the advice of a medical practitioner.
Vitamin D and DR

- Vitamin D deficiency more common among Type 2 diabetics than non-diabetics
  - 22.9 vs 30.3 ng/mL
  - More than 75% of diabetics are vitamin D deficient
  - Diabetics with no eye disease have highest vitamin D levels
  - Diabetics with proliferative disease have lowest levels of vitamin D

VITAMIN D3 and GLAUCOMA

- The link of Vitamin D3 to glaucoma is associated with vascular perfusion issues as well as neuroprotection and the immune system
- There is even recent work suggesting topical vitamin D3 is of benefit lowering the IOP by increasing drainage in a primate model. *(Arch Biochem Biophys, 2012 Feb 1;518(1):53-60)*

http://www.eyelessons.com/articles/item/nutrition-and-behavior-as-it-applies-to-glaucoma

THE IMPACT OF THE PATIENT CHARACTERISTICS ON THE EFFECT OF BIOAVAILABILITY FROM NUTRITION

LARRY J ALEXANDER OD FAAO

VITAMIN D3 and GLAUCOMA

- Obtain From Diet, Sunlight
- There is evidence to recommend supplementation of vitamin D3 beyond that obtained in the normal diet for minimizing the risk of glaucoma damage.
WHAT IS THE NEWEST TREATMENT FOR EXUDATIVE ARM?

Analysis of 600 cases with exudative central chorioretinopathy undergoing acupuncture therapy showed an overall results of cured or improved in 586 cases (97.66%) and unsatisfactory in 14 cases (2.34%).

THE PATIENT IS THE X-FACTOR
DEFINITION: a variable in a given situation that could have the most significant impact on the outcome.

WE ARE ALL DIFFERENT
WE ALL REACT DIFFERENTLY TO DIFFERENT STIMULI BASED ON OUR PROGRAMMING

THE GENOMIC IMPACT ON ASSIMILATION AND UTILIZATION OF COMPONENTS OF THE DIET...HOW IMPORTANT IS IT?
NEGATIVE EFFECTS OF GREAT NUTRITION

OXALATES

- SOURCES
  - RHUBARB
  - SPINACH
  - BEET GREENS
  - OKRA
  - PARSLEY
  - LEEKS
  - COLLARD GREEN

- THERE ARE A FEW, RELATIVELY RARE HEALTH CONDITIONS THAT REQUIRE STRICT OXALATE RESTRICTION. THESE CONDITIONS INCLUDE ABSORPTIVE HYPERCALCIURIA TYPE II, ENTERIC HYPEROXALURIA, AND PRIMARY HYPEROXALURIA.

NUTRITION AND OCULAR DISEASE

IS THERE ABSOLUTE PROOF?

Osteo Bi-Flex helps revitalize your joints.

Oral Glucosamine Supplements as a Possible Ocular Hypertensive Agent.
Murphy RK, Ketzler L, Rice RDE, et al. Study finds that supplementation with glucosamine may increase intraocular pressure in some patients and discontinuation may result in reversal. This was suggested to be associated with glycosaminoglycans (GAGS) and the effect is similar to corticosteroid response. Monitoring of patients supplementing with glucosamine is in order. [JAMA Ophthalmol, 2013;131(7):950-957.]
SMOKING AND OCULAR DISEASE

http://www.eyelessons.com/articles/item/is‐there‐a‐significant‐relationship‐of‐smoking‐and‐ocular‐disease

IS THERE ABSOLUTE PROOF?

OBESITY AND OCULAR DISEASE

http://www.eyelessons.com/articles/item/is‐there‐a‐significant‐relationship‐of‐smoking‐and‐obesity‐to‐glaucoma

IS THERE ABSOLUTE PROOF?

The Eye on Fire

Modulating The Morbidity of Inflammation

Prospective Study of Inflammatory Biomarkers and Risk of Diabetic Retinopathy in the Diabetes Control and Complications Trial ONLINE FIRST. Rajeev H. Muni, MD, MSc, FRCSC; Radha P. Kohly, MD, PhD, FRCSC; Eudocia Q. Lee, MD, MPH; JoAnn E. Manson, MD, DrPH; Richard D. Semba, MD, MPH; Debra A. Schaumberg, ScD, OD, MPH


After adjusting for known risk factors, increasing quintiles of baseline high-sensitivity C-reactive protein (hsCRP) level may be associated with higher risk of incident CSME and macular hard exudates in the DCCT cohort. Circulating levels of intercellular adhesion molecule 1 (ICAM-1) may also be associated with the development of retinal hard exudates.
Overall, these pooled findings from 5 prospective cohorts add further evidence that elevated levels of hsCRP predict greater future risk of AMD. This information might shed light on underlying mechanisms and could be of clinical utility in the identification of persons at high risk of AMD who may benefit from increased adherence to lifestyle recommendations, eye examination schedules, and therapeutic protocols.

"After matching for age and controlling for cigarette smoking, individuals with baseline hsCRP levels more than 3 mg/L had a 50% increased risk of incident AMD and a nearly 2-fold increased risk of neovascular AMD," the authors write.

**WHAT KIND OF BEHAVIOR MODIFICATION AND SUPPLEMENTS MODULATE INFLAMMATION**

- Employ an Anti-Inflammatory Diet
- Stop smoking
- Lose Weight
- Exercise
- Get Plenty of Sleep
- Balance Omega 6 Intake With Omega 3 Supplementation
- Check Vitamin D Levels and Consider Supplementation
- Consider the Benefits of a High Quality Vitamin Supplement
- Consider Curcumin Supplementation and Other Immune System Modulators Like Colostrum

**CONTROL OF BIOAVAILABILITY**

- TAKEN WITH FOODS? WHAT ABOUT CERTAIN DIETS?
- WHAT IS LIVER FUNCTION?
- IS THE GALL BLADDER WORKING?
- WHAT IS KIDNEY FUNCTION?
- IMPACT OF BARIATRIC SURGERY?
- WHAT IS THE DELIVERY SYSTEM?

**CONTROL OF BIOAVAILABILITY**

http://www.totalhealthinstitute.com/digestive-disorders/

- WHAT ABOUT THE INFLAMED GUT?
  - 10% OF AMERICANS OVER 40 HAVE DIVERTICULITIS
  - 10% OF AMERICANS HAVE GERD
  - 20-25% OF AMERICANS HAVE IRritable BOWEL SYNDROME
  - 90% OF AMERICANS HAVE LEaky GUT SYNDROME
  - OVER 40% OF AMERICANS REPORT MORE THAN ONE DIGESTIVE SYMPTOM/MONTH
  - 90% OF AMERICANS REPORT CONSTIPATION
REMEMBER IF THIS DOESN’T WORK
SUPPLEMENTATION WON’T WORK
INFLAMMATION IS THE CAUSE

ISSUES OF COST AND BIOAVAILABILITY

HOW CAN YOU GET THE MOST BANG FOR THE BUCK WHILE USING THE BEST OF INGREDIENTS? THE LEAST EXPENSIVE APPROACH IS TO FIRST MODIFY BEHAVIOR THAT LENDS TO THE WORSENING OF OCULAR DISEASE. THEN DESIGN THE SUPPLEMENT USING WHAT IS ABSOLUTELY INDICATED USING A GOOD MULTIVITAMIN TO COMPLETE THE PACKAGE. THEN MAKE IT READILY BIOAVAILABLE...SUBLINGUAL.

WHAT IS THE $$$$ THRESHOLD FOR THE PATIENT?
• $5 TO $10/DAY TO SMOKE
• $5 TO $10/DAY TO DRINK
• $5/DAY FOR STARBUCKS
• $1/DAY FOR NUTRITIONAL SUPPLEMENTS
• GOOD HEALTH.....PRICELESS AS LONG AS IT IS UNDER $1/DAY

THEN WE HAVE THE ISSUE OF CHOKING TO DEATH FROM ASPIRATION OF A PILL
R.I.P
“DON’T JUST STAND THERE LOOKIN AT ME”
“I AM HERE BECAUSE OF AN OMEGA 3”

THE POTENTIAL EFFECTS OF SUPPLEMENTS??? WHICH ONES???

IS THERE ABSOLUTE PROOF?