

THE ROLE OF NUTRITION IN OCULAR DISEASE



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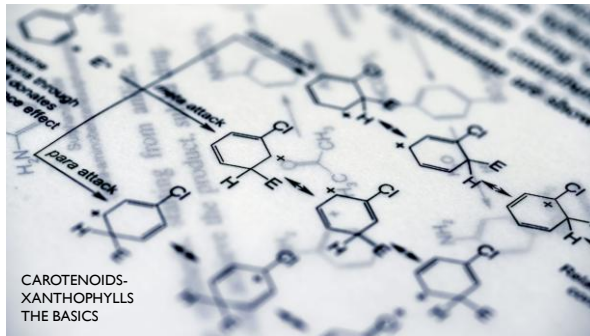
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DISCLOSURE

- Sanofi Speaker
- Innova System Consultant
- EyePromise Employee

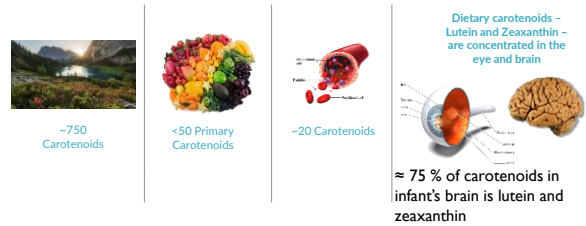
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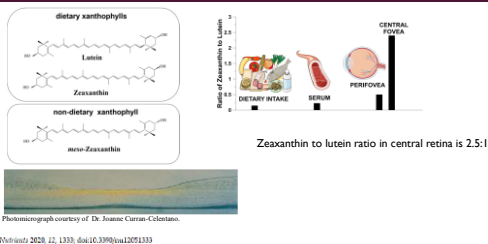
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WHILE ~750 CAROTENOIDS ARE FOUND IN NATURE, ONLY TWO ARE CONCENTRATED IN THE RETINA



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CAROTENOIDS IN RETINA-XANTHOPHYLLS



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MACULAR XANTHOPHYLLS

- Two dietary carotenoids – lutein and zeaxanthin – make it to all over the body – eyes, brain, adrenal glands, skin.
- Only in the eye- RPE65 isomerase converts lutein to meso-zeaxanthin.
 - So don't need Meso if you have Lutein in diet
 - Everyone has it RPE65 if they have a functional retina that can see
 - In advanced stages of the disease if the RPE is broken down, lutein may have a tough time converting to meso-zeaxanthin but zeaxanthin is still absorbed
- Meso-zeaxanthin is not found in common foods – it is found in shrimp shells, turtle fat, and fish skin.

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CAROTENOIDS FOOD SOURCES

Foods	Serving Size	Lutein + Zeaxanthin Content (mg)
Spinach, frozen (cooked)	1 cup	29.8
Kale, frozen (cooked)	1 cup	25.6
Swiss chard (cooked)	1 cup	11.0
Collard greens, frozen (cooked)	1 cup	8.9
Summer squash (cooked)	1 cup	4.0
Peas, frozen (cooked)	1 cup	3.8
Brussel sprouts, frozen (cooked)	1 cup	2.4
Broccoli, frozen (cooked)	1 cup	2.0
Edamame, frozen	1 cup	1.6
Sweet yellow corn (boiled)	1 cup	1.5
Asparagus (boiled)	0.5 cup	0.7
Avocado, raw	1 medium-size	0.4
Egg yolk, raw	1 large	0.2



Meso-zeaxanthin is not found in common food : in shrimp shells, turtle fat, and fish skin

Lein, D.W., Gierhart, D.L., Davey, P.G. A Systematic Review of Carotenoids in the Management of Diabetic Retinopathy. *Nutrients* 2021, 13, 2441. <https://doi.org/10.3390/nu13072441>

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Review

Why is Zeaxanthin the Most Concentrated Xanthophyll in the Central Fovea?

Justyna Widomska ^{1,*}, John Paul SanGiovanni ^{1,2} and Witold K. Subczynski ¹



- Very potent antioxidant-particularly in region of high oxygen tension and metabolism compared to lutein
- Zeaxanthin structure more stable in the lipid bilayer membranes
- Zeaxanthin is less predisposed to destruction than lutein when counteracting oxygen singlets

Nutrients 2018, 10, 1001. <https://doi.org/10.3390/nu10011001>

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CAROTENOIDS INFLUENCE VISUAL FUNCTION



Optical mechanisms

- Glare Disability,
- Color Contrast
- Visual Range
- Contrast Sensitivity



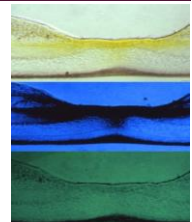
Biological mechanisms

- Glare Recovery
- Neural Efficiency
- Biomarker for Sleep Issues
- Systemic Diseases

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MEASUREMENT OF MACULAR PIGMENT OPTICAL DENSITY

- Heterochromatic flicker Photometry- principle
- Macular pigment absorbs blue light (not green light)
- More macular pigment = longer time you see flicker
- Results are quantified via software



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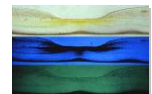
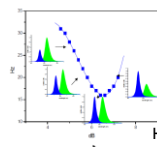
WHY MEASURE THE MACULAR PIGMENT?

- Can predict your levels of carotenoid in brain!
- Is an indicator of health
- Is an indicator of eyes ability to fight disease
- Aids in evaluating benefits of supplements
- Best indicator of digital eye strain/computer vision syndrome
- Indicator of sleep health
- Blue light protection
- Because you need baseline!
- Do you expect to do blood work to lower a l.c. cholesterol?
- Baseline data to know current status.
- Know what and how much is needed.
- Measure improvement
- Keep people compliant when they see their "eye health numbers" improve

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(SIMPLE EFFICIENT ,APPROX 2 MINUTE TEST)

Centre Flickering Target



Heterochromatic flicker photometry is the most common form of technique used to measure MPOD. It has excellent correlation with brain levels of carotenoids.

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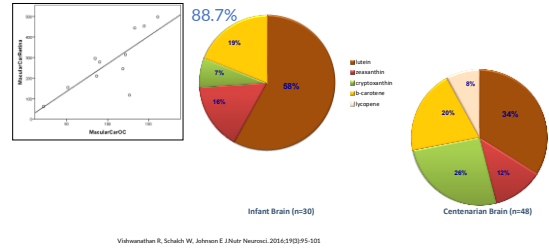
- Is it easy? Yes
- Do I need to perform in both eyes? No
- How long does it take? 2 minutes for testing
- Dominant eye? Any eye
- Can it measure changes? Yes



Davey PG et al., *Clin Ophthalmol*. 2016 Aug 29;10:1671-8. doi: 10.2147

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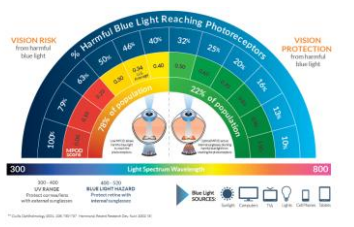
MPOD is a neural biomarker



Vishwanathan R, Schulz W, Johnson E. *J Nutr Neurosci*. 2016;19(3):95-101

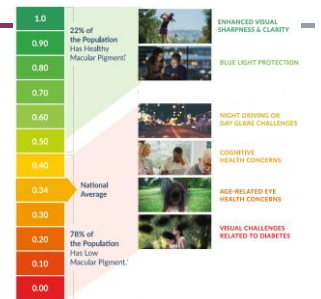
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HOW IS AMERICA DOING?



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78%
Of The US Is
Below The
Optimal
MPOD Score
of 0.50

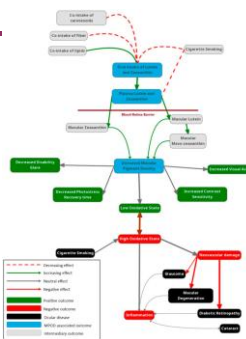


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MPOD MODEL OF CONTROLLING INFLAMMATION IN THE EYE

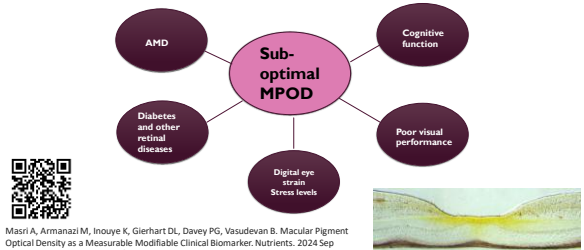


Masri A, Armanazi M, Inouye K, Gierhart DL, Davey PG, Vasudevan B. Macular Pigment Optical Density as a Measurable Modifiable Clinical Biomarker. *Nutrients*. 2024 Sep 27;16(19):3273. doi: 10.3390/nu16193273. PMID: 39408240; PMCID: PMC11478551.



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MPOD IS A BIOMARKER



Masri A, Armanazi M, Inouye K, Gierhart DL, Davey PG, Vasudevan B. Macular Pigment Optical Density as a Measurable Modifiable Clinical Biomarker. *Nutrients*. 2024 Sep 27;16(19):3273. doi: 10.3390/nu16193273. PMID: 39408240; PMCID: PMC11478551.

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IMPORTANCE OF CAROTENOIDS IN DEVELOPMENTAL YEARS

REVIEW

Possible influences of lutein and zeaxanthin on the developing retina

J Paul Zimmer¹Billy R Hammond Jr²¹Wright Nutrition, Clinical Nutrition Research, Collegeville, PA, USA,
²Vision Science Laboratory, University of Georgia, Athens, GA, USA

Abstract: The carotenoids lutein and zeaxanthin (LZ) are found throughout the central nervous system but reach their highest concentration within the macular region of the primate retina where they are commonly referred to as the macular pigments. Although LZ are a major integral feature of the central force, no information currently exists regarding the effects of variability in the concentration of these pigments on the developing retina. In particular, the long term effects of very low levels of macular pigment are not known and potentially meaningful. Macular pigment levels depend upon dietary intake since LZ cannot be synthesized *de novo*. **Low intake of LZ** (eg, infants receiving unfortified infant formulas or breast milk from mothers with low carotenoid status) would be expected to have considerably lower macular pigment compared with infants with high LZ intake (eg, breast-fed infants with mothers on carotenoid-rich diets). In this paper we discuss possible **implications** of this difference and the available evidence suggesting that LZ **could influence the developing visual system**.

Keywords: lutein and zeaxanthin, carotenoids, macular pigment, infant



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The Journal of Nutrition 153 (2023) 2205–2215



JN THE JOURNAL OF NUTRITION

journal homepage: <https://jn.nutrition.org/>

Nutrient Physiology, Metabolism, and Nutrient-Nutrient Interactions

Systemic Effects of Prenatal Carotenoid Supplementation in the Mother and her Child: The Lutein and Zeaxanthin in Pregnancy (L-ZIP) Randomized Trial —Report Number 1

Emmanuel K. Addo^{1,2}, Susan J. Allman¹, Ranganathan Arunkumar¹, Joanna E. Gorka¹, Deborah Y. Harrison¹, Michael W. Varner¹, Paul S. Bernstein^{1,2,*}

Conclusion: Prenatal carotenoid supplementation significantly increased maternal and infant systemic (skin and serum) carotenoid status, which may benefit pregnant women and their infants' health. This trial was registered at clinicaltrials.gov as NCT03750968.

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Ocular Effects of Prenatal Carotenoid Supplementation in the Mother and Her Child: The Lutein and Zeaxanthin in Pregnancy (L-ZIP) Randomized Trial - Report Number 2

Emmanuel K. Addo, OD,^{1,2} Joanna E. Gorka, BS,¹ Susan J. Allman, CCRC,¹ Deborah Y. Harrison, MSc,¹ Mohsen Shafizadeh, PhD,¹ Robert O. Hoffman, MD,¹ M. Elizabeth Harnett, MD,¹ Michael W. Varner, MD,¹ Paul S. Bernstein, MD, PhD^{1,2}

Conclusion: Prenatal carotenoid supplementation significantly increased maternal and infant systemic carotenoids and caused a pattern of increased infant ocular carotenoid status, which may benefit both mothers and their infants' ocular development and function. This study provides important data to design and power a future multicenter study of prenatal carotenoid supplementation in higher-risk pregnancies.

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Maternal Intake of Lutein and Zeaxanthin during Pregnancy Is Positively Associated with Offspring Verbal Intelligence and Behavior Regulation in Mid-Childhood in the Project Viva Cohort

Haya A. Mahdawi¹, Karim M. Saadouni², Tamara M. Kozak³, Elizabeth J. Johnson⁴¹Wayne J. Miller School of Medicine, Wayne State University, Detroit, MI, USA; ²Department of Pediatrics, Wayne State University School of Medicine, Detroit, MI, USA; ³Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI, USA; ⁴Department of Psychology, Wayne State University School of Medicine, Detroit, MI, USA

Conclusions: Higher maternal LZ intake during pregnancy was associated with better offspring verbal intelligence and behavior regulation ability in mid-childhood, suggesting a potential benefit during prenatal development. We did not find a benefit of higher maternal LZ intake on other child cognitive or behavioral outcomes. Project Viva is registered at clinicaltrials.gov as NCT02820402. *J Nutr* 2021;00:1–13.

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Original Article

Macular pigment optical density is positively associated with academic performance among preadolescent children

Sasha M. Gorman¹, Nauman A. Khan², Anne M. Wills, Lauren B. Rame, Christopher Macdonald, Neal R. Cohen³

Page 103-108 | Published online 22 May 2015

Results: The regression analyses revealed that MPOD improved the model, beyond the covariates, for overall academic achievement ($\Delta R^2 = 0.10$, $P < 0.01$), mathematics ($\Delta R^2 = 0.07$, $P = 0.02$), and written language composite standard scores ($\Delta R^2 = 0.15$, $P < 0.01$).

Discussion: This is the first study to demonstrate that retinal L and Z, measured as MPOD, is positively related to academic achievement in children, even after accounting for the robust effects of IQ and other demographic factors. These findings extend the positive associations observed between MPOD and cognitive abilities to a pediatric population.

AMD CLINICAL SCENARIOS

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Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration
The Age-Related Eye Disease Study 2 (AREDS2)
Randomized Clinical Trial

JAMA. 2013;309(19):2005-2015.
Published online May 5, 2013. doi:10.1001/jama.2013.4997



No true placebo- patients got AREDS formula



Addition of lutein (10 mg)+zeaxanthin (2mg) favored treatment and can safely be used in past smokers



More lung cancer was noticed in β -carotene group compared to no β -carotene in current or past-smokers

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CAN CAROTENOIDS BENEFIT ALL STAGES OF AMD AND AT RISK POPULATION?

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antioxidants

Systematic Review A Systematic Review of Carotenoids in the Management of Age-Related Macular Degeneration

Drake W. Lim^{1,2}, Pinakin Gurnani Davey^{1,2,3}, Dennis L. Gierhart² and Richard B. Rosen³

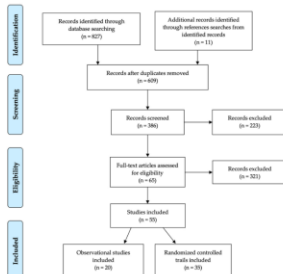


There is robust evidence all stages of AMD are helped by carotenoid vitamin therapy



Antioxidants 2021, 10, 1255. <https://doi.org/10.3390/antiox10081255>

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SUMMARY OF BENEFITS OF CAROTENOIDS IN AMD

Increase in serum levels

Increase in MPOD

Enhanced central retinal functions mfERG

Slight benefits to BCVA

Contrast improvements

Glare improvements

Mesopic vision improvements

Risk reduction to progression

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CASE 1

- Age 45, Vision 20/20 OU Family history of AMD. Ocular health normal, Fundus normal
- MPOD testing 0.22
- What next?

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CASE 2

- Age 55 Vision 20/20 OU Family history of AMD. All ocular health normal except fundus OU small hard drusen OU
- MPOD testing 0.41
- What next?
- Would your management be different if MPOD 0.55 Why or Why not ?

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WHAT CAN WE DO DIFFERENT THAN AREDS?

Testing

- Measure MPOD
- Measure functional tests
 - Contrast sensitivity
 - Color Contrast
 - Glare function

Management

- More amounts of carotenoids
- NSF certification
- Omega-3 Enhances carotenoid absorption
- Measure baseline MPOD Check it every 3 months Monitor compliance Monitor uptake
- Check Functional vision tests Monitor improvement

MPOD values greater than 0.5 du
If baseline is already at .5 or higher increase it by 0.15 du

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SCREEN TIME
STRESS AND
COGNITIVE
PERFORMANCE

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FRONTIERS IN NUTRITION

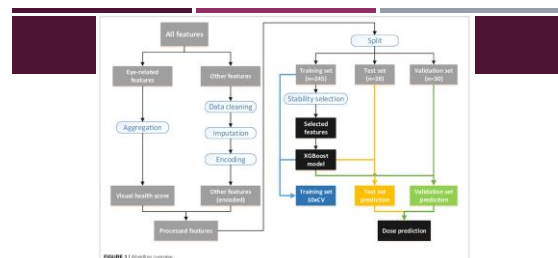
A Machine Learning Based Dose Prediction of Lutein Supplements for Individuals With Eye Fatigue

Juntao Kan^{1*}, Ao Li^{2†}, Hong Zou², Liang Chen¹ and Jun Du^{1*}

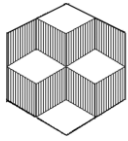
¹Nutrilite Health Institute, Shanghai, China, ²Department of Bioinformatics, WUW NextCODE Genomics, Shanghai, China

November 2020 | Volume 7 | Article 577903

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■ Visual health score (VHS) was a composite score developed from 4 most correlated/predictive parameters

1. Total score of eye fatigue,
2. Visuognosis persistence,
3. **Macular pigment optical density (most predictive)**
4. Schirmer's test

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SCREEN TIME ISSUES- PREDICTION AND PRECISION NUTRITION

Most individuals
67.24% need high
dose of carotenoids –
14 mg lutein
equivalent

29.31% may take a
lower dose – 10 mg
lutein equivalent

3.45% cannot be
helped

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MANAGEMENT OF DIGITAL EYE STRAIN

- Refraction
- Dry eye issue
- Accommodation / convergence
- Ergonomics
 - Regular break
 - Blinking
 - Working distance
 - Light levels

MPOD is low
Need at least 13 mg of
carotenoids probably 24
mg/day for 6 months to year

Increase it to 0.5 du or higher
If at 0.5 increase 0.15 du



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CAN NUTRITION PROVIDE SIGNIFICANT DRY EYE RELIEF



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OMEGA -3 AND DRY EYE

Journal of
Clinical Medicine

MDPI

Systematic Review Efficacy of Omega-3 Intake in Managing Dry Eye Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Wei-Kiang Wang¹ and Mei-Lan Ko^{2,3,*}

Based on the evidence, omega-3 FAs effectively reduce DED symptoms, especially in high doses, for a long duration, and with increased EPA levels. However, given the heterogeneity in study results and diverse patient characteristics, caution is needed in generalizing these findings. In conclusion, omega-3 FA supplementation is still recommended for DED management in clinical settings.

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SOME BENEFITS OF OMEGA 3

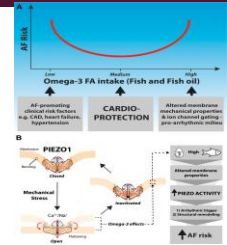
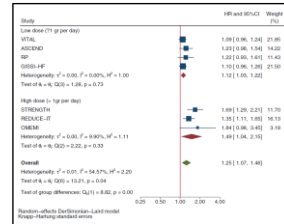
LOW OMEGA 3
INCREASED RISK OF CORONARY ARTERY DISEASE
RISK OF HTN
INCREASED RISK OF MORTALITY
DRY EYE

SO WHAT DOSE IS GOOD FOR YOU?



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IS THERE ANY POTENTIAL HARM TO A HIGH-DOSE OMEGA-3 SUPPLEMENT?



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Clinical Perspective

What Is New?

- In this updated meta-analysis of 7 randomized controlled trials including **81,200 patients**, marine ω -3 fatty acid supplementation was associated with a significant increased risk of atrial fibrillation (AF) compared with placebo.
- The incremental risk of AF associated with ω -3 fatty acid appeared to be greater in trials testing **>1 g/d** of ω -3 fatty acid supplementation.

What Are the Clinical Implications?

- The **potential risk of developing AF** should be discussed with the patients when prescribing marine ω -3 supplementation, especially when prescribing a higher dosage.
- Postmarketing surveillance for AF along with systematic ascertainment of AF outcomes in future trials of marine ω -3 supplementation will be needed to better define the risk-benefit ratio across ω -3 formulations.

ORIGINAL RESEARCH ARTICLE

Effect of Long-Term Marine ω -3 Fatty Acids Supplementation on the Risk of Atrial Fibrillation in Randomized Controlled Trials of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis

Ben Smeets MD, MPH, Luc D'Amico MD, PhD, MPH, Oscar T. Alvarado MD, Nancy R. Cook, PhD, John S. Wiggins MD, DPH, Christine M. Albert MD, MPH

IS HIGH OMEGA -3 OUR ONLY OPTION?

- Omega -3 important anti inflammatory. Vitamin E along side works synergistically
- Vitamin A is crucial for epithelial integrity and mucin
- Turmeric is an excellent anti inflammatory inhibits MMPs
- Systemic inflammation can also be an important issue
 - Green tea
 - Vitamin D
 - Mixed Tocotrienols/Tocopherols

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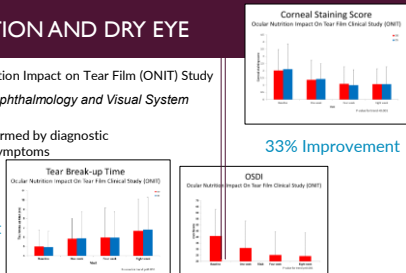
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NUTRITION AND DRY EYE

The Ocular Nutrition Impact on Tear Film (ONIT) Study

- Advances in Ophthalmology and Visual System**
- 8 weeks
- Dry eye confirmed by diagnostic markers and symptoms

45% Improvement



Mulligan J, Davis RL, Townsend W, et al. The ONIT study: ocular nutrition impact on tear film. *Adv Ophthalmol Vis Syst*. 2015;2(2):55-61. DOI: 10.1155/2015/2015020058

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DIABETES AN ENDEMIC CONDITION?

Diabetes 30.3
million diabetes or
84 million
prediabetes in USA

4.2 million adults
have DR and
655,000 had vision-
threatening DR.

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Retina takes a good 10-15 years of beating

Elevated blood glucose is the culprit

DIABETIC EYE
DISEASE

Metabolic control is a must

Furthermore, there is a big body of literature
that MPOD is depleted in diabetics

Can we do anything with nutritional
supplements without changing A1c?

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nutrients MDPI

Review
A Systematic Review of Carotenoids in the Management of Diabetic Retinopathy

Duke W. Lam ^{1,†}, Dennis L. Gierhart ² and Pinakin Gurnant Darvy ^{1,*}

of DR, specifically in patients with type 2 or poorly managed type 1 diabetes. Meanwhile, early interventional trials with dietary carotenoid supplementation show promise in improving their levels in serum and macular pigments concomitant with benefits in visual performance. These findings provide a strong molecular basis and a line of evidence that suggests carotenoid vitamin therapy may offer enhanced neuroprotective effects with therapeutic potential to function as an adjunct nutraceutical strategy for management of diabetic retinopathy.

Nutrients 2021, 13, 2441. <https://doi.org/10.3390/nu13072441>

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THE DIABETES VISUAL FUNCTION SUPPLEMENT STUDY (DIVFUSS)

The Diabetes Visual Function Supplement Study (DIVFUSS) was designed to test the effects of a novel, multi-component nutritional supplement on visual function. Participants included patients with both type 1 and type 2 diabetes.

- British Journal of Ophthalmology
- six-months
- placebo controlled

CLINICAL STUDY RESULTS WITH DVS

Randomized, placebo-controlled study demonstrated:

- 21% improvement in color vision**
- 19% improvement in contrast sensitivity (easier to read link on an newspaper)**
- 12% improvement in central and peripheral vision**

Carotenoid vitamin supplement benefits individuals with diabetes and diabetic eye disease



BJO 2016 Feb;100(2):227-34.

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CASE: DIABETES EXAM- WHAT'S YOUR DIAGNOSIS?

Courtesy of Pinakin Darvy OD, PhD

- 49 YO Asian male,
- HO DM type 2, 10 years "recently" not compliant with meds
- HO HTN x10 years
- Restarted metformin recently but has side effect of diarrhea
- Blood pressure today 168/96

What was his MPOD 0.28
Dominant eye

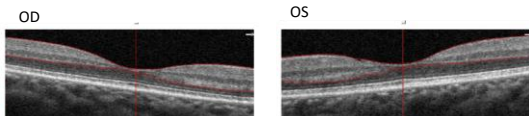
Diabetic Eye Exam Standard of Care



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Patient worried enough about change in vision that he returned
for 1 Month follow-up visit

Foveal Avascular Zone measurements OCT-A done 1 month later



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WHAT WOULD BE A GOOD PLAN FOR HIM

- Adding MPOD testing
- Revealed changes from early diabetic eye disease which otherwise would have been missed
- Motivated patient to follow-up with 1 month visit
- Allowed for detailed discussion about diet, lower blood pressure
- Patient began diabetes nutritional supplements

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Communication

Night Vision and Carotenoids (NVC): A Randomized Placebo Controlled Clinical Trial on Effects of Carotenoid Supplementation on Night Vision in Older Adults

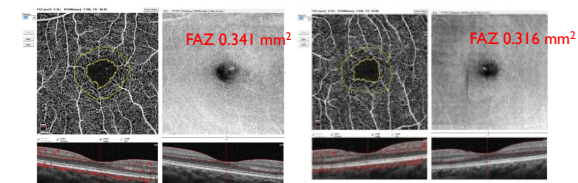
Stuart Richer ^{1,2,*}, Steven Novil ¹, Taylor Gullett ², Arni Dervishi ², Sherwin Nassiri ², Co Duong ², Robert Davis ³ and Pinakin Guvant Davey ^{4,*}

Aim:

Can carotenoid improve night vision and comfort in driving in individuals that complain of nighttime driving issues?



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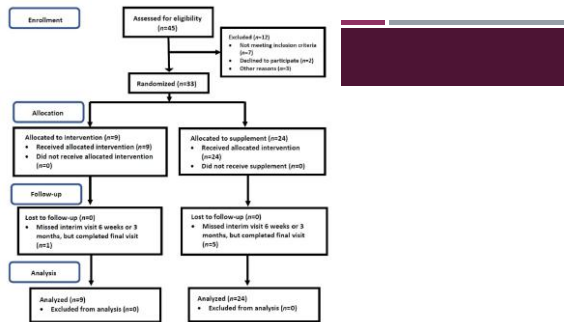
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NIGHT VISION AND CAROTENOIDS

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Active Ingredients	Amount per Serving
Zeaxanthin	14 mg
Lutein	7 mg
Vitamin A	2500 IU
Vitamin C	60 mg
Vitamin D	1000 IU
Vitamin E	60 IU
Vitamin B6	2 mg
Folic Acid	400 mcg
Vitamin B12	6 mcg
Zinc	15 mg
Selenium	70 mcg
Manganese	2 mg
Fish Oil	150 mg
Coenzyme Q10	15 mg
Bilberry	15 mg
Berry Anthocyanin Extract	15 mg
Alpha Lipoic Acid	10 mg
Mixed Tocopherols	6 mg

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RESULTS

- Improvements in contrast sensitivity with glare in both eyes
- Monocularly tested glare recovery time improved 2.76 and 2.54 s, respectively, ($p = 0.008$ and $p = 0.02$),
- decreased preferred luminance required to complete visual tasks
- Improvements in UFOV scores of divided attention ($p < 0.001$) and improved composite crash risk score ($p = 0.004$) were seen in the supplemented group.
- The placebo group remained unchanged.

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Dietary carotenoids related to risk of incident Alzheimer dementia (AD) and brain AD neuropathology: a community-based cohort of older adults

Chunghong Yuan,^{1,2,3} Hai Chen,¹ Yunni Wang,² Julie A Schneider,⁴ Walter C Willett,^{2,5,6} and Martha Clare Morris²

¹Department of Big Data and Health Science, Zhejiang University School of Public Health, Hangzhou, Zhejiang, China; ²Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA; ³Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; ⁴Frank Institute for Healthy Aging, Rush University Medical Center, Chicago, IL, USA; ⁵Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA; and ⁶Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA

927 participants (No AD) were followed up for 7 years- Rush Memory and Ageing project
AD neuropathy was assessed in 508 deceased participants

Results were controlled for Age, sex, education, cognitively stimulating activities, physical activities, Apolipoprotein

Conclusions: Our findings support a beneficial role of total carotenoid consumption, in particular lutein/zeaxanthin, on AD incidence that may be related to the inhibition of brain β -amyloid deposition and fibril formation.

Am J Clin Nutr 2021;113:200–208.

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GLOBAL SUMMARY



- It is tough to get perfect nutrition everyday.
- Nutritional supplements can be a reliable way of augmenting your diet.
- Carotenoids are important for vision
- Maybe even more for health than we thought!
- Measuring MPOD allows for a trackable measure in various health and disease states- compliance and bioavailability measure.
- An ounce of prevention...

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