Carotenoid Levels in Ocular Disease and Systemic Health

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September 10, 2022

Forum on Optometry

Mystic, CT

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Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

- The content of this activity was prepared independently by me - Dr. Caldwell
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Thank You for This Opportunity

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Agenda

Thanks for the Opportunity

- My ocular disease focus to prevention
- Ocular diseases from oxidative stress
- Evidence based medicine proves antioxidant intervention
- Measuring carotenoids
- Phospholipid bilayer membrane – damage and protection
- Partial versus total supplementation
  - Inner and outer retina
  - Ocular supplements or full body

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Ocular Disease Career

- OCT - Spectral domain
- OCT Angiography
- Visual Fields
- AMD, glaucoma, retinal degenerations, diabetic retinopathy
- Dark Adaptation

- Focusing on structure and function loss or damage
- Patients asking what about supplements
  - Reading about it on internet
- Promised I would do my due diligence

- Ocular disease optometrist to an Integrative Optometrist

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Patients Are Expecting

- Early detection
- Wellness
- Prevention

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Question?

- Who in here would consider themselves as an integrative optometrist?
- Who has done or recommended?
  - Supplements, vitamins, AREDS2
  - Omegas, EPA, DHA
  - Vital tears – ASED
  - Regener-Eyes
  - Amniotic membranes
  - CBD
  - Probiotics

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Allopathic vs Integrative Medicine

- "Allopathic medicine" is a term used for modern or mainstream medicine
  - Conventional medicine, mainstream medicine, Western medicine, biomedicine
  - Treating conditions and symptoms with its "opposite"
  - Health system in which medical doctors, nurses, pharmacists, and other healthcare professionals are licensed to practice and treat symptoms and diseases
  - Using medication, surgery, radiation, therapies, and procedures
- Complementary and integrative medicine are commonly used along with mainstream medicine
  - Homeopathy, naturopathy, chiropractic care, Chinese medicine
- Allopathic or modern medical schools have recently added more study and information on how food and nutrition can help prevent and treat disease
  - More education is being offered on integrative approaches and potential interactions with mainstream medicine

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Medical Practices

- Allopathic medicine
  - Western medicine
- Alternative "homeopathic"
- Functional
  - Medicine of why, treat the cause
- Integrative medicine
  - Complementary medicine - Eastern complimenting Western

What is integrative medicine?

The practice of integrative medicine refers to the **blending of conventional and evidence-based natural and complementary medicines and/or therapies with lifestyle interventions** to deliver holistic, patient-centred care.

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Chronic and Low-Grade Inflammation

Science has proven that chronic, low-grade inflammation can turn into a silent killer that contributes to cardiovascular disease, cancer, type 2 diabetes, diabetic retinopathy, cataracts, macular degeneration, and many other conditions

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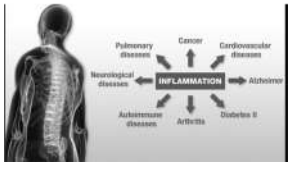
Chronic and Low-Grade Inflammation

Like cancers and other slow-burn diseases, identifying these conditions early can make the difference between full recovery or a dramatically reduced quality of life or even death (vision loss or blindness)



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"Choose Your Parents Wisely"

- This just isn't as true as it's used to be
- Lifetime health
  - 8% genetics "Picking your parents wisely"
    - DNA in our nucleus
      - Can't be influenced
  - 92% epigenetics
    - Lifestyle choices = we can influence
    - Turn on/off gene expression

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Biomarker

- Test that has meaning
- Biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.
- A biomarker may be used to see how well the body responds to a treatment for a disease or condition
- Blood pressure, blood work, heart rate, genetic testing, IOP

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Predictive Biomarker

- Used to identify individuals who are more likely to respond to exposure to a particular medical product or environmental agent
- The response could be a symptomatic benefit, improved survival, or an adverse effect
- A value that we can guide therapy around
  - HbAlc
  - C-Reactive Protein
  - Plasma Homocysteine
  - Vitamin D (25-HydroxyD)
  - Omega 3 index
  - Carotenoid

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Measure?

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Chronic and Low-Grade Inflammation

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DNA Sciences

- Genomics = all of our genes
- Genetics = individual genes

- Epigenetics – the study of how our cells control gene activity without changing the DNA
  - Internal and external environments

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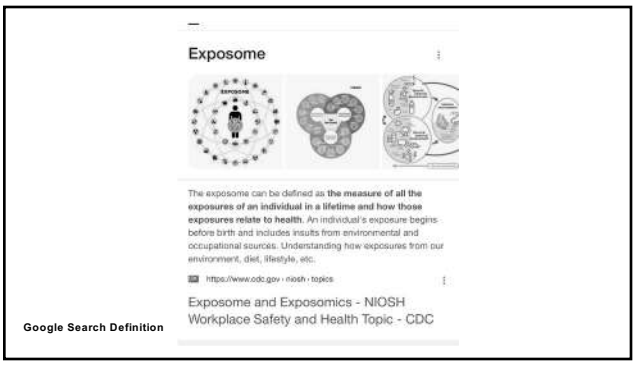

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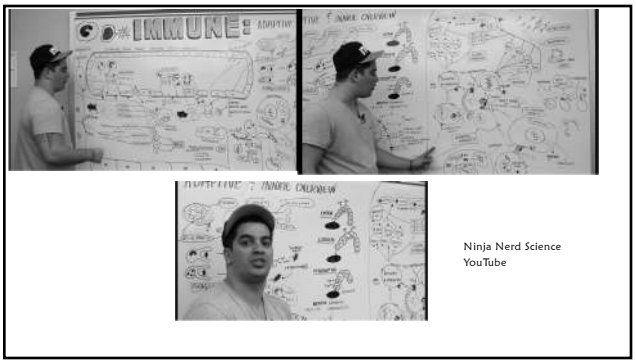

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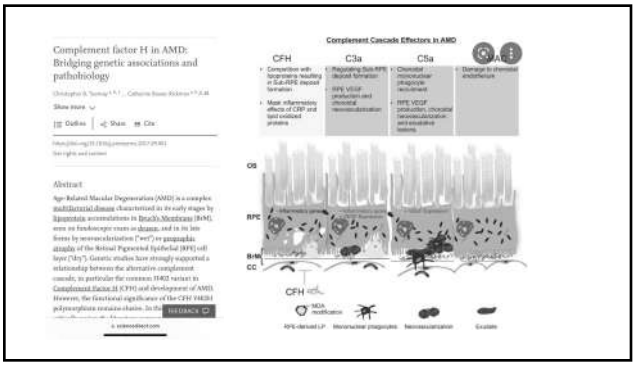

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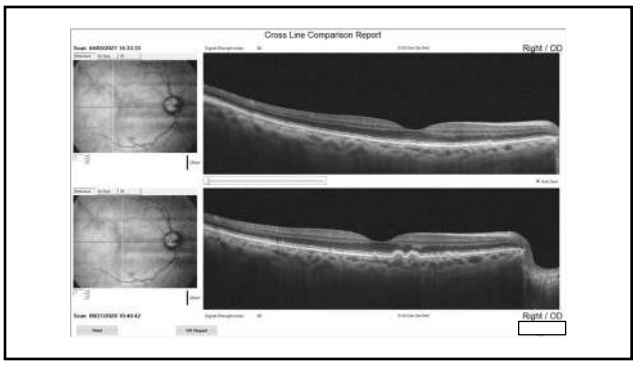

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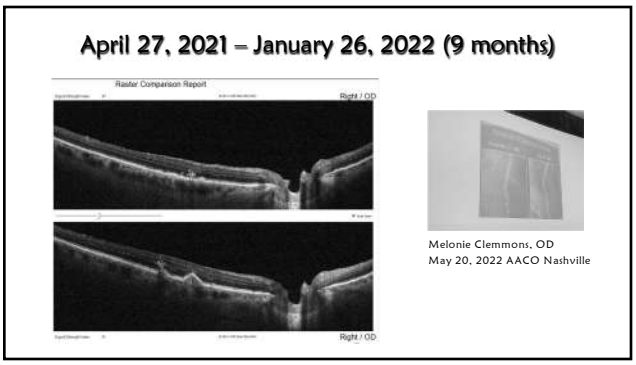

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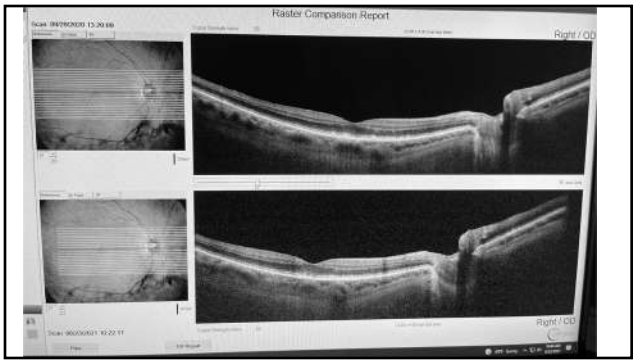

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Credit to: James LaValle, RPh, CCN

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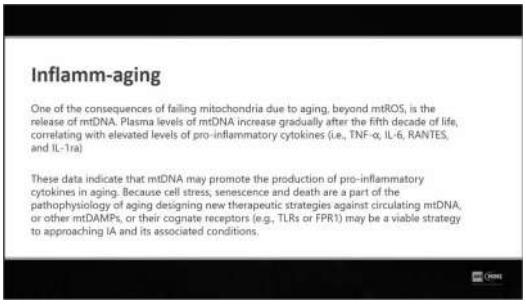

Credit to: Elroy Vojdani, MD - Dead Batteries: The Role of Mitochondrial Dysfunction in Immunological Decline - Emerging Diagnostic Tools and Nutraceutical Interventions

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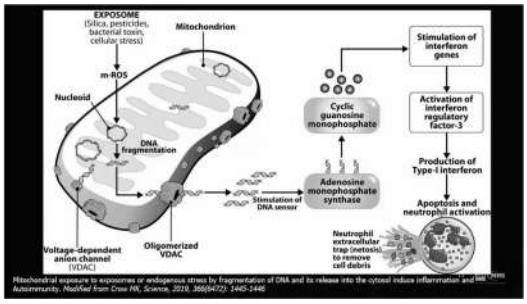

Credit to: Elroy Vojdani, MD - Dead Batteries: The Role of Mitochondrial Dysfunction in Immunological Decline - Emerging Diagnostic Tools and Nutraceutical Interventions

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Fun Facts I Have Learned About the Mitochondria

- Mitochondria produce energy from organic matter
- Live about 100 days
- They produce 90% of energy in the body
- In return they product 90% of the free radicals
- When they become dysfunction when get many clinical consequences
- Mitochondria are very sensitive to reactive oxygen and need antioxidant support
- Mitochondria are one of cellular organelles
  - Electron transport chain – uses co-enzyme 10, and many other micronutrients
  - Brain cell has 1-2 million/single neuron
  - Heart cell has 5,000/cell
  - Liver cell has 1000-2000/cell
  - Photoreceptors 498/cell
  - RPE cells >700/cell

The ellipsoid contains a densely-packed array of mostly elongated mitochondria arranged broadly parallel to the long axis of the photoreceptor. The cell contained **498 individual mitochondria**

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Question

- Do you agree that free radical formation is a progressive process that leads to cell damage or death?
  - Yes
  - No

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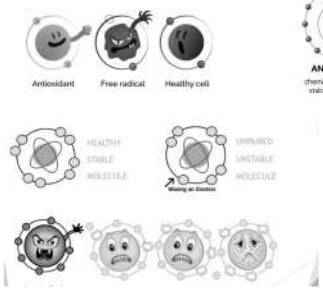
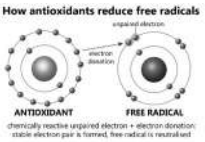
Free Radials and Antioxidants



How antioxidants reduce free radicals



chemically reactive unpaired electron + electron donation: stable electron pair is formed, free radical is neutralised

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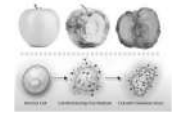
Oxidative Stress

- Small percentage of oxygen is not completely reduced
- Accumulation of free radicals
- Oxidative damage
- Oxidative stress
- Considered the starting of several diseases
- Responsible for epigenetic alterations
- Mitochondria – vulnerable
- Not going to make this apple new again
  - Prevention is the one of the best medicines



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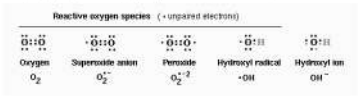
Free Radicals

- During metabolism the O_2 molecule splits and energy is released
  - Endogenous free radical formation
- Regain stability the free single oxygen atom (oxygen free radical) seeks and steals electrons from other molecules
  - Superoxide anion – will accept one electron
  - Peroxide – will accept two electrons
- These molecules can be proteins, lipids, and DNA
  - Proteins (enzymes) – kinases, phosphatases, and transcription factors



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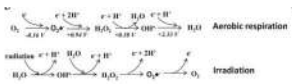
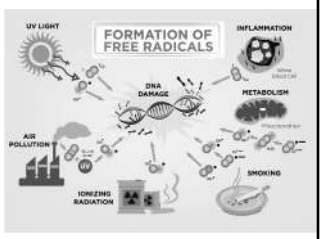
Endogenous and Exogenous Free Radial Formation





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Oh no

- Increasing exogenous free radicals
- Less antioxidant protection in our diet
- More bad and less good

Is an orange of the 1950's equivalent to 21 of today's oranges?

An orange from the 1950's was full of vitamin A, precious for our sight and our immune defenses. To attain the same amounts today, you would have to consume 21 of them. Onions and potatoes no longer contain any trace of it. The iron content in meat? Divided by 2. Calcium in broccoli? Divided by 4. To ingest the vitamin C contained in an apple from yesteryear, you would have to eat 100 today.

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The Equalizer

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October 23, 2021

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October 23, 2021

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M Lounge

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Nutritional Antioxidants

- Exogenous antioxidants
  - Tocopherols (E), ascorbic acid (C), carotenoids, ubiquinone, and polyphenols
- Well know antioxidants
  - Vitamin C, E, Beta-carotene, lutein, zeathanin, selenium, quercetin, and resveratrol
- Mechanisms of action;
  - Neutralize free radicals
  - Repair oxidized membranes
  - Decrease reactive oxygen species
  - Neutral reactive oxygen species

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Endogenous and Exogenous Antioxidants

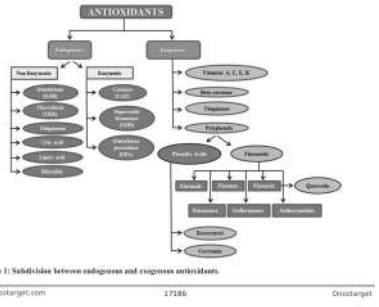

Figure 1: Subdivision between endogenous and exogenous antioxidants.

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Carotenoids

- Why do hear so much about carotenoids
- Melonie Clemmons, OD May 20, 2022 AACO Nashville

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Carotenoids

- Organic pigments produced by plants, algae, and bacteria
- Cannot be synthesized by the human body
  - Hydrophobic compounds
    - Important for the phospholipid bilayer
- 600 in nature – 50 human food chain – 15-20 human blood stream
- Macular carotenoids (L and Z) – highest concentration found in the human body
  - Diet derived
  - Henle fibers – between the inner and outer plexiform layers
  - Sequester or absorb blue light

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Question

- Do you measure carotenoid levels in your office?
  - Yes
  - No

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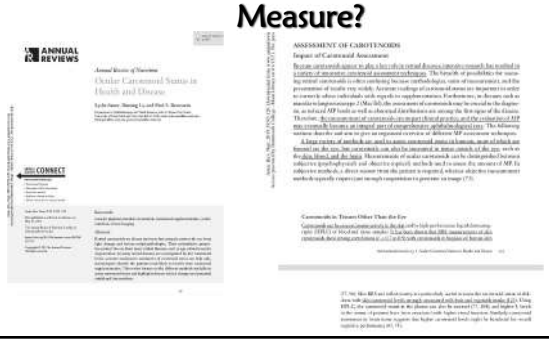
Measure?



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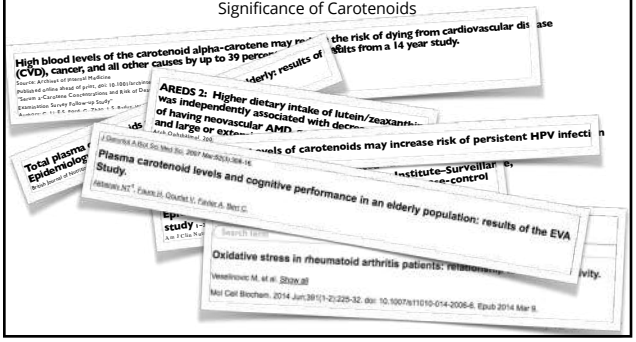
Significance of Carotenoids



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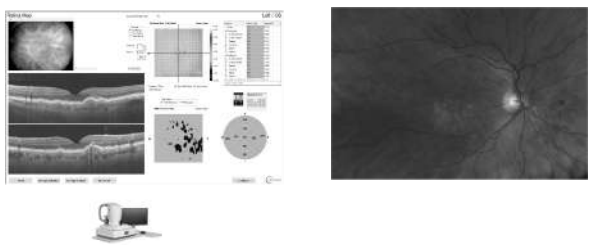
Oxidative Stress with Your OCT



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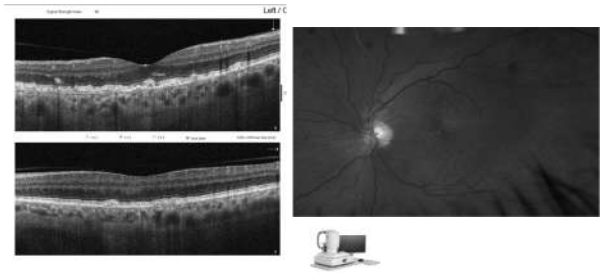
Oxidative Stress with Your OCT



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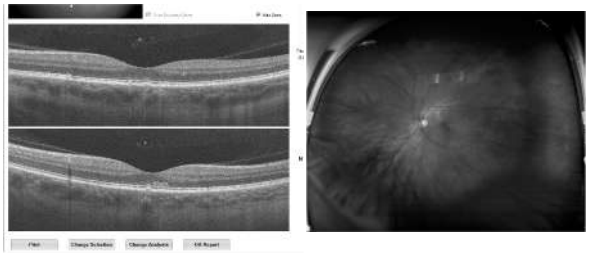
Oxidative Stress with Your OCT



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Healthy choriocapillaris, Bruch's, RPE, and Photoreceptors

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Cholesterol barrier deposited along Bruch's and RPE

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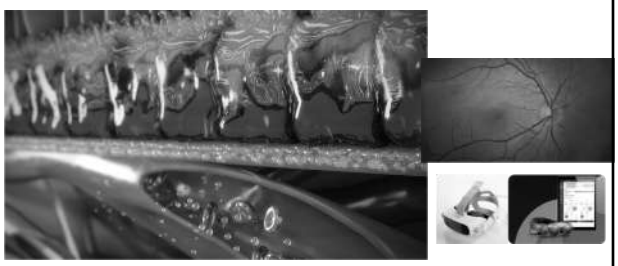
RPE Secretes even more cholesterol and degenerates



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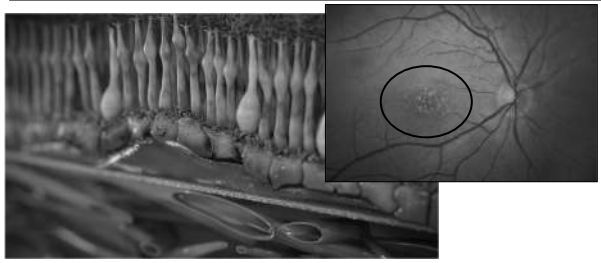
Finally, visibly evident drusen on fundus evaluation



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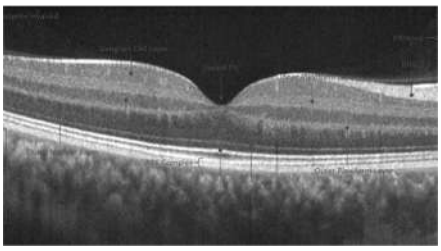
The ellipsoid zone (EZ) is considered to be **formed mainly by mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors**. However, it was previously known as the junction between the photoreceptor IS/OS).



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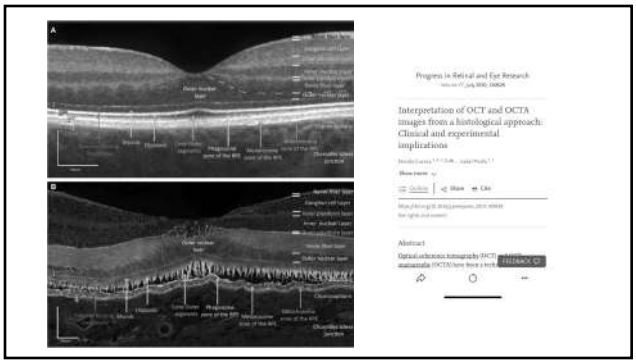

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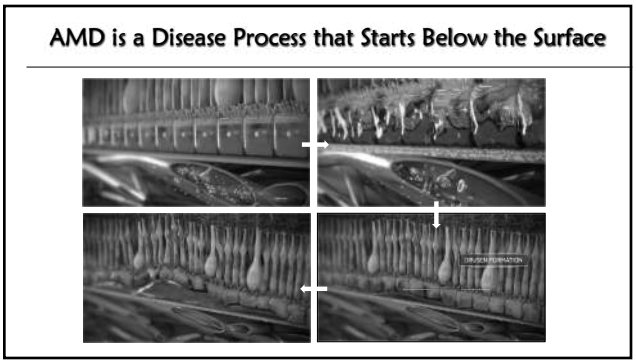

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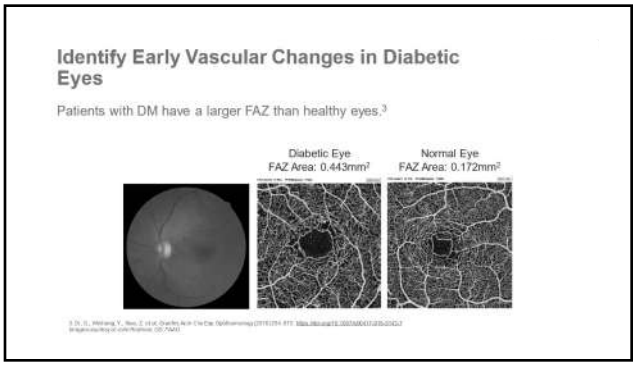

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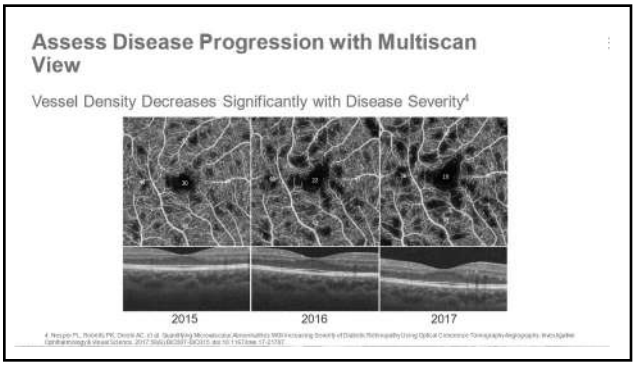

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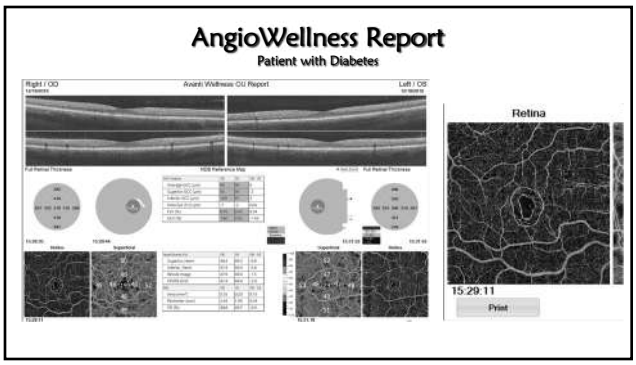

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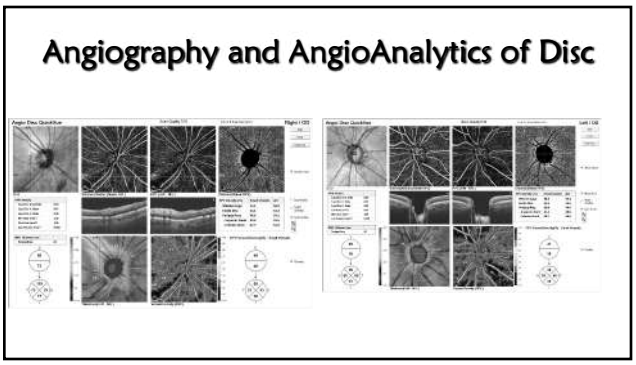

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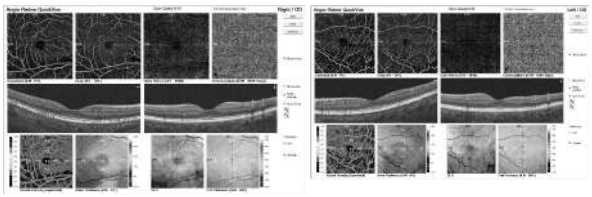
Angiography and AngioAnalytics of Retina



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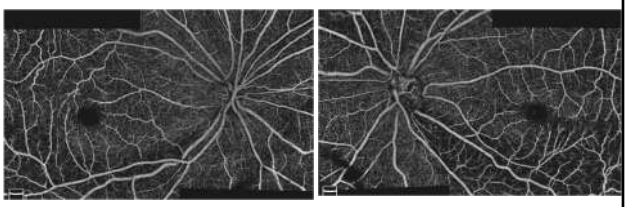
Montage OU



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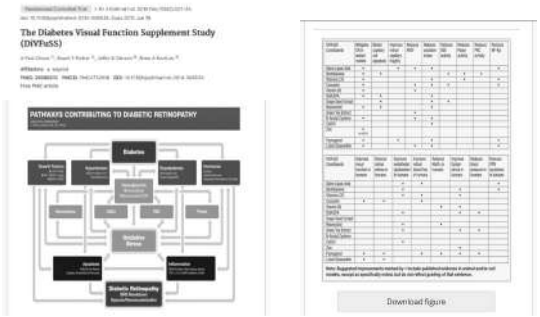

The Diabetes Visual Function Supplement Study (DIVFuSS)

PATHWAYS CONTRIBUTING TO DIABETIC RETINOPATHY

Download figure

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Nutraceuticals for the Treatment of Diabetic Retinopathy

Abstract

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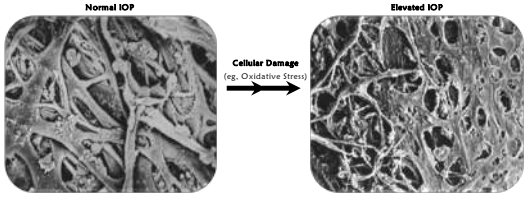
Disease at the TM is responsible for elevated IOP in glaucoma[1,2]



Scanning electron microscopy (2000x) was used to examine human TM under physiological conditions and in patients with POAG.[1]
POAG, primary open-angle glaucoma; TM, trabecular meshwork.
1. He et al. Invest Ophthalmol Vis Sci. 2008;49:1447.
2. Saeedi et al. J Cell Physiol. 2019;234:5176.

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Glaucoma

PERSPECTIVES ON GLAUCOMA

Antioxidants enhance ocular perfusion in Open Angle Glaucoma

Harris A, et al. Acta Ophthalmol. 2018;doi:10.1111/aos.13530.

"In agreement with previous findings, our results indicate that the supplementation of certain antioxidants may increase blood supply to the orbit and within retinal capillary beds following 4 weeks administration," the authors wrote. "Our data suggest oral antioxidant supplementation may decrease vascular resistance over a longer period of time than previous trials investigated."

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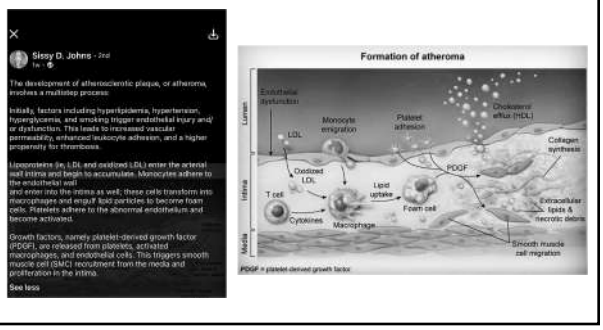

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Treatments for AMD

- Early detection and meaningful treatments with significant value, do not cure, but have been shown to slow or halt progression. Not limited to early stages but all stages of AMD
  - Prescribe smoking cessation programs
    - Smoking and AMD
      - Depletes serum antioxidants
      - Decreases pigmentary density
      - Increases risk to advanced AMD
  - Lifestyle changes
    - Diet
    - Exercise
  - Systemic disease management
    - Cardiovascular disease, DM, obesity, high cholesterol

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Treatment for AMD

- Nutritional supplements
  - Sub-clinical/sub-structural or early disease
    - Controversy flourishes
      - No definitive guideline exists
      - Despite consensus evidence suggests using supplements
  - Intermediate – advance disease
    - No controversy on advocating for supplements
  - AREDS 1
    - Contains Beta-carotene and no lutein or zeaxanthin, no longer recommended
    - Investigated early AMD, no statistically significant benefit
  - AREDS 2
    - Recommended for intermediate and advanced AMD, study protocol
  - The Practical Guide for the Treatment of AMD - 3 primary options
    - Macular pigment supplement
      - Carotenoids: lutein, zeaxanthin, meso-zeaxanthin
    - Carotenoids, antioxidants, zinc, and vitamins C &E
      - AREDS 2
    - Carotenoid macular supplement in subclinical and early AMD. Carotenoid and antioxidant is intermediate and AMD that is progressing

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Measuring Macular Pigment

- Retina macula biopsy
- Clinical Imaging
  - Subjective
    - ZeaVision MPSII
    - Guardion Mapcat SF
  - Clinical
    - ZeaVision MPR
    - Zeiss Visucam 200
    - Spectralis HRA+OCT
    - Spectralis MPOV

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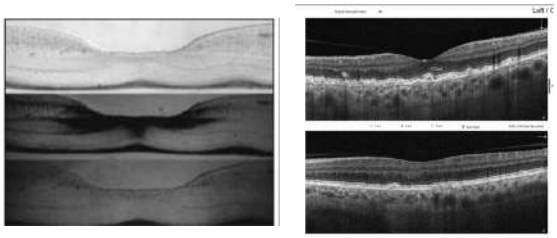
Macular Pigment



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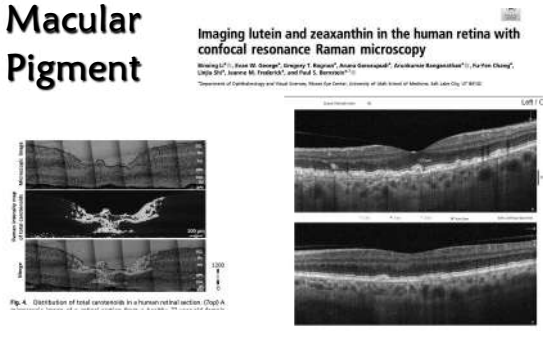
Macular Pigment



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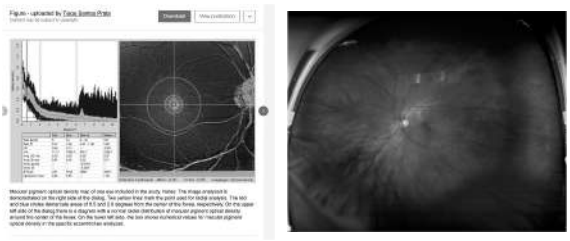
Macular Pigment and the Retina



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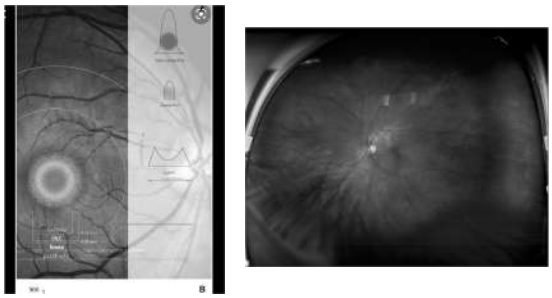

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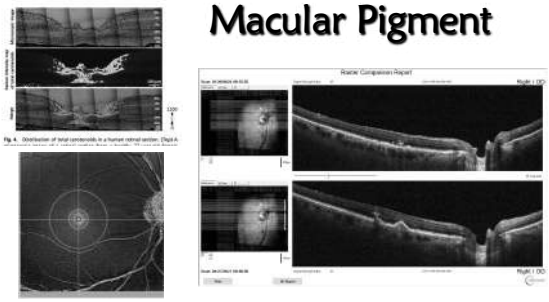
Macular Pigment



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When it cold outside what are good for your feet and head?

78

Question

- Do you recommend resveratrol and quercetin antioxidants when treating ocular/retinal conditions?
  - Yes
  - No

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Why Are We Only Treating Half the Retina?

Oxidative Medicine and Cellular Longevity

Health Benefits of Polyphenols and Carotenoids in Age-Related Eye Diseases

Abstract

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Carotenoids and Polyphenols

Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging

Resveratrol can be implied in anti-aging actions by influencing the mitochondrial environment and metabolic processes, by regulating the levels of some inflammatory mediators and cytokines and by modulating lipolysis [125, 152, 153]. Mitochondrial dysfunction has been proved to be associated with aging and disease development [154], and it was seen

19 Oncotarget

Furthermore, resveratrol maintains the vascular fitness through its antioxidant and anticoagulant activities, and on the other hand is relevant in blocking the formation of new blood vessels, in inhibiting the VEGF release and attenuating Hypoxia-Inducible Factor (HIF-1α) in different tumor cells [163].

ASSESSMENT OF CAROTENOIDS

Impact of Carotenoid Assessment

81

Measuring Carotenoids and the Macular Pigment

- Biophotonic Scanner
  - ✶ Measures carotenoids
  - ✶ Based on an optical method known as Resonant Raman Spectroscopy (RSS)
    - Used for many years in research laboratories
  - ✶ Skin RRS measurements
    - Noninvasive
    - Objective
    - Reliable methods to assess carotenoid levels
      - Ocular
      - Systemic

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Carotenoid Levels

- Biomarker of health for diet and lifestyle
  - ✶ Yale University
- Phospholipid bi-layer
- Carotenoids, flavonoids, and polyphenols

Correlations Between Macular, Skin, and Serum Carotenoids

83

The New Standard

NIH National Institutes of Health
Turning Discovery Into Health

Quick Test (approx. 30 sec)

Portable

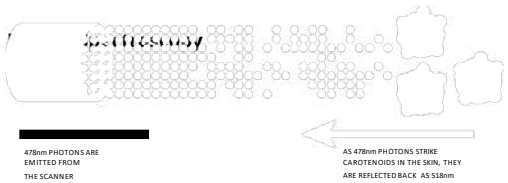
Cost Effective

Remeasure in 60 days

Reassurance to you and patient

84

Raman Spectroscopy



478nm PHOTONS ARE EMITTED FROM THE SCANNER

AS 478nm PHOTONS STRIKE CAROTENOIDS IN THE SKIN, THEY ARE REFLECTED BACK AS 518nm PHOTONS

85

Resonance Raman spectroscopic evaluation of skin carotenoids as a biomarker of carotenoid status for human studies

Susan T. Mayne [a,*], Brenda Cartmel [a], Stephanie Scarmo [a,b], Lisa Jahns [c], Igor V. Ermakov [d], Werner Gellermann [d]

Yale CANCER CENTER

90 STUDIES

ARTICLE INFO

Keywords:
Carotenoids
Skin
Resonance Raman spectroscopy
Beta-carotene
Biomarker

*Arch Biochem Biophys. PMC 2014 Nov 15.

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ARVO STUDY

Interrelationships between Macula, Skin and Serum Carotenoids- Paul Bernstein, Werner Gellerman et al ARVO May 2016

Conclusions:

"Our results emphasize the importance of measuring the total amount of carotenoids in the macula region using an objective image based modality such as AFI w Spectralis rather than subjective MPOD."

Skin resonance Raman Spectroscopy of skin carotenoids is a reasonable biomarker of macula carotenoid status. and correlates better than than subjective MPOD tests.

The objective hand scanner is better than the subjective Macuscope, QuantifEYE, and Densitometer for estimating macula pigment.

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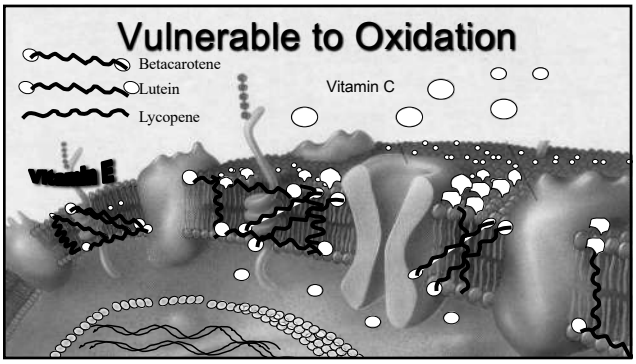

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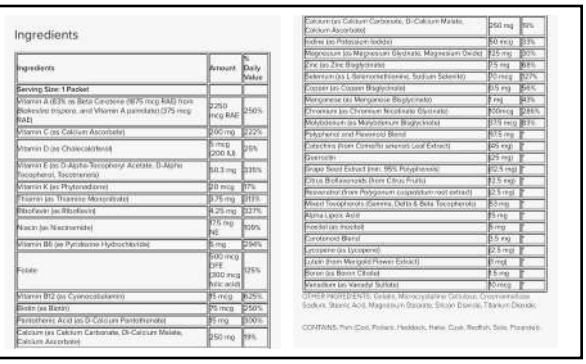
Are you taking a supplement?

89

53-year-old man

- Family history of AMD
  - Dad with 43 injections for AMD
- Pre-diabetic with borderline HbA1c
- Vision 20/20 OU
- DFE- retina clear
- OCT normal
- Passes dark adaptation

90



Ingredients

Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (875 mcg RAE) from Rosa laxa rugosa and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha-Tocopherol, Tocomenols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	0.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	170 mg NE	1063%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	680 mcg DFE (300 mcg folic acid)	425%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	60 mcg	39%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	75 mg	682%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	150 mcg	429%
Molybdenum (as Molybdenum Bisglycinate)	375 mcg	833%
Polyphenol and Flavonoid Blend	675 mg	†
Catechins (from Camellia sinensis Leaf Extract)	425 mg	†
Quercetin	125 mg	†
Grape Seed Extract (min. 95% Polyphenols)	62.5 mg	†
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg	†
Resveratrol (from Polygonum cuspidatum root extract)	12.5 mg	†
Mixed Tocopherols (Gamma, Delta & Beta Tocopherols)	83 mg	†
Alpha Lipoic Acid	25 mg	†
Inositol (as Inositol)	5 mg	†
Carotenoid Blend	3.5 mg	†
Lycopene (as Lycopene)	2.5 mg	†
Lutein (from Marigold Flower Extract)	2 mg	†
Boron (as Boron Citrate)	1.5 mg	†
Vanadium (as Vanadyl Sulfate)	10 mcg	†

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Croscarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollock, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

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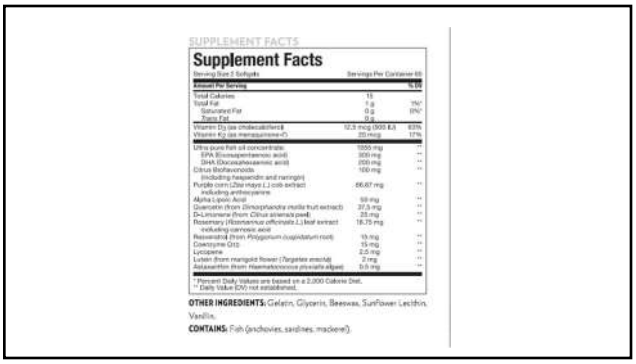

SUPPLEMENT FACTS

Supplement Facts

Amount Per Serving		% DV
Total Calories	15	
Total Fat	1 g	1%*
Saturated Fat	0 g	0%*
Trans Fat	0 g	
Vitamin D3 (as cholecalciferol)	12.5 mcg (500 IU)	63%
Vitamin K2 (as menaquinone-7)	20 mcg	17%
Ultra pure fish oil concentrate:	1650 mg	**
EPA (Eicosapentaenoic acid)	300 mg	**
DHA (Docosahexaenoic acid)	200 mg	**
Citrus Bioflavonoids (including hesperidin and naringin)	100 mg	**
Purple corn (Zea mays L.) cob extract (including anthocyanins)	66.67 mg	**
Alpha Lipoic Acid	50 mg	**
Quercetin (from Sophora japonica bud extract)	37.5 mg	**
D-Limonene (from Citrus sinensis peel)	25 mg	**
Rosemary (Rosmarinus officinalis L.) leaf extract (including carnosic acid)	16.75 mg	**
Resveratrol (from Polygonum cuspidatum root)	15 mg	**
Coenzyme Q10	15 mg	**
Lycopene	2.5 mg	**
Lutein (from marigold flower (Tagetes erecta))	2 mg	**
Astaxanthin (from Haematococcus pluvialis algae)	0.5 mg	**

* Percent Daily Values are based on a 2,000 Calorie Diet.
** Daily Value (DV) not established.

OTHER INGREDIENTS: Gelatin, Glycerin, Beeswax, SunFlower Lecithin, Vanilla.

CONTAINS: Fish (anchovies, sardines, mackerel).

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53-year-old man

CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

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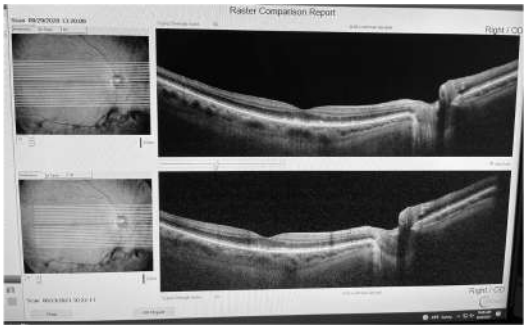

N of 3
So Far

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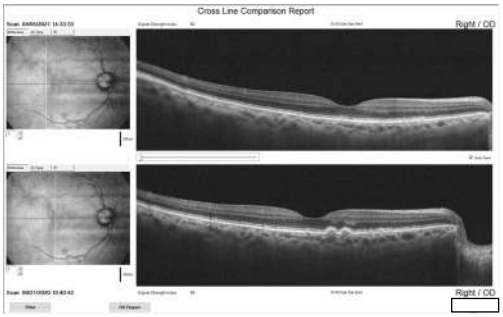

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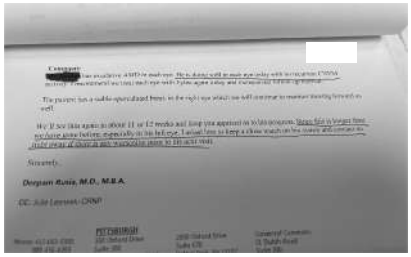
Treat and Extend!



Dirgam Ruia, M.D., M.B.A.

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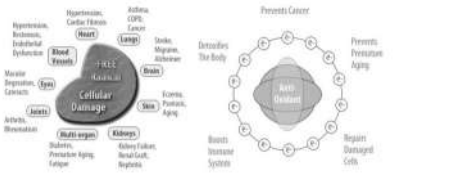
Screen Everyone



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Carotenoid and Antioxidant Levels in Ocular Disease and Systemic Health

- Plenty of evidence that carotenoids are beneficial in ocular and systemic prevention
- Patients are looking for guidance
  - Many are on supplements
    - Surprised what they are doing is minimally helping
- Measuring ensures the patient
- Antioxidants in the eye and body go beyond lutein and zeaxanthin
- Dr. Oz "Ultimate nutritional lie detector"
- Best benefit of all…

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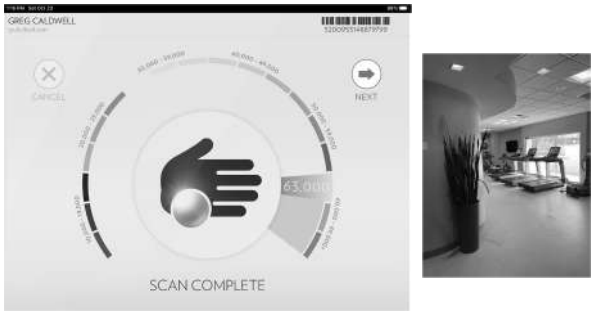

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Thank You for This Opportunity

- Do it for:
  - Yourself
  - Your family
  - Your staff
  - Your patients

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Questions and Thank You!

Carotenoid Levels in Ocular Disease and Systemic Health

Greg Caldwell, OD, FAAO

September 10, 2022
Forum on Optometry
Mystic, CT

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