

Maximizing Carotenoids in Eye Care

Tracy Offerdahl, PharmD, RPh, FAAO

Disclosures: Tracy Offerdahl, PharmD All relevant relationships have been mitigated

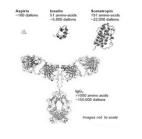
- Dr. Offerdahl has the following financial disclosure: • Boiron: honorarium, webinar/speaker
 - · Non-salaried financial affiliation with Pharmanex

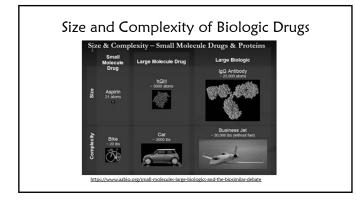
Text me your comments and questions

267-241-9146

Biologic Drugs versus Small Molecule Drugs

- **Biologic Drugs** * Larger, complex, dynamic structures Diverse populations of molecules
 Not easily characterized
- * Complicated manufacturing * Example: Teprotumumab (Tepezza)
- Small Molecule Drugs * Synthetic
- Manufactured using a defined chemical process
- * Smaller and simpler * Example: Aspirin





Biosimilars

- "Highly similar" to the "reference product" (ie. The biologic/reference or innovator product) FDA's approach: The biosimilar company's research is to RROVE "biosimilarity" between the proposed biosimilar product and the reference product...NOT to independently establish the safety and effectiveness of the proposed product
- There are no clinically meaningful differences in terms of:
 - * Safety * Purity * Potency
- Why is there no such thing as a <u>GENERIC biologic</u> medication? * Biologics come from LIVING "things", so it is not likely to be EXACTLY the same as the reference product! USUALLY differs in terms of inactive ingredients
 - Generic medications are chemically synthesized so that the active ingredient is IDENTICAL to the brand name medication *

Monitoring Parameters Biologics

- Biologics are Immunomodulating/Immunosuppressive medications! * HICH immunogenicity potential because they "tinker" with the immune system & come from nature * Small molecule drugs have LOW immunogenicity because they are synthetic
- Many of the systemic agents for autoimmune disease can cause significant morbidity and mortality!
 - * Once a biologic is initiated, watch for any signs or symptoms of infection If the patient has a "cold", "flu", or is taking antibiotics
 Then biologic dose must be HELD until the patient is healthy

 - FULL work-up for signs/symptoms of infection!
 ASK your patients about meds!
 - * We will look at the diversity of the side effects with these newer biologics

Why we use them...

- Autoimmune disease
- * TED, RA, psoriatic arthritis, GCA, PMR, wet AMD, macular edema, uveitis, keratitis, etc.

Cancer

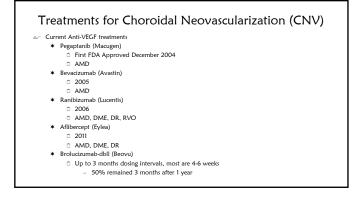
- \star Which, arguably, has an autoimmune component
- * More specific mechanisms of action
- We also have biologics to treat SIDE EFFECTS associated with cancer and cancer treatment protocols
- With MANY of these diseases, patients OVER EXPRESS certain inflammatory mediators that contribute to their disease or condition!

Examples of Common Agents

Biologic response modifiers approved for the treatment of chronic inflammatory conditions

Biologic target	Product	Description	Route of administration	
TNF	Adalimumab	Human monoclonal antibody	Subcutaneous	
	Etanercept	Human soluble receptor	Subcutaneous	
	Infliximab	Chimeric monoclonal antibody	Intravenous	
T-cell	Abatacept	Human soluble fusion protein	Intravenous	
	Alefacept	Human dimeric fusion protein	Intravenous	
	Efalizumab	Humanized monoclonal antibody	Subcutaneous	
B-cell	Rituximab	Chimeric monoclonal antibody	Intravenous	
IL-1	Anakinra	Human IL-1 receptor antagonist	Subcutaneous	

	Target of antibody		Used to treat:
Anakinra	IL-1 Receptor	٠	Rheumatoid arthritis (RA)
Basiliximab	IL-2 Receptor on activated T lymphocytes	•	Kidney transplant immunosuppression to prevent acute graft rejection
Daclizumab	IL-2 Receptor	٠	Relapsing multiple sclerosis (MS)
Mepolizumab	IL-5	:	Asthma Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Tocilizumab	IL-6 Receptor	:	Giant cell arteritis (GCA) Rheumatoid arthritis (RA)
Ustekinumab	IL-12 & 23	:	Psoriasis Psoriatic arthritis Crohns/UC
Secukinumab	IL-17A	÷	Psoriasis Psoriatic arthritis Ankylosing spondylitis (AS)



ByoovizTM (ranibizumab-nuna)

↔ Reference drug Ranibizumab (Lucentis™)

- * Ten manufacturers are working on Ranibizumab biosimilar (as of 2021)
- * First ophthalmology biosimilar approved by US-FDA Treat wet AMD, Macular Edema following RVO, and myopic CNVM,
- * 705 patients were enrolled and randomized (1:1) to receive Byooviz or reference Ranibizumab every 4 weeks through week 48.
- \star The safety and immunogenicity profile of SB11 and reference ranibizumab were comparable at all points up to week 52

Oxervate™ (cenegermin-bkbj)

- Ophthalmic solution indicated for the treatment of neurotrophic keratitis
 Dosing: Instill 1 drop in affected eye 6 times per day (at 2-hour intervals) for 8 weeks
 - ★ Used as eye drop☐ Not infused or injected
- Storage issues: in the freezer at the pharmacy

 Patient keeps the individual vials in the fridge once "actively ready" for use, then it is only stable for 12 hours
- Contraindications
- ★ None

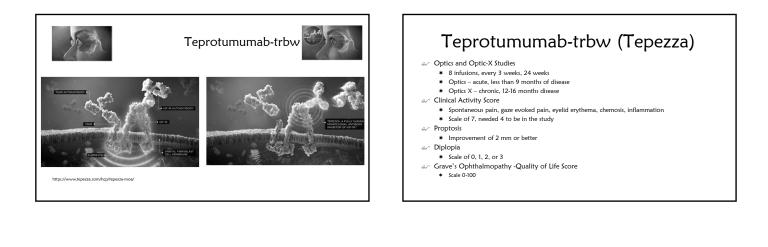
OXERVATE[™] (cenegermin-bkbj) ophthalmic solution 0.002% Weekly Device Kit

OXERVATETM is supplied in a weekly carton containing 7 multiple-dose vials*
 A separate weekly Delivery System Kit contains the supplies needed to administer treatment

The Delivery System Kit Contains:

- 7 vial adapters
- 42 pipettes
- 42 sterile disinfectant wipes
- 1 dose recording card
- 1 extra adapter, 3 extra pipettes, 3 extra wipes are included as spares
 - *Extra drug is available in each vial to take into consideration for loss or spillage during treatment administration

KERVATE^{IM} (cenegermin-bibl) ophthalmic solution 0.002% (20 mcg/ml) [US package insert]. Boston, MA: Dompe U.S. Inc.; 2018.



Deprotumumab-trbw (Tepezza) Infusion Reactions (mlid/moderate): approximately 4% of patients transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain will occur within 1.5 hours of an infusion For those who have had a previous reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, or corticosteroid and/or administering at a slower infusion rate. Prescisting Inflammatory Bowel Disease: may cause an exacerbation of preexisting inflammatory bowel disease ("IBD") * Monitor patients for flare: may require discontinuation of Teprotumumab (Tepezza) Hyperglycemia: Increased blood glucose on hyperglycemia * In clinical trials, 10% of patients experienced hyperglycemia * Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with teprotumumab

* Patients with preexisting diabetes should be euglycemic before beginning treatment

Humira™ (adalimumab)

↔ Company: Abbvie

- ★ Approved July 2016
- ★ Indication: uveitis
 - Specifically indicated for the treatment of non-infectious intermediate, posterior and panuveitis
- Dosage: subcutaneous injection
 Recommended dose is 80 mg initial dose
 Followed by 40 mg every other week starting one week after initial dose
- * The significance of this FDA approval is important! Many insurance companies (ex. Medicare) will not pay for "off-label" uses.

Humira[™](adalimumab)

G√Monitoring parameters:

- Must place PPD before initiating = if PPD+, then initiation of Humira may convert latent TB to ACTIVE tuberculosis
- * Once Humira is initiated, watch for any signs or symptoms of infection ... if the patient has a "cold", "flu", or is taking antibiotics, then Humira dose must be HELD until the patient is healthy.

Humira[™] (adalimumab) HadlimaTM (adalimumab-bwwd)

- WARNING: SERIOUS INFECTIONS AND MALIGNANC See full prescribing information for complete boxed warning.
- w ARNING: SERIOUS INFECTIONS AND MALIGNANCY So full prescribing information for complete based warning. SERIOIS INFECTIONS (51, 61): Increased risk of reviews infections leading to hospitalization or deth, users histophenomis, and infections due to other opportunistic pathogene. Discontinue IIUMINA if a patient develops a serious infection or sepsi Discontinue IIUMINA if a patient develops a serious infection or sepsi a starting IIUMINA. Mattern all patients for active TB during treatment, even if initial MALIGNANCY (52): I. Jornhoum and other malignancies, some fatal, have been reported infuture.

- HUMIRA. Post-marketing cases of hepatosplenic T-cell lymphoma (HSTCL), a rare type of T-cell lymphoma, have occurred in addescent and youn adults with inflammatory bowel disease treated with TNF blockers including HUMIRA.

Actemra[™] (tocilizumab)

Ger Actemra™ (tocilizumab)- Genetec

- * First innovative therapy for GCA in more than 50 years
- * Design to speed the development for treatments of serious diseases such as GCA and certain cancers

Tocilizumab (Actemra)

- WARNING: RISK OF SERIOUS INFECTIONS See full prescribing information for complete boxed warning. Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other
- opportunistic infections have occurred in patients receiving
- ACTEMRA. (5.1)
- If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Perform test for latent TB; if positive, start treatment for TB prior to starting ACTEMRA. (5.1)

The Cluster of Conditions

3 of these 5 leads to:

Heart disease, stroke, DM, dementia, cancer...

Monitor all patients for active TB during treatment, even if initial

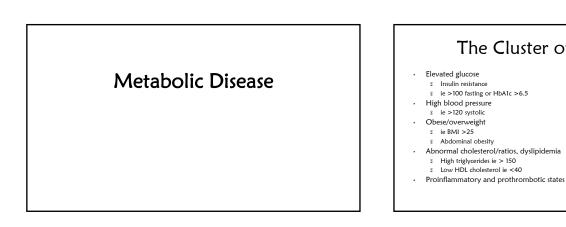
Insulin resistance

≗ ie BMI >25 a Abdominal obesity

ie >100 fasting or HbA1c >6.5

3 High triglycerides ie > 150 8 Low HDL cholesterol ie <40</p>

latent TB test is negative. (5.1)



Incretin mimetics - (AKA glucagon like peptide – 1(GLP-1) agonists)

Exenatide injection (Byetta) -SQ injection = Bydureon Liraglutide injection (Victoza) Saxenda brand name = weight loss only Abiglutide (Tanzeum) Dulaglutide (Trulicity)

<u>Semaglutide (Ozempic)</u> <u>Wegovy brand name = weight loss</u>

Lixisenatide (Adlyxin)

Mechanism of Action

- Stimulate the GLP-1 receptor this receptor enhances glucose-dependent insulin secretion by the pancreatic beta-cell (in response to high blood glucose levels), suppresses secretion of glucagon after meals, and slows gastric emptying; some appetite suppression and weight loss
 - Also change "white fat" to "brown fat" =

Adverse Effects:

- Nausea and vomiting
- Hypoglycemia
- Pancreatitis
- Liraglutide
- thyroid C-cell tumors
 - Contraindicated in patients with medullary thyroid cancer (active or PMH)
- GLP1 agonists in diabetic retinopathy?!?
 - 2018 data versus today...

Journal of Diabetes and its Complications

- "Our meta-analysis based on the 4 major RCTs demonstrates that the use of GLP1 RA drugs which have CV benefits including Liraglutide, semaglutide (both subcutaneous and oral), and dulaglutide, may be associated with an increased risk of progression of DR.
 - * However, given the primary purpose of these trials were not for DR, and that they lack systematic DR measurement throughout, further data from largescale, well-designed clinical studies with systematic evaluation of DR are warranted."

Tirzepatide (Mounjaro)

- T2DM is only indication to date
- Tirzepatide, known as a 'twincretin', is a 'first-in-class' and the only dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) receptor agonist
 - can significantly reduce glycemic levels and improve insulin sensitivity, as well as reducing body weight by more than 20% and improving lipid metabolism
 - Seem to have same "white fat to brown fat" benefit
 - On "fast-track" approval for weight loss indication

Tirzepatide ADRs

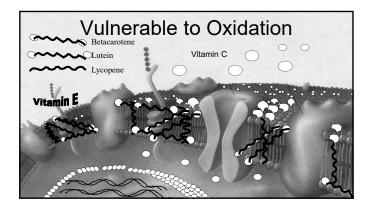
- Similar to GLP1 agonists
- * N, V, D, C
 - * Gallbladder issues
 - ★ hypoglycemia
 - Particularly when used with other anti-diabetes medications
 - Thyroid C-cell tumors
 - ★ Pancreatitis
 - Risk with diabetic retinopathy?

 Has not been studied

Patients Are Expecting

← Early detection ⊕∽Wellness A Prevention

Early Detection and Allopathic Treatments Rabin Cone Contrast Test ERG and VEP



Comprehensive Antioxidant Support

- Scell membrane support
- ⊕ Immune support
- Support to the oxidative stress to the extracellular matrix
- Support to cell signaling

Question?

& Who in here would consider themselves as an integrative optometrist?

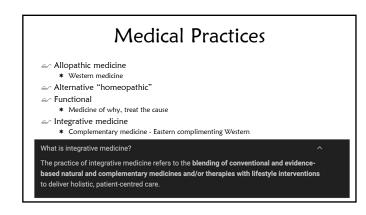
- Who has done or recommended?
 - * Supplements, vitamins, AREDS2 * Omegas, EPA, DHA
 - ★ Vital tears ASED
 - * Regener-Eyes
 - * Amniotic membranes
 - * CBD
 - * Probiotics

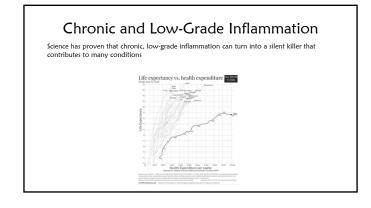
Allopathic vs Integrative Medicine

- "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





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)



"Choose Your Parents Wisely"

& This just isn't as true as it used to be

- ↔Lifetime health
 - 8% genetics "Picking your parents wisely"
 DNA in our nucleus

 Can't be influenced
 - ★ 92% epigenetics
 - \Box Lifestyle choices = we can influence
 - Turn on/off gene expression

Biomarker

- Ger Test that has meaning
- Biological molecule ound 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

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 measure of all antioxidants

Biohacking

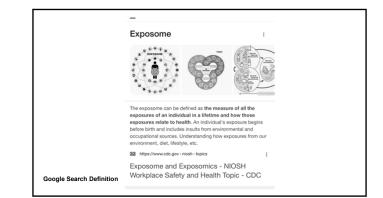
- ↔ The Art and Science of changing the environment around you and inside you so you have more control over your own biology.
- Somebody who uses science and technology to make his or her body function better and more efficiently – Dave Asprey

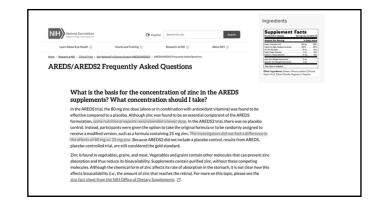
Chronic and Low-Grade Inflammation



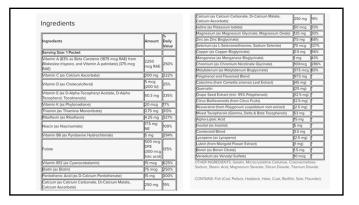
DNA Sciences

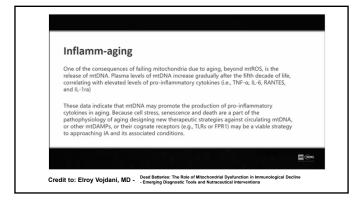
- Geodesic Genomics = all of our genes
- $G_{\mathcal{A}}$ Genetics = individual genes
- Epigenetics the study of how our cells control gene activity without changing the DNA
 - \star Internal and external environments





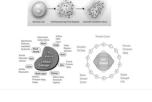






Oxidative Stress

- Geo 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



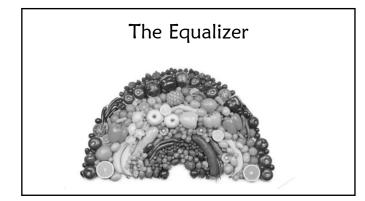
Oh no

ls an orange of the 1950's equivalent to 21 of today's

oranges?

- Archaring exogenous free radicals
- & Less antioxidant protection in our diet
- AMOre bad and less good

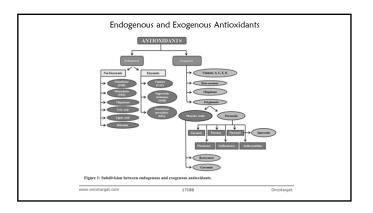
An orange from the 1950's was full of vitamin A, precious for our sight and our immune defenses. To attain the same amounts today, you would have to consume 21 of them. Onions and potatoes no longer contain any trace of it. The iron content in meat? Divided by 2. Calcium in broccoil? Divided by 4. To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



Nutritional Antioxidants

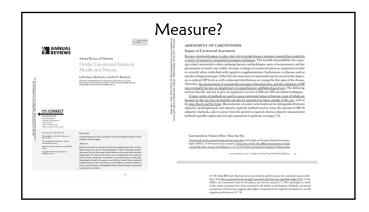
Ser Exogenous antioxidants

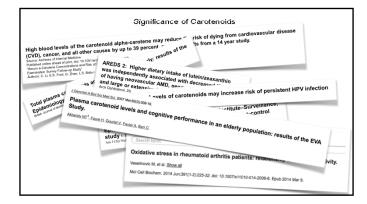
- * Tocopherols (E), ascorbic acid (C), carotenoids, ubiquinone, and polyphenols
- &√Well know antioxidants
 - Vitamin C, E, Beta-carotene, lutein, zeathanin, selenium, quercetin, and resveratrol
- Ger Mechanisms of action;
 - Neutralize free radicals
 - Repair oxidized membranes
 - * Decrease reactive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

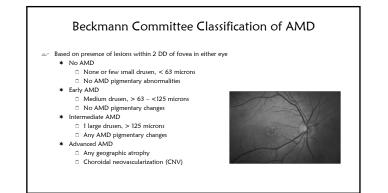


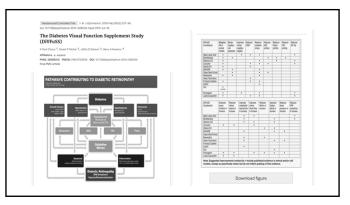
Comprehensive Antioxidant Support

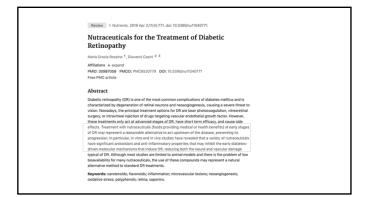
- Scell membrane support
- Almmune support
- $\operatorname{{\scriptscriptstyle G\!{\scriptscriptstyle L\!\! C}}}$ Support to the oxidative stress to the extracellular matrix
- Support to cell signaling

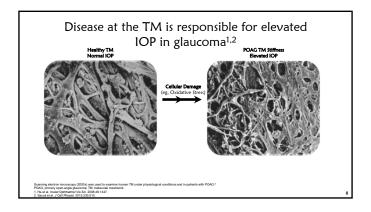












Glaucoma

PERSPECTIVES ON GLAUCOMA Antioxidants enhance ocular perfusion in Open Angle Glaucoma Harris A, et al. Acta Ophthalmol. 2018;doi:10.1111/aos.13530.

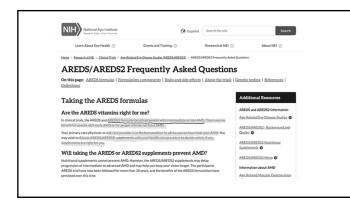
"In agreement with previous findings, our results indicate that the supplementation of certain antixidiants may processe biolog supply to the orbit and within return capillary beds following 4 weeks administration," the authors wrote. "Our data suggest <u>oral antioxidant supplementation</u> may decrease vascular resistance over a longer period of time than previous trials investigated."

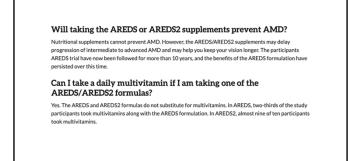
Treatments for AMD

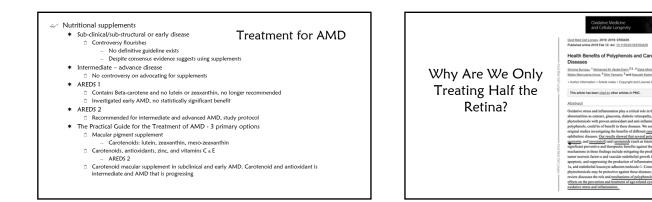
 $\mathop{\mbox{\tiny GeV}}$ Early detection and meaningful treatments with significant value, do not cure, but have been shown to slow or halt progression. Not limited to early stages but all stages of AMD

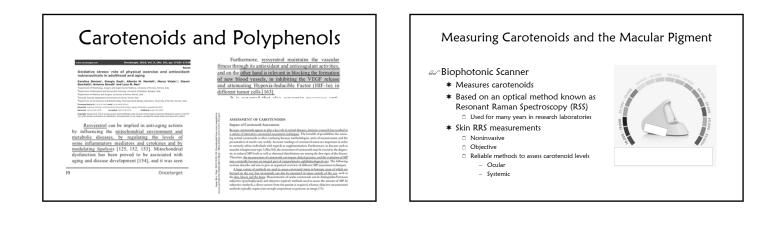
- * Prescribe smoking cessation programs
- Smoking and AMD
 - Depletes serum antioxidants
 Decreases pigmentary density

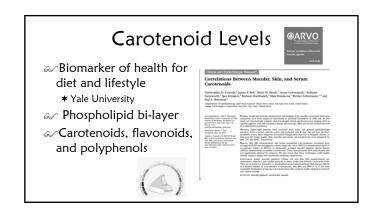
 - Increases risk to advanced AMD
- * Lifestyle changes
- Diet
- Exercise
- * Systemic disease management Cardiovascular disease, DM, obesity, high cholesterol





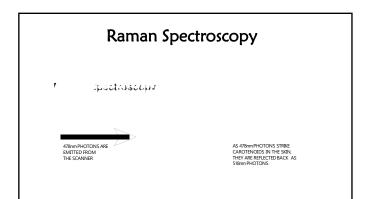


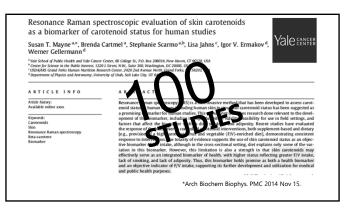






lated Eye





ARVO STUDY

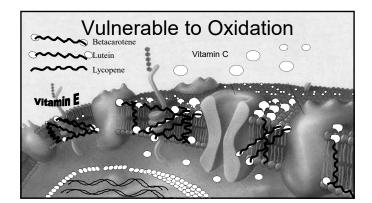
Interrelationships between Macula, Skin and Serum Carotenoids- Paul Bernstein, Werner Gellerman et al ARVO May 2016

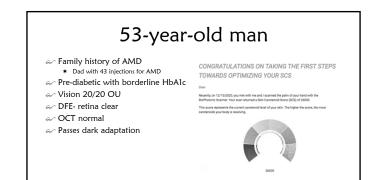
Conclusions: "Our results emphasize the importance of measuring the total amount of carotenoids in the macula region using an objective image based modality such as AFI w Spectralis rather than subjective MPOD."

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



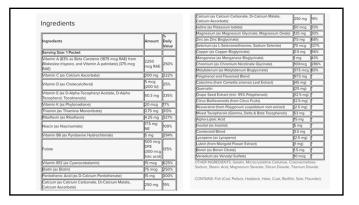
The objective hand scanner is better than the subjective Macuscope, QuantifEYE, and Densitometer for estimating macula pigment.

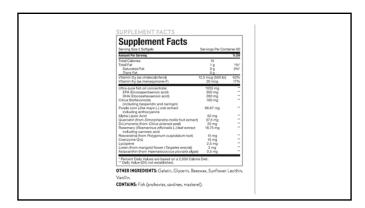


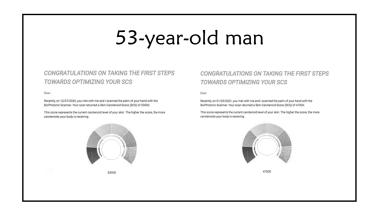


drofferdahl@gmail.com 267-241-9146

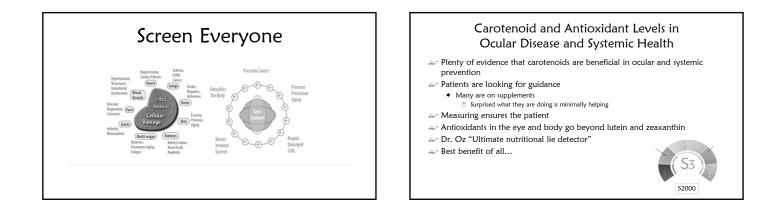
Use of Supplements







Ingredients		Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19		
ngredients	odine (as Potassium lodide)	S0 mcg	ត្រ			
			Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30	
Ingredients	Amount	Daily	Zinc (as Zinc Bisglycinate)	7.5 mg	68	
ing counts		Value	Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127	
Serving Size: 1 Packet	-i	i i i i	Copper (as Copper Bisglycinate)	0.5 mg	66	
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from	- L	i — i	Manganese (as Manganese Bisglycinate)	1 mg	43	
Blokeslea trispora, and Vitamin A palmitate) (375 mcg	2250 mcg RAE	250%	Chromium (as Chromium Nicotinate Glycinate)	100mcg	28	
RAE)			Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83	
Vitamin C (as Calcium Ascorbate)	200 mg	222%	Polyphenol and Flavonoid Blend	97.5 mg	F	
Vitamin D (as Cholecalciferol)	5 mcg	25%	Catechins (from Camellia sinensis Leaf Extract)	(45 mg)	ïF	
	(200 IU)		Quercetin	(25 mg)	î T	
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%	Grape Seed Extract (min. 95% Polyphenols)	(12.5 mg)	E	
Vitamin K (as Phytonadione)	20 mcg	17%	Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg)	E	
		313%	Resveratrol (from Polygonum cuspidatum root extract)	(2.5 mg)	E	
Thiamin (as Thiamine Mononitrate)	3.75 mg		Mixed Tovopherols (Gamma, Delta & Beta Tocopherols)	53 mg	Ē	
Riboflavin (as Riboflavin)	4.25 mg	327%	Alpha-Lipoic Acid	15 mg	F	
Niacin (as Niacinamide)	17.5 mg NE	109%	Inositol (as Inositol)	5 mg	F	
			Carotenoid Blend	3.5 mg	ΪĒ	
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%	Lycopene (as Lycopene)	(2.5 mg)	îF.	
	500 mcg DFE (300 mcg folic acid)		Lutein (from Marigold Flower Extract)	(1 mg)	F	
Folate		125%	Boron (as Boron Citrate)	1.5 mg	F	
			Vanadium (as Vanadyl Sulfate)	10 mcg	ΪĒ	
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%	OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, C			
Biotin (as Biotin)	75 mcg	250%	Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide,	Titanium Di	oxid	
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%				
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%	CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder			





Questions? Thank You!

tofferdahl@salus.edu 267-241-9146