



Off the Menu – A Nutritional Approach to Dry Eye

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 **UC DAVIS**
EYE CENTER


Disclosures

- ABB
- Acculens
- Alden Optical
- Alcon
- Allergan
- Anthem, INC
- Bausch + Lomb
- Contamac
- CooperVision
- JVC Vistakon
- Gas Permeable Lens Institute (GPLI)
- Novabay
- Ocusoft
- Paragon Biotech
- Percept
- Science Based Health
- Scleral Lens Education Society
- Shire
- Sjogren's Syndrome Foundation
- STAPLE program
- SynergEyes
- Visioneering Technologies



DREAM study
Dry Eye Assessment and Management (DREAM)

- Supplementation with high dose fish oil or olive oil helped alleviate the symptoms and improve objective signs of dry eye disease (DED) similarly
- RCT
- NIH-sponsored study
- Fish oil (2,000 mg EPA and 1,000 mg DHA daily) or refined olive oil (5,000 mg daily, intended as a placebo)
- 12-month period
- 329 patients – omega-3 group
- 170 patients – olive oil group



DREAM

- Adjunct therapy in DED
- Structured to model "real world" conditions
- Participants could use current DED therapies
 - Artificial tears, prescription cyclosporine drops, warm lid soaks and fish oil supplements if less than 1,200 mg EPA + DHA daily




Improvement in OSDI

- Mean change from baseline for OSDI
 - 13.9 points in the omega-3 group
 - 12.5 points in the placebo group
- Not statistically significant
- 61% of the omega-3 group and 54% of the control group achieved at least a 10-point reduction in the OSDI score
- No significant differences between groups in DED signs (conjunctival and corneal staining scores, TBUT, Schirmer's test)

Olive oil – a true placebo?
 Was the effect due to the activity of the oil itself?

- Oleic acid – predominant fatty acid in olive oil
- Substitute a modest amount of oleic acid for saturated or trans-fatty acids in the diet significantly decreases IL-6?
 - Pro-inflammatory cytokine and biomarker in DED



1. Gremmelmeier M et al. Potential health benefits of olive oil and plant polyphenols. Int J Mol Sci. 19; 647. 2018.
 2. Sassi A et al. Dietary factors that promote or retard inflammation. Arterioscler Thromb Vasc Biol. 24:995-1001. 2004.

Olive oil – a true placebo?
 Was the effect due to the activity of the oil itself?

- Palmitoleic acid (0.3 to 3.5%) – small amount in olive oil
- Fatty acid with anti-inflammatory properties
- Oral palmitoleic acid
 - Preserved tear secretion
 - Suppressed inflammatory cytokines of lacrimal gland
 - Murine model of dry eye

Nakamura S et al. Restoration of tear secretion in a murine dry eye model by oral administration of palmitoleic acid. Nutrients. 9:364. 2017.

DREAM study lessons

- Both treatment and placebo groups improved over time
 - Heterogeneous study population
 - DED is a complex and multifactorial disease state
 - Difficult to measure the effect of a single, non-specific intervention
- Traditional measurements used (OSDI and Schimers) have limited sensitivity and specificity
 - Limited by the type of measurement
 - The results were not expected
 - Is it the treatment that doesn't work, or are we just not using the right measuring stick?


Laura Peitman, MD Ophthalmology Management June 2018

DREAM study lessons

- Perhaps we shouldn't lump dry eye together into a few types
- Perhaps dry eye is actually a dozen different subtypes
- Need better tests to
 - More precisely categorize patient subtypes
 - Rule out comorbidities and masqueraders
 - Measure disease state activity in response to therapies

Laura Pestron, MD Ophthalmology Management June 2018

What your patient sees when you tell them to buy an omega 3...



Slide credit Nathan Schramm, OD, CNS, FSLs

Fatty acid composition: w6	Fatty acid composition: w3
Dietary sources: Sunflower oil, safflower oil, corn oil, soy oil	Dietary sources: Flaxseed oil, walrus oil, canola oil, fish oil
w6 fatty acid metabolism Linoleic acid	w3 fatty acid metabolism α-Linolenic acid
↓	↓
Gamma-linolenic acid (GLA)	Stearidonic acid
↓	↓
Dihomo-gamma-linolenic acid (DGLA)	Eicosapentaenoic acid (EPA)
↓	↓
Prostaglandin E1 (PGE1) anti-inflammatory	Docosahexaenoic acid (DHA)
↓	↓
Arachidonic acid	Anti-inflammatory & thrombolytic-inhibiting Eicosanoids
↓	
Inflammation & platelet aggregation including thromboxane (Causes: thrombosis, coronary heart disease)	


Omegas and Dry Eye: More Knowledge, More Questions. Hom, Milton; Asbell, Penny; Barry, Brendan Optometry & Vision Science. 92(9):948-956, September 2015. DOI: 10.1097/OPX.0000000000000655

Slide credit Nathan Schramm, OD, CNS, FSLs


Omega-3 fatty acids and dry eye disease

Omega-3 fatty acids glossary of terms

- Alpha-linolenic acid (ALA) - omega-3
- Linoleic acid (LA) - omega-6
- Docosahexaenoic acid (DHA)
- Eicosapentaenoic acid (EPA)
- Arachidonic acid (AA)
- Gamma-linolenic acid (GLA)
- Dihomo-gamma-linolenic acid (DGLA)



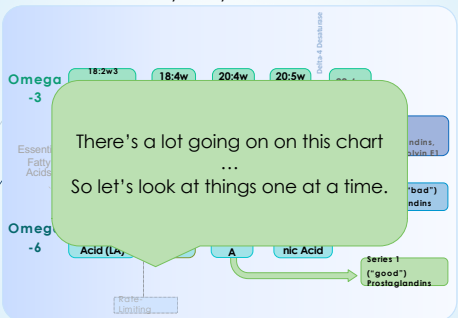
DHA and EPA



- DHA and EPA are formed when fish eat algae and are found in the triglyceride form ^{1,2}
- A triglyceride consists of a three-carbon glycerol "backbone" with each carbon linked to a fatty acid molecule.
- Each triglyceride molecule contains three fatty acids.
- In normally produced fish oil – 20% to 30% of the fatty acids are EPA and DHA
- Highly concentrated oils – 60% to 85% EPA and DHA
- Check the label for the actual EPA/DHA concentrations in a formula

1. Visoli F, Cole P, Barassi MC, et al. Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. *Lipids*. 2003 Apr;38(4):415-8.
2. Dyerberg S, Madsen P, Møller JM, et al. Bioavailability of marine n-3 fatty acid formulations. *Prostaglandins Leukot Essent Fatty Acids*. 2010 Sep;83(3):137-41.

Anti-inflammatory Fatty Acids



There's a lot going on on this chart
...
So let's look at things one at a time.

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Anti-inflammatory Fatty Acids

ALA & LA:
Most abundant omega 3/6s in diet. Both must convert to other omegas to effect inflammation, but are inefficiently / inconsistently converted (due to rate-limiting enzyme), reducing their effectiveness (example: only 10-20% of ALA converted)

LA conversion under hormonal / metabolic control. Factors inhibiting conversion include obesity, diabetes, the B3/Mg deficiency, trans fats, high cholesterol, rheumatoid arthritis, and more...

Anti-inflammatory Fatty Acids

EPA & GLA
are the powerhouses of the omegas - they are effective precursors of anti-inflammatory compounds

(DHA is also precursor to a prolectin, NPD) - though no dry eye role for NPD is established)

Anti-inflammatory Fatty Acids

Flaxseed oil provides ... mostly ALA (plus small amount of LA)
Both inefficiently used

Anti-inflammatory Fatty Acids

Fish oil provides EPA and DHA

Efficiently used, good health benefits overall

20:5w3 EPA → 20:4w3DHA

20:5w3 EPA → 20:3w6DGLA → 20:4w6Arachidonic Acid

Series 3 ("good") Prostaglandins (EPA, DHA)

Series 2 ("bad") Prostaglandins

Series 1 ("good") Prostaglandins

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Anti-inflammatory Fatty Acids

Black currant seed oil provides GLA (plus ALA & LA). GLA efficiently reduces inflammation through a unique pathway – and with dry eye specific effects. GLA is not obtainable through diet, fish or flax.

Omega-3: 18:2w3 Alpha linolenic (ALA) → 18:4w3 SDA → 20:4w6

Omega-6: 18:2w6 Linoleic Acid (LA) → 18:3w6 GLA

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GLA Targeted Action for Dry Eye: lacrimal production

- GLA is precursor of an anti-inflammatory prostaglandin, PGE1
- PGE1 found in tears, lacrimal gland & conjunctiva (1,2)

GLA → DGLA → PGE1

1. Mui, Sabrina, et al. Graefes Arch Clin Exp Ophthalmol 247:8 (2009): 1029-1030.
2. Aragonis, Pasquale, et al. Invest Ophthalmol Vis Sci 46:12 (2005): 4474.

2016, Zoe Denning, ScienceBased Health, zdenning@sbh.com

Gamma-linolenic acid (GLA)

- GLA improves markers of inflammation / inflammatory mediators in dry eye
- GLA may reduce inflammation in other diseases
 - Rheumatoid arthritis, IBD, dermatitis and diabetic retinopathy
 - Possibly by acting on T-cells to modulate the immune response
- Suggests anti-inflammatory Potency:
 - 2,000-3,000 mg omega-3s usually required to have significant effect
 - In contrast **235 mg** of GLA significantly reduced 2 different inflammatory markers in the HydroEye trial (n=38)

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GLA

- GLA, unaccompanied by fish oil, has been found to alleviate dry eye symptoms
 - Increase tear production and improve CL discomfort in CL associated dry eye¹
 - Reduce ocular surface inflammation in Sjögren's syndrome²
 - GLA with eyelid hygiene, decrease eyelid margin inflammation and improve symptoms in mgd more than either treatment alone³
 - Post-menopausal women (HydroEye)⁴
 - Mild-moderate DED⁵



1. Koske E et al. Oral omega-6 fatty acid treatment in contact lens associated dry eye. Cont Lens Anter Eye. 31:141-48, 2008.
 2. Sjogren's Syndrome. Omega-3 essential fatty acid treatment and PGE2 tear content in Sjogren's syndrome patients. Invest Ophthalmol Vis Sci. 44:4474-79, 2003.
 3. Fink A et al. Effect of oral linoleic and gamma linolenic acid on meibomian gland dysfunction.
 4. HydroEye. HydroEye. 41:101-106, 2013.
 5. Sjogren's Syndrome. Acta Ophthalmologica. 89:481-7, 2007.


GLA

- Studies show GLA (alone, or with modest amounts of EPA and DHA) improves dry eye signs and/or symptoms
- EPA is added to GLA-supplemented diets to
 - Prevent accumulation of arachidonic acid
 - Decrease levels of pro-inflammatory prostaglandin E2 produced from arachidonic acid

Omega-3 and Omega-6 Ratio

- Omega-3 leads to an anti-inflammatory prostaglandin
 - Sounds good?
- We also need pro-inflammatory prostaglandins to fight off infections, diseases and a whole host of conditions.
- Ideal ratio of omega-6 to omega-3 is about 4/1
- Standard American diet ratio closer to 25 to 1
- Thus, the pro-inflammatory pathway is pushed to the chronic inflammatory state



Mikropoulos, Iliadis KA, Dora MR, et al. Relation between dietary n-3 and n-6 fatty acids and clinically diagnosed dry eye syndrome in women. Am J Clin Nutr. 2005;82(4):888-91.
 Eric RT, Vekrellis KT, McClellan JL, et al. Reducing the dietary omega-6:omega-3 utilizing a biotinic acid: not an sufficient therapy for attenuating high-fat-diet-induced retinopathy. Invest Ophthalmol Vis Sci. 2017;58(14):4926-4932.

Omega-3 and Omega-6 Ratio

- With Omega-3 balance, the omega-3 molecules of DHA and EPA will block the conversion to AA
- Allow omega-6 molecules GLA and DGLA to convert to a mucus-specific anti-inflammatory prostaglandin E1
- Thus, reducing inflammation in all mucous membranes in the body
- Reduces inflammation in the tear film

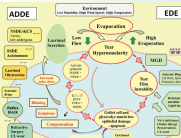



Image TFOS DEWS II

Too much Omega-3

- Not good!
- Fish oil is a blood thinner
- Ingesting excessive amounts could lead to easy bruising and other blood-thinning effects
- Better to reduce the amount of omega-6 fatty acids while moderately increasing the omega-3 fats in our diet

Vitamin A



- Vital for corneal and conjunctival epithelial cell health
- Necessary for the immune system to function
- Needed for goblet cell and lacrimal gland production of a variety of mucins for the base layer of the tear film
- Sources of Vitamin A
- Red, orange, yellow, and dark green leafy vegetables


Osaka A, Sakuma H, Ohta T, et al. Efficacy of retinal palmitate eye drops for dry eye in rabbits with lacrimal gland resection. Clin Ophthalmol. 2012;4:185-93.
 Smith JJ, Dreyer EH, Riquelme J, et al. Storage, release, and reabsorption in the lacrimal gland. Cornea Res. 1993;1(4):107-22.
 Smith JJ, Mollnes TM. Vitamin A is present as retinol in the tears of humans and rabbits. Cornea Res. 1984;2(4):815-22.

Vitamin A Deficiency

- Begin as dry eyes
- Progress to becoming the leading cause of preventable childhood blindness
- Vitamin A deficiency almost never seen in the developed world
- Reports of intentional vitamin A deficiency
 - A report from the 1960s
 - A man deliberately ate a vitamin A-deficient diet
 - Lived off of bread and lime juice for five years
 - His eyes developed corneal vascularization and ulceration of the cornea

Vitamin A Deficiency

- Report of a woman in a cult
 - Lived off of brown rice and herbal tea
 - Her eyes literally melted and collapsed
- Report of autistic children
 - Refused to eat anything but French fries or exclusively bacon, blueberry muffins, and Kool-Aid
 - Became vitamin A deficient
- Report from the Bronx
 - Child refused to eat vegetables
 - Ate only potato chips, puffed rice cereal with non-fortified soymilk, and juice drinks
 - Became vitamin A deficient



Ocular sequelae of vitamin A deficiency. Sunil Karama, Saji Jagtap and Richard T. Le. Retina Int J Ophthalmol. 2008; 18(1): 208. 11. doi: 10.1097/IIO.0b013e3181724537.2008.1801208.x

Vitamin B12 deficiency and neuropathic ocular pain

- OSDI score
- 3rd OSDI question score (have you experienced painful or sore eyes during last week?)
- TBUT
- Schirmer's
- Improved after 12 weeks (p < 0.001 for each group)
- Group 1 mean vitamin B12 level at enrollment was 144.24 ±43.36 pg/ml
- Group 2 mean vitamin B12 level at enrollment was 417.53 ±87.22 pg/ml
- Group 1 reached 450 ±60.563 pg/ml after 12 weeks of treatment

Ozen S, Ozer MA, Akdemir MO. Vitamin B12 deficiency evaluation and treatment in severe dry eye disease with neuropathic ocular pain. Graefes Arch Clin Exp Ophthalmol. 2017 Mar 15; doi: 10.1007/s00417-017-3632-y. [Epub ahead of print]


Vitamin B12 deficiency and neuropathic ocular pain

- The decrease in the OSDI questionnaire score (-30.80 ±5.24) and 3rd OSDI question score (-2.82 ±0.53) were remarkable in group 1
- Findings indicate that vitamin B12 deficiency is related with NOP
- ★ Consider measuring the serum vitamin B12 level in patients with severe DED presenting with resistant ocular pain despite taking topical treatment

Ozen S, Ozer MA, Akdemir MO. Vitamin B12 deficiency evaluation and treatment in severe dry eye disease with neuropathic ocular pain. Graefes Arch Clin Exp Ophthalmol. 2017 Mar 15; doi: 10.1007/s00417-017-3632-y. [Epub ahead of print]

Vitamin C

- Vitamin C as ascorbyl palmitate (fat-soluble form) modulates PGE1 synthesis
- This vitamin C form enhances the production of IgE concentrates in tears, the first line of basophil and mast cell defense against invading pathogens and allergens that frequently cause dry eye symptoms
- Sources of Vitamin C
- Citrus



Horrobin DJ, Campbell A. Sjögren's syndrome and the sicca syndrome: the role of prostaglandin E1 deficiency. Treatment with essential fatty acids and vitamin C. Med Hypotheses. 1980 Mar;4(3):225-32.

Vitamin D



- Improves tear hyperosmolarity 1,2
- Should be included in all formulations that include vitamin A due to an increased risk of fractures in older patients taking large amounts of supplemental vitamin A
- However, up to 50% of the world's population may not get enough sun, and 40% of US residents are deficient in vitamin D 3,4
- Sources of Vitamin D
 - Salmon, herring, sardines, canned tuna, oysters, shrimp, egg yolks, mushrooms

1. Rowland G, Hashemi M, Calero A, et al. Effect of retinoic acid and vitamin D3 on osteoblast differentiation and activity in aging. *J Bone Miner Metab*. 2014 Jun;34(1):45-78.
 2. Kraljic M, et al. Vitamin D replacement improves tear osmolarity in patients with vitamin D deficiency. *Semin Ophthalmol*. 2013;32(1):289-294.
 3. Hoq M, et al. Vitamin D deficiency in a large section of patients from The Emirates. *J Dermatol Sci Technol*. 2014;14(2):207-213. doi: 10.1016/j.jdermst.2014.02.007. Epub 2014 Feb 11.

Vitamin E

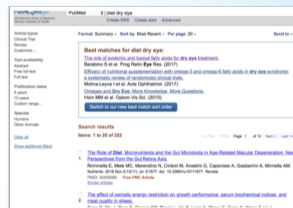


- Helps prevent or slow lipid oxidation
- Recommend to include in all fatty acid-based formulations including any formulation that includes flaxseed oil or fish oil
- Sources of Vitamin E
 - Cooking oils, nuts, sunflower seeds, almonds, hazelnuts, olive, pine nuts, salmon, peanuts, avocado, raw peppers, mango

Jiang Q, Elion-Schwab I, Courtemanche C, Ames BN. gamma-tocopherol and its major metabolite, in contrast to alpha-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. *Proc Natl Acad Sci U S A*. 2000 Oct 10;97(21):11474-9.

Which diet is best for dry eye?

- Plant based diet
- Paleo diet
- Vegan
- Gluten free
- Whole 30



The Dry Eye Diet

- Lower protein, total fat, and cholesterol intake
- And
- Increase complex carbohydrates
- Increase vitamin A content (red, orange, yellow, and dark green leafy vegetables)
- Increase zinc and folate intake (whole grains, beans, raw vegetables, especially spinach)
- Ensure sufficient vitamin B6 and potassium intake (by eating nuts, bananas, and beans)
- Ensure sufficient vitamin C intake (by eating citrus)
- Eliminate alcohol and caffeine
- Reduce sugar and salt intake
- Consume six to eight glasses of water per day

20190410005_2019_AJ_20190410005_2019_AJ_10101000_2017-01-04_Epub 2019 Apr 4
Impact of lifestyle intervention on dry eye disease in office workers: a randomized controlled trial.
 Kawashima M¹, Saito K¹, Shimizu M¹, Tsubota K¹


- Study to evaluate the effects of a 2-month lifestyle intervention for DED in office workers.
- Prospective interventional RCT
- 41 middle-aged Japanese office workers (22 men, 19 women, 39.2 ± 8.0 years) with DED
- Two groups
- Intervention group (n = 22)
 - Diet modification, increase physical activity, positive thinking
- Control group (n = 19)

- Primary outcome
- Change in DED diagnoses
- Secondary outcome
- Change in disease parameters - dry eye symptoms (Dry Eye-Related Quality of Life Score), corneal and conjunctival staining scores, TBUT, and Schirmer test results.

20190410005_2019_AJ_20190410005_2019_AJ_10101000_2017-01-04_Epub 2019 Apr 4
Impact of lifestyle intervention on dry eye disease in office workers: a randomized controlled trial.
 Kawashima M¹, Saito K¹, Shimizu M¹, Tsubota K¹

- 2-month lifestyle intervention
- Improved dry eye disease
- Considerable decrease in subjective symptoms
- ★ Lifestyle intervention may be a promising management option for DED

No more coffee?



The effect of caffeine on tear secretion

- Caffeine is the most widely consumed psychoactive substance
- Conflicting effects on tear film dynamics
- Orally ingested caffeine on tear secretion
- Examiner-masked, placebo-controlled, crossover experimental study
- Effect of caffeine intake on tear secretion

©Wai I.K.A., Oveisian-Ghoms G., Kyri, et al. The effect of caffeine on tear secretion. Optom Vis Sci. 2014 Feb;91(2):171-7. doi:10.1097/OVS.0000000000000129.

The effect of caffeine on tear secretion

- 41 healthy volunteers
- Aged 20 to 26 years (mean, 23.0 ± 2.1 years)
- Randomly assigned into two groups, A and B
- Two different treatments in two sessions
- Subjects in group A – visit 1
- 5.0 mg/kg body weight of caffeine dissolved in 200 mL of water
- Subjects in group B – visit 1
- 200 mL of water
- Visit 2 – order of treatment was reversed

©Wai I.K.A., Oveisian-Ghoms G., Kyri, et al. The effect of caffeine on tear secretion. Optom Vis Sci. 2014 Feb;91(2):171-7. doi:10.1097/OVS.0000000000000129.

The effect of caffeine on tear secretion

- Schirmer 1 scores
 - Measured repeatedly at 45, 90, 135, and 180 minutes after treatment
- Baseline Schirmer 1 scores compared with posttreatment scores
- Schirmer 1 scores increased after caffeine intake.
- Statistically significant at 45 and 90 minutes ($p < 0.05$) after caffeine intake.
- No influence of gender in caffeine's effect on tear secretion ($F = 0.994, p = 0.399$)
- ★ Orally ingested caffeine appears to stimulate tear secretion in healthy non-dry eye subjects.

Gopal EA, Overman-Ogbonna G, Kyei, et al. The effect of caffeine on tear secretion. *Optom Vis Sci*. 2014 Feb;91(2):171-7. doi: 10.1097/OFX.0000000000000129

Drink water!

- Mild dehydration makes dry eye problems worse.
- Especially during hot, dry and windy weather
- Drink more water to reduce the symptoms of dry eye syndrome



Microbiome and Ocular Health

- Microbiome and human health.¹
- Gut microbiota is significant in health and disease.^{3,6}
- An average human body harbors as many microbial species as human cells.²
- Many studies have linked microbiome to cancer, obesity, asthma, arteriosclerosis, and diabetes.



1. Pedersen CT, Sharma V, Eskin L, Pedersen SK. Immune homeostasis, dysbiosis and therapeutic modulation of the gut microbiota. *Cell Exp Immunol*. 2015;179:343-57.
 2. Sender R, Fuchs S, Miloš R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell*. 2016;144:127-40.
 3. Vitell L, Dolnik E, Bonacc IG, et al. Gut Microbiome and Anticancer Immune Response: Really hot 5'9". *Cell Death Differ*. 2015;22:199-214.
 4. Cibulka H. Microbiome and cancer. *Semin Immunopathol*. 2015;7:65-72.
 5. Sano Y, Okazaki M, Miyao-Peña A, Aguilera C. Understanding the role of gut microbiome in metabolic disease risk. *Pediatr Res*. 2015;77:234-44.
 6. Dominguez A, Cruz GA. Interactions between host factors and the skin microbiome. *Cell Mol Life Sci*. 2015;271:499-515.

- Ask about diet when evaluating DED
- Discuss supplementation
- Review caffeine and water intake
- The eyes will thank you

- Thank you for your time and attention!