Off the Menu – A Nutritional Approach to Dry Eye

Melissa Barnett, OD, FAAO, FSLS, FBCLA

Disclosures

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


VOTE
VOTE

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
- NEI -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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

n–3 Fatty Acid Supplementation for the Treatment of Dry Eye Disease

The Dry Eye Assessment and Management Study Research Group*

ABSTRACT

BACKGROUND

Dry eye disease is a common chronic condition that is characterized by ocular discomfort and visual disturbances that decrease quality of life. Many clinicians recommend the use of supplements of n–3 fatty acids (often called omega-3 fatty acids) to relieve symptoms.

METHODS

In a multicenter, double-blind clinical trial, we randomly assigned patients with moderate-to-severe dry eye disease to receive a daily oral dose of 3000 mg of fish-derived n–3 eicosapentaenoic and docosahexaenoic acids (active supplement group) or an olive oil placebo (placebo group). The primary outcome was the mean change from baseline in the score on the Ocular Surface Disease Index (OSDI; scores range from 0 to 100, with higher scores indicating greater symptom severity), which was based on the mean of scores obtained at 6 and 12 months. Secondary outcomes included mean changes per eye in the conjunctival staining score (ranging from 0 to 6) and the corneal staining score (ranging from 0 to 15), with higher scores indicating more severe damage to the ocular surface, as well as mean changes in the tear break-up time (seconds between a blink and gaps in the tear film) and the result on Schirmer's test (length of wetting of paper strips placed on the lower eyelid), with lower values indicating more severe signs.

RESULTS

A total of 349 patients were assigned to the active supplement group and 186 to the placebo group; the primary analysis included 329 and 170 patients, respectively. The mean change in the OSDI score was not significantly different between the active supplement group and the placebo group (–13.9 points and –12.5 points, respectively; mean difference in change after imputation of missing data, –1.9 points; 95% confidence interval [CI], –5.0 to 1.1; P=0.21). This result was consistent across prespecified subgroups. There were no significant differences between the active supplement group and the placebo group in mean changes from baseline in the conjunctival staining score (mean difference in change, 0.0 points; 95% CI, –0.2 to 0.1), corneal staining score (0.1 point; 95% CI, –0.2 to 0.4), tear break-up time (0.2 seconds; 95% CI, –0.1 to 0.5), and result on Schirmer's test (0.0 mm; 95% CI, –0.8 to 0.9). At 12 months, the rate of adherence to treatment in the active supplement group was 85.2%, according to the level of n–3 fatty acids in red cells. Rates of adverse events were similar in the two trial groups.

CONCLUSIONS

Among patients with dry eye disease, those who were randomly assigned to receive supplements containing 3000 mg of n–3 fatty acids for 12 months did not have significantly better outcomes than those who were assigned to receive placebo. (Funded by the National Eye Institute, National Institutes of Health; DREAM ClinicalTrials.gov number, NCT02128763.)

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*The study investigators and other personnel are listed in the Supplementary Appendix, available at NEJM.org.

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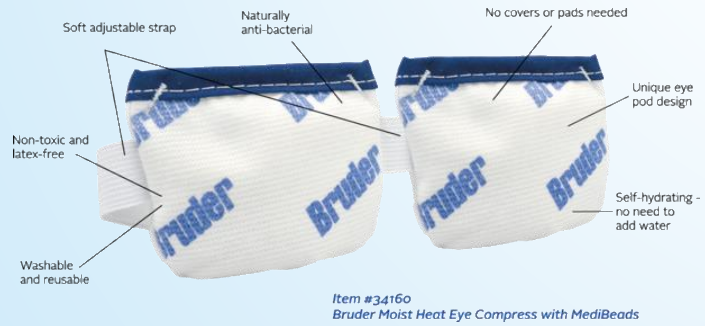
DREAM

- 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 [2]
  - Pro-inflammatory cytokine and biomarker in DED

1. Gorzynik-Debicka M et al. Potential health benefits of olive oil and plant polyphenols. Int. J. Mol. Sci. 19: 547, 2018.
2. Basu A et al. Dietary factors that promote or retard inflammation. Arterioscler Thromb Vasc Biol. 26:995-1001, 2006.

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

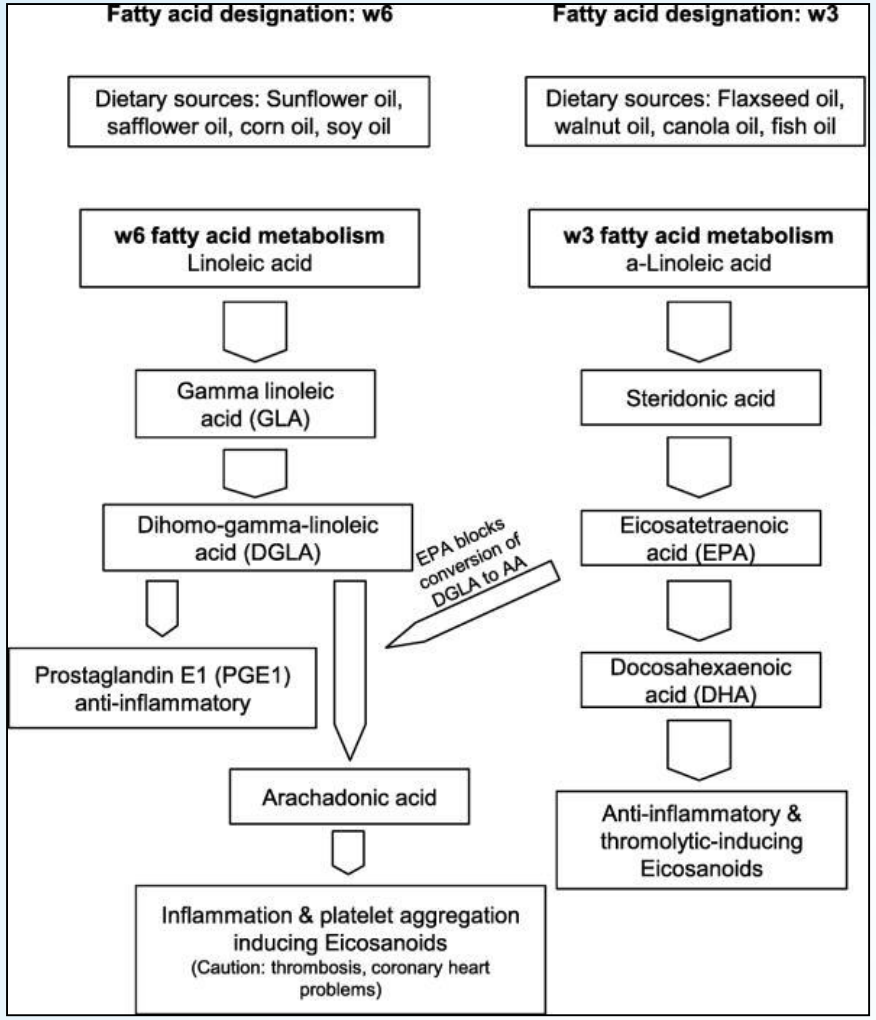
- Both treatment and placebo groups improved over time
  - Heterogeneous study population
  - DED is a complex and multifactorial disease state
  - Difficult to measure the effect of a single, non-specific intervention
- Traditional measurements used (OSDI and Schirmers) have limited sensitivity and 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?

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

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

Slide credit Nathan Schramm, OD, CNS, FSLS



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

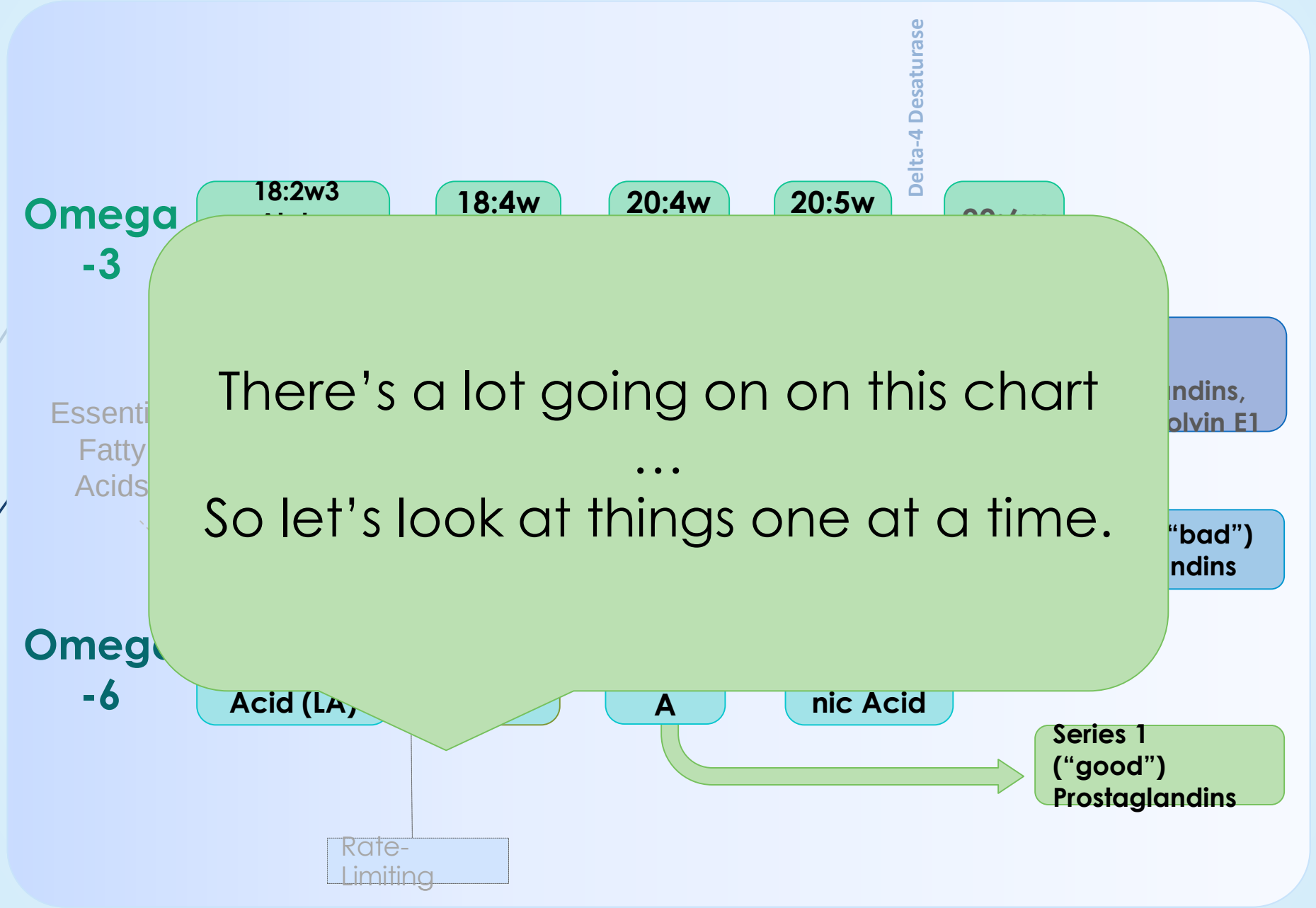
- Alpha-linolenic acid (ALA) - omega-3
- Linoleic acid (LA) - omega-6
- Docosahexaenoic acid (DHA)
- Eicosapentaenoic acid (EPA)
- Arachidonic acid (AA)
- Gamma-linolenic acid (GLA)
- Dihomo-gamma-linolenic acid (DGLA)

DHA and EPA

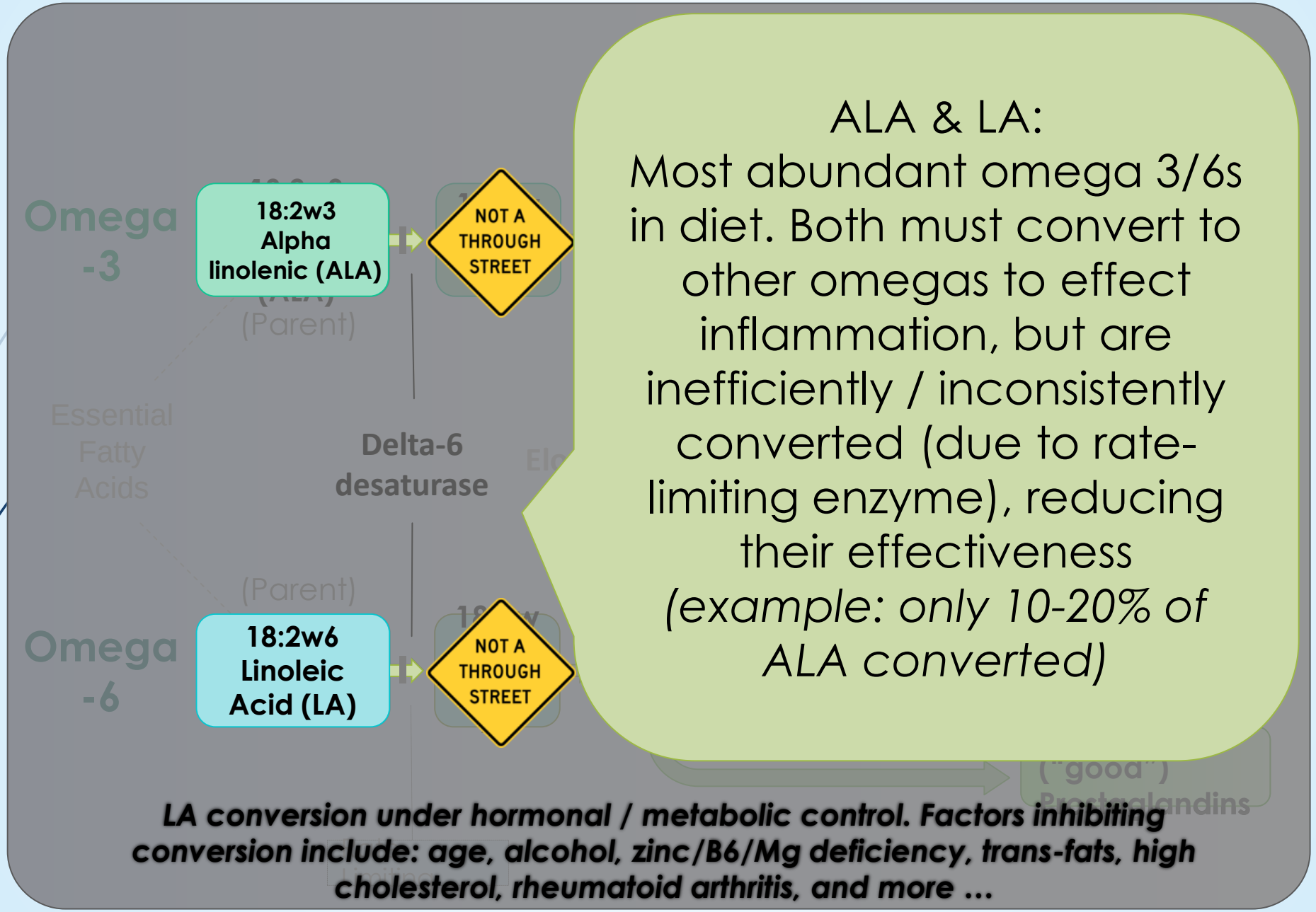
- DHA and EPA are formed when fish eat algae and are found in the triglyceride form [1,2]
- A triglyceride consists of a three-carbon glycerol "backbone" with each carbon linked to a fatty acid molecule.
- Each triglyceride molecule contains three fatty acids.
- In normally produced fish oil – 20% to 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. Visioli F, Risé 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 J, 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



Anti-inflammatory Fatty Acids

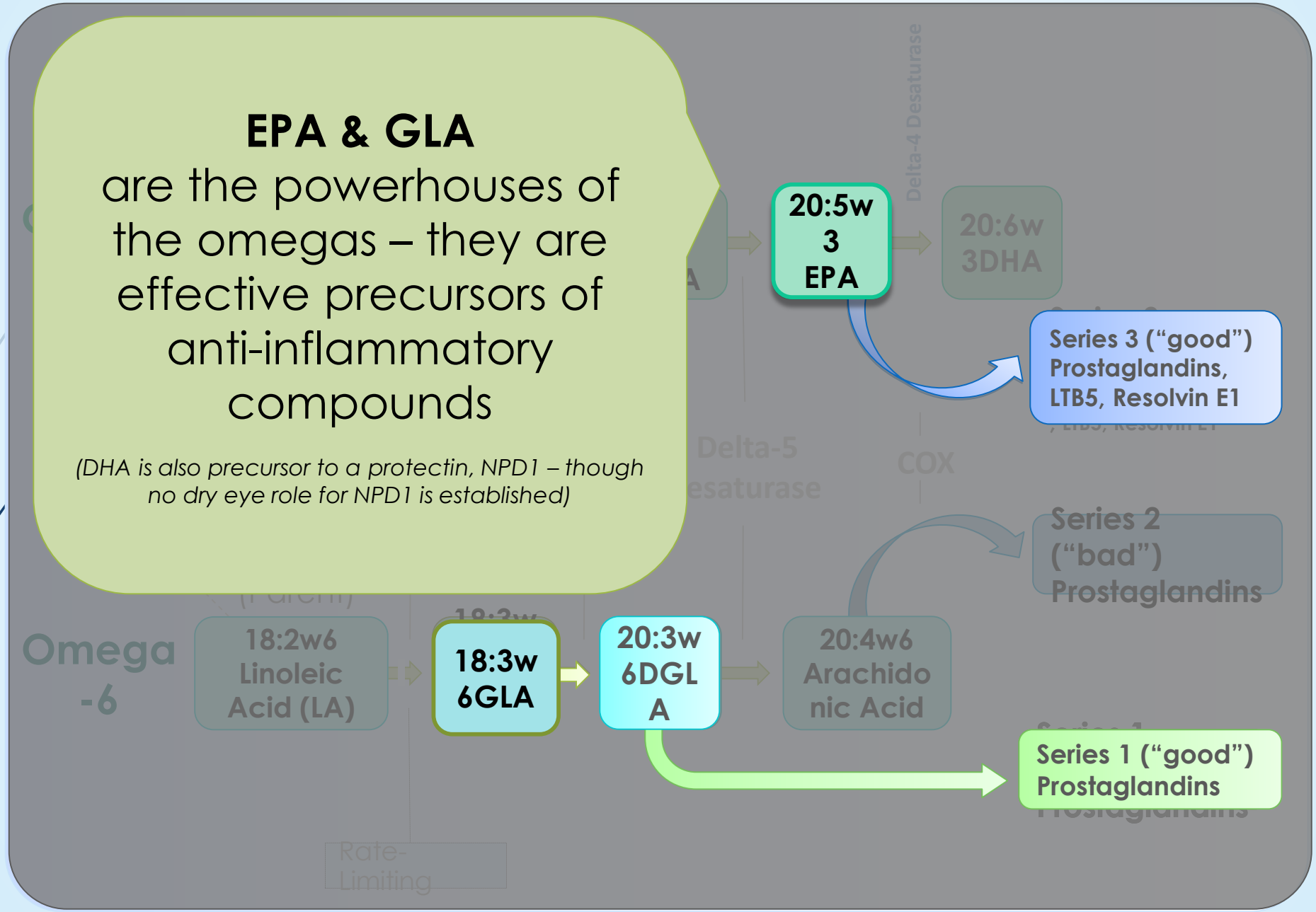


2016, Zac Denning, ScienceBased Health, zdenning@sbh.com

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 protectin, NPD1 – though no dry eye role for NPD1 is established)



Anti-inflammatory Fatty Acids

Flaxseed oil provides … mostly ALA (plus small amount of LA)

Both inefficiently used

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Anti-inflammatory Fatty Acids

Fish oil provides EPA and DHA

Efficiently used, good health benefits overall

20:5w3 EPA

20:6w3DHA

Series 3 ("good") Prostaglandins

Delta-5 Desaturase

COX

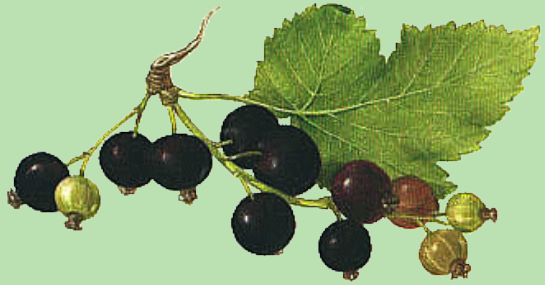
Series 2 ("bad") Prostaglandins

20:3w6DGLA

20:4w6 Arachidonic Acid

Series 1 ("good") Prostaglandins

Anti-inflammatory Fatty Acids



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

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

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)*

1.Viau, Sabrina, et al. Graefe's Arch Clin Exp Ophthalmol 247.8 (2009): 1039-1050.
2.Aragona, Pasquale, et al. Invest Ophthalm Vis Sci 46.12 (2005): 4474.

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 a clinical trial (n=38)

GLA

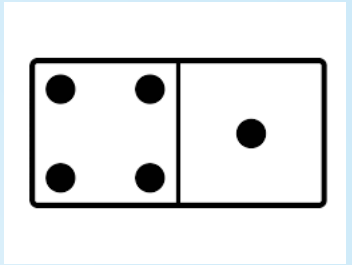
- GLA, unaccompanied by fish oil, has been found to alleviate dry eye symptoms
  - Increase tear production and improve CL discomfort in CL associated dry eye[1]
  - Reduce ocular surface inflammation in Sjögren's syndrome[2]
  - GLA with eyelid hygiene, decrease eyelid margin inflammation and improve symptoms in mgd more than either treatment alone[3]
  - Post-menopausal women[4]
  - Mild-moderate DED [5]

1.Kokke KH et al. Oral omega-6 fatty acid treatment in contact lens associated dry eye. Cont Lens Anter Eye. 31:141–46, 2008.
2.Aragona P et al. Systemic omega-3 essential fatty acid treatment and PGE1 tear content in Sjogren's syndrome patients. Invest Ophthalmol Vis Sci. 46:4474–79, 2005.
3. Pinna A et al. Effect of oral linoleic and gamma-linolenic acid on meibomian gland dysfunction.
4. Sheppard JD, Pflugfelder SC, et al. Cornea 32 :1297-1304, 2013.
5.(Brignole-Baudouin et al. Acta Ophthalmologica 89:e591-7, 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

Miljanović B, Trivedi KA, Dana 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 Oct;82(4):887-93.
Enos RT, Velázquez KT, McClellan JL, et al. Reducing the dietary omega-6:omega-3 utilizing a-linolenic acid; not a sufficient therapy for attenuating high-fat-diet-induced obesity development nor related detrimental metabolic and adipose tissue inflammatory outcomes. PLoS One. 2014 Apr 14;9(4):e94897.

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

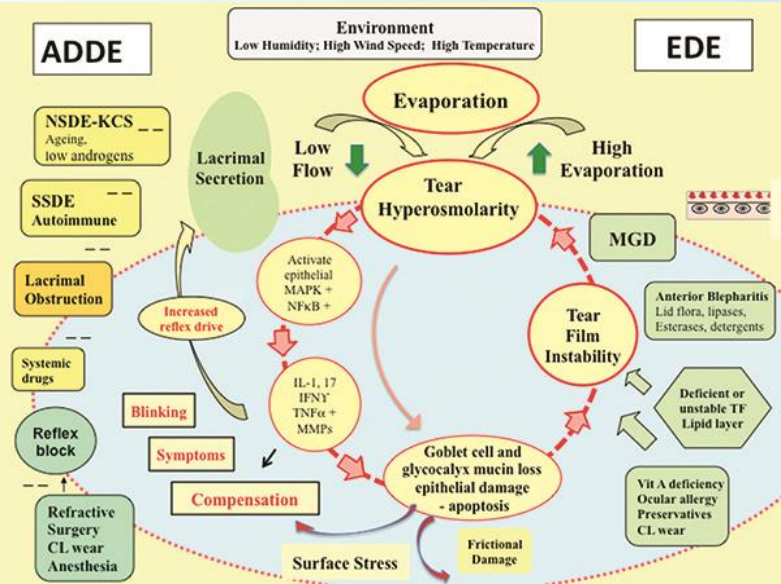


Image TFOS DEWS II

Ethyl Ester (EE) vs Trigylceride (TG)

- EE must convert in the liver (produces ethanol)[1]
- EE reduces bioavailability and often results in:
  - GI distress,
  - "fish burps," and other GI symptoms.[2]
  - Blood thinning (often from Vitamin E)

1. Saghir M, Werner J, et al Rapid in vivo hydrolysis of fatty acid ethyl esters, toxic nonoxidative ethanol metabolites. Am J Physiol. 1997 Jul;273(1 Pt 1):G184-90.
2. Alexander LJ.Is there a difference between re-esterified triglyceride and ethyl ester fish oil? *Advanced Ocular Care.* January/February 2011;2(1):20-21.

Slide credit Nathan Schramm, OD, CNS, FSLS.

EE converted to TG in lab

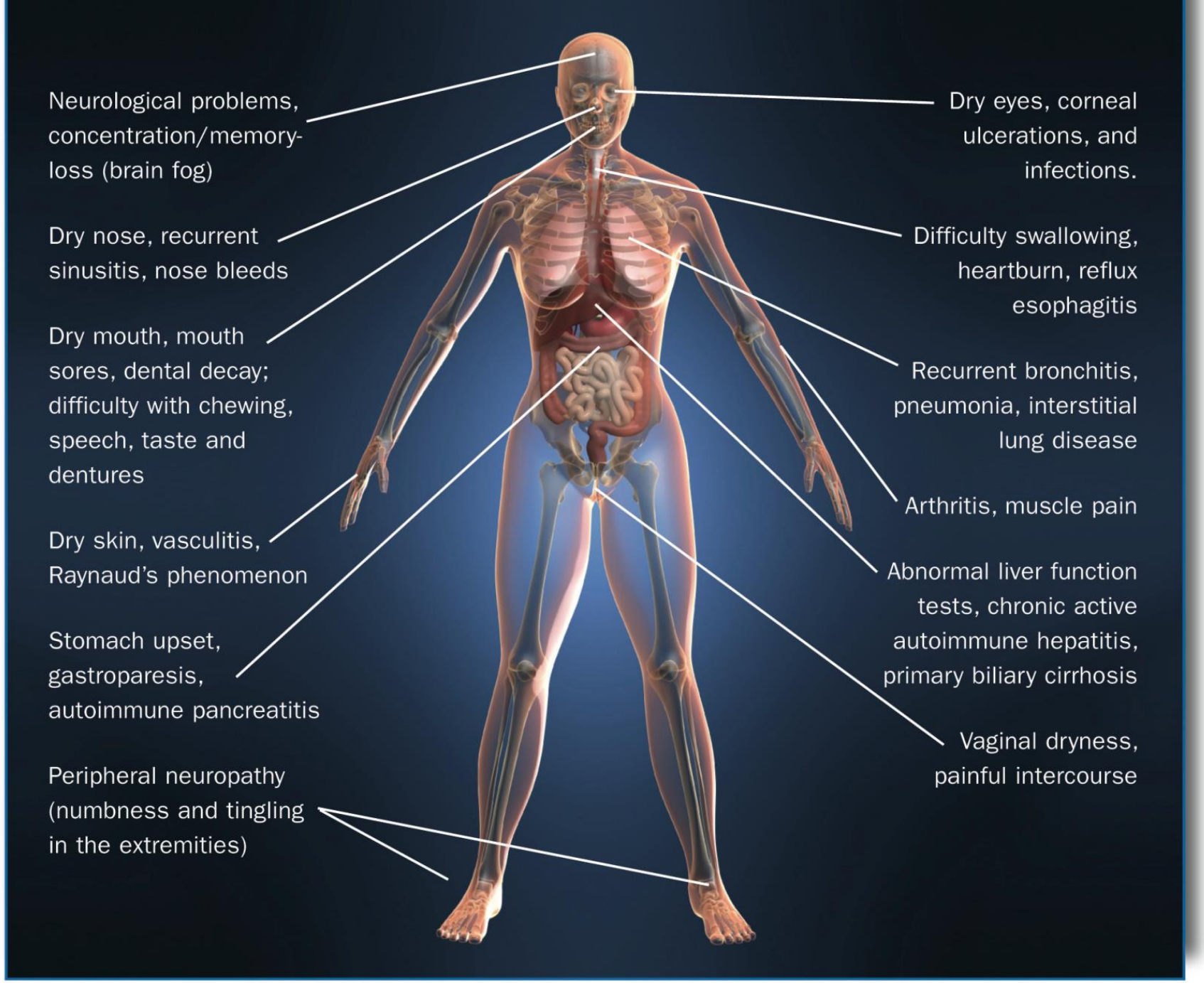
- re-esterified Triglyceride (rTG)
  - when alcohol is removed, and oil is converted back to more natural triglyceride form.
- rTG
  - 2x better absorption than EE[1,2]

1. Beckermann B, Beneke M, Seitz I. Comparative bioavailability of eicosapentaenoic acid and docosahexaenoic acid from triglycerides, free fatty acids and ethyl esters in volunteers. Arzneimittelforschung. 1990 Jun;40(6):700-4. PMID: 2144420
2. Visioli F, Rise 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. PMID: 12848287

Slide credit Nathan Schramm, OD, CNS, FSLS

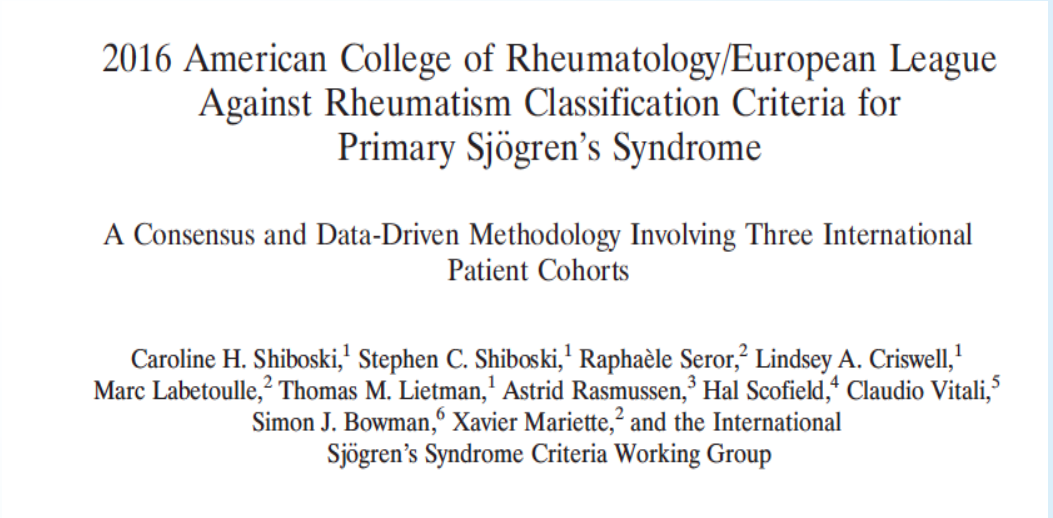
Too much Omega-3

- 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


Neurological problems, concentration/memory-loss (brain fog)
Dry nose, recurrent sinusitis, nose bleeds
Dry mouth, mouth sores, dental decay; difficulty with chewing, speech, taste and dentures
Dry skin, vasculitis, Raynaud's phenomenon
Stomach upset, gastroparesis, autoimmune pancreatitis
Peripheral neuropathy (numbness and tingling in the extremities)
Dry eyes, corneal ulcerations, and infections.
Difficulty swallowing, heartburn, reflux esophagitis
Recurrent bronchitis, pneumonia, interstitial lung disease
Arthritis, muscle pain
Abnormal liver function tests, chronic active autoimmune hepatitis, primary biliary cirrhosis
Vaginal dryness, painful intercourse

ACR, EULAR classification criteria for Sjögren's syndrome

- anti-Sjögren'-syndrome-related antigen A (anti-SSA/Ro) antibody positivity
- focal lymphocytic sialadenitis with a focus score of at least 1 foci per 4 mm^2
- abnormal ocular staining score of at least 5 or a van Bijsterveld score of at least 4
- Schimer's test result of no greater than 5 mm per 5 minutes
- an unstimulated salivary flow rate of no greater than 0.1 mL per minute



2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome

A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts

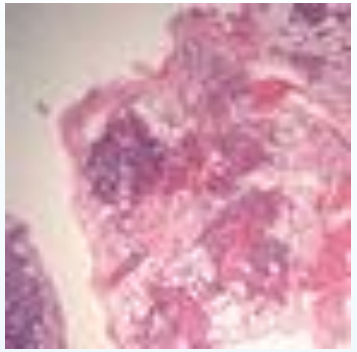
Caroline H. Shiboski,[1] Stephen C. Shiboski,[1] Raphaèle Seror,[2] Lindsey A. Criswell,[1] Marc Labetoulle,[2] Thomas M. Lietman,[1] Astrid Rasmussen,[3] Hal Scofield,[4] Claudio Vitali,[5] Simon J. Bowman,[6] Xavier Mariette,[2] and the International Sjögren's Syndrome Criteria Working Group

ACR, EULAR classification criteria for Sjögren's syndrome

- anti-SSA/Ro and sialadenitis items
  - Weight of three
- Remaining three items
  - Weight of one

Sjögren's Syndrome

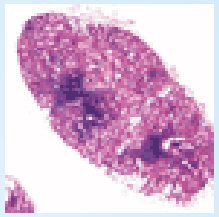
- Primary Sjögren's syndrome
  - Any 4 of the 6 criteria
  - Must include either item IV (Histopathology) or VI (Autoantibodies)
  - Or any 3 of the 4 objective criteria (III, IV, V, VI)



Sjögren's Syndrome

- Secondary Sjögren's syndrome
- All characteristics of Primary Sjögren's syndrome
  - + another well-defined major connective tissue disease
  - The presence of one symptom (I or II)
  - And 2 of the 3 objective criteria (III, IV and V)
- With autoimmune connective tissue disease
- Most commonly rheumatoid arthritis
- Nine out of ten patients with Sjögren's are women

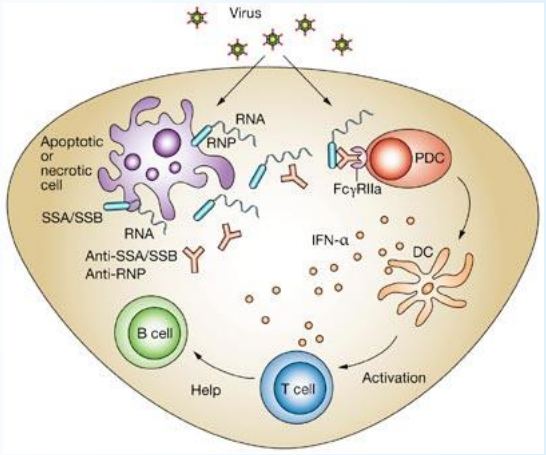
Sjögren's Syndrome



- In both Primary and Secondary Sjögren's syndrome
- Lacrimal and salivary gland function and anatomy are altered by the immune cell infiltrate
- Primary Sjögren's
  - Pathogenesis involves complex interaction between genes and the environment
- Recent large-scale Genome-Wide Association Study (GWAS)
  - Goal – Define genetic factors of KCS and focal lymphocytic sialoadenitis
  - Study of 3,334 Sjögren's patients
  - Outcome – ocular and oral manifestations of Sjögren's influenced by both shared and trait-specific genetic factors
  - ★ Non-Hodgkin lymphoma occurs in 5-10% of primary Sjögren's patients

Sjögren's Syndrome

- Traditional testing
- Autoantibodies as diagnostic markers
- Anti-Ro / SSA
  - 70% positive in Sjögren's patients
- Anti – La / SSB
  - 40% positive in Sjögren's patients
- Anti-nuclear antibodies (ANA)
  - 70% positive in Sjögren's patients
- Rheumatoid Factor (RH)
  - Positive in many rheumatic diseases
  - Performed for the diagnosis of rheumatoid arthritis (RA)
  - Positive 60-70% of patients with Sjögren's



Sjögren's Syndrome

- New studies - additional autoantibodies in Sjögren's Syndrome to
  - Salivary gland protein 1 (SP-1)
  - Carbonic anhydrase 6 (CA6)
  - Parotid secretory protein (PSP)
- Occurred earlier in the course of the disease
- Antibodies found in 45% of patients meeting the criteria for Sjögren's Syndrome who lacked antibodies to Ro or La
- SP-1, CA6 and PSP
  - Useful markers to identify patients with Sjögren's Syndrome at early stages of the disease
  - Useful markers to identify those that lack antibodies to either Ro or La

Sjö testing

- Finger prick
- Obtain a blood sample
- Apply sample to the collection card
- Send card to be analyzed

- Test done at local lab

The Presentation of Sjögren's Disease in North American Optometric Practices

Jennifer Harthan[1], Sruthi Srinivasan[2], Mira Acs[3], Melissa Barnett[4], Charles Edmonds[5], Larisa Johnson-Tong[6], Richard Maharaj[7], Bart Pemberton[5], Dominik Papinski[2], Barbara Caffery[3]

[1]Illinois College of Optometry, Chicago, IL, [2]Centre for Contact Lens Research, University of Waterloo, Ontario [3]Toronto Eye Care, Toronto, ON, [5]Edmonds, Husz & Pemberton Eye Center, Tucxon, AZ

BACKGROUND

Sjögren's Disease (SD) is a chronic autoimmune infla
systemic disorder characterized by the presence of
lymphocytic infiltration of the exocrine glands and t
presence of autoantibody production.[1] SD has an es
prevalence of 0.6% to 1%, making it the most comm
systemic autoimmune rheumatic disease.[2]

- The lacrimal and salivary glands are the principal t
of the inflammatory process. As a result, ocular an
dryness are the hallmark symptoms of SD.[1,5]
- The dry eye aspect of SD can be debilitating as it c
to multiple complications.[3,4]
- As dry eye is the main ocular manifestation of SD,
patients first seek care from their eye care professi
the chronic nature of their disease leads to freque

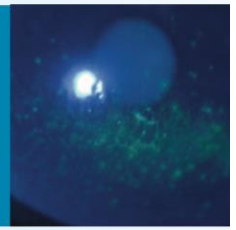


Figure 1: Corneal Staining Commonly Seen in Sjögren's Disease Patients

PURPOSE

The purpose of this multi-center, cross-sectional retrospective chart review was to describe the symptoms and signs of dry eye in Sjögren's Disease (SD) patients as they presented in optometric practices.

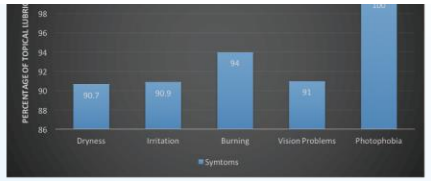
METHODS

SD charts from 6 North American clinical sites were identified by a dry eye diagnostic code.

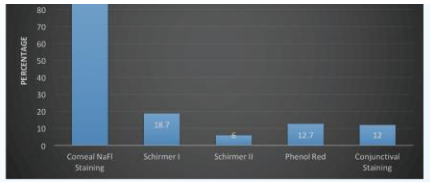
- Starting with the first visit after diagnosis of SD, variables were recorded including:
  - o Age
  - o Sex
  - o Year of diagnosis
  - o Symptoms of dry eye
  - o Signs of dry eye
  - o Treatments
- Various corneal staining scales were used across sites that were harmonized to a global staining score (0-100).
- Data from the 1st observed visit was analyzed.

RESULTS

- SD patients presented in optometric offices with a variety of dry eye symptoms and signs.
- The most common presenting symptom was dryness and the most common sign was corneal fluorescein staining.
- The degree of corneal staining varied widely and was not severe in most patients.
- Regardless of symptoms, topical lubricants were highly utilized in management.
- Future studies with standardized testing and prospective analysis will help to elucidate the course of dry eye in SD.



- Topical lubricants were used over 90% of the time in SD patients who experienced symptoms of photophobia, burning, vision problems, irritation, and dryness.
  - o 100% of patients who reported photophobia used topical lubricants.



- Corneal fluorescein staining was the most commonly recorded dry eye sign.
  - o It was recorded in 120 charts (98%) and was present in 85 (69.3%) patients.
  - o The average corneal staining score of the worst eye was 28 +/- 29 (range 0 to 75).
- Other signs were recorded with less regularity; Schirmer I (28/105=18.7%), Schirmer II (9/105=6%), phenol red (19/105=12.7%), conjunctival staining (18/105=12%).

CONCLUSIONS

tients presented in optometric offices with a variety
eye symptoms and signs.

ost common presenting symptom was dryness and
ost common sign was corneal fluorescein staining.

egree of corneal staining varied widely and was not
in most patients.

dless of symptoms, topical lubricants were highly
d in management.

studies with standardized testing and prospective
is will help to elucidate the course of dry eye in SD.

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r E, Andersson SI, Manthorpe R, Jacobsson LT. Proposed core set of outcome
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n K, Moen K, Jacobsen H, Jonsson R, Brun JG. Exocrine function in primary Sjogren
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49-954.

PPORT

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Resources: Fellows Doing Research SIG of the American Academy of Optometry
Guidance: Peter Bergenske OD, FAAO, Robin Chalmers OD, FAAO

DISCLOSURES

Jennifer Harthan: Allergan, Bausch + Lomb, Contamac, Metro Optics, Shire; Sruthi Srinivasan and Dominik Papinski: *Over the past three years members of the CCLR have received research funding and/or honoraria from the following companies:* Advanced Vision Research, Alcon, Allergan, Contamac US, CooperVision, Essilor, Inflamax Research, Johnson & Johnson Vision Care, Ocular Dynamics, Oculus, TearScience, TearLab; Mira Acs: Alcon; Melissa Barnett: Acculens, Alden Optical, Alcon, Allergan, Bausch + Lomb, CooperVision, JJVC Vistakon, Novabay, Gas Permeable Lens Institute (GPLI), Paragon Biotek, Scleral Lens Education Society, Shire, STAPLE Program; Charles Edmonds: None; Larisa Johnson-Tong: None; Richard Mahara: None; Bart Pemberton: None; Barbara Caffery: Santen, Allergan, Shire; Robin Chalmers: AcuFocus, Inc., Alcon Research, Ltd, CooperVision, JJVC

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The Correlation of Corneal Staining with Age and Years of Disease in Sjogren's Syndrome

5683 - A0029

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AFFILIATIONS: [1]Toronto Eye Care, Toronto, Ontario, Canada, [2]Illinois College of Optometry, Chicago, IL, USA,[3]UC Davis Eye Center, Sacramento, California, USA, [4]Edmonds, Husz & Pemberton Eye Center, Tuscon, Arizona, USA, [5] eyeLABS Optometry and Centre for Ocular Surface Disease, Brampton, Ontario, Canada, [6] Centre for Contact Lens Research, University of Waterloo, Ontario, Canada

BACKGROUND

Sjogren's Syndrome (SS) is a chronic autoimmune inflammatory progressive disease characterized by the presence of lymphocytic infiltration of the exocrine glands and autoantibody production. SS has a prevalence of approximately 0.6%, making it the most common systemic autoimmune rheumatic disease.[1]

- The lacrimal and salivary glands are the principal targets of the inflammatory process.[2] As a result, ocular and oral dryness are the hallmark symptoms of SS.
- The dry eye aspect of SS can be debilitating as it can lead to multiple complications.[3,4]
- As dry eye is the main ocular manifestation of SS, many SS patients first seek care from their eye care professional and the chronic nature of their disease leads to frequent visits.[4]
- The natural history of dry eye in Sjogren's syndrome is poorly documented.

PURPOSE

The purpose of this multi-center retrospective chart review was to measure the relationship between corneal fluorescein staining and age and corneal staining and years since diagnosis of SS.

METHODS

Study Design:

SS charts from 6 North American clinical sites were identified by a dry eye diagnostic code.

- Charts with a positive diagnosis of primary or secondary SS were included.
- Data was reviewed from the year 2000 onward.
- All relevant data was collected as long the patients were seen for at least 2 visits within 10-15 consecutive months.
- The first visit was the diagnostic visit or the one closest following the date of diagnosis.
- Multiple variables were collected from charts using a template.
- Starting with the first visit after diagnosis of SS, variables were recorded including:
  - Age
  - Sex
  - Year of diagnosis
  - Type of Practitioner who diagnosed
  - Corneal staining with fluorescein
  - Other ocular surface signs and symptoms
- Various corneal staining scales were used across sites that were harmonized to a global staining score (0 to 100).
- Data from the 1st observed visit was analyzed.

Statistics:

- Pearson correlations between grade of cornea staining of the worst eye and a) patient age and b) years since diagnosis were conducted by SPSS statistical package.

RESULTS

- 123 SS patient charts were included:
  - 115 (93.5%) female
  - Average age: 56.1 + 11.9 (range 24 to 84 years)
  - Average time since diagnosis: 7.2 + 5.1 (n = 72; range 0 to 17 years; 51 with unknown)

FIGURE 1: Average Patient Age per Clinical Site

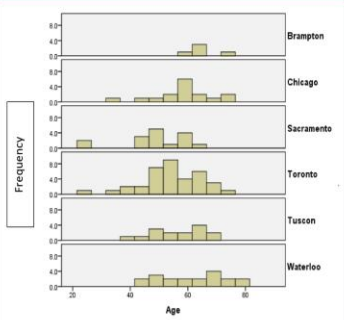
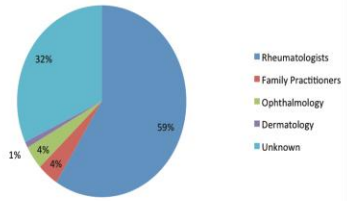


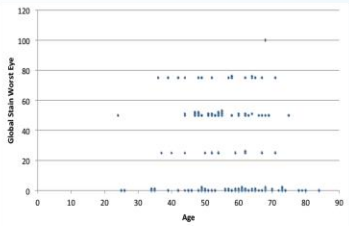
FIGURE 2: Diagnosis of Sjogren's Syndrome by Practitioner



- Corneal fluorescein staining was recorded on 98.4% (121) of the patients and was present in 69.3% (85).
  - Global corneal staining was documented on a scale of 0 to 100.
  - The average corneal staining score of the worst eye was 37.48 + 33.95 (range 0 to 100).

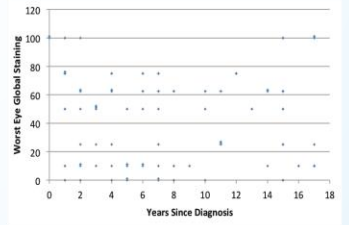
FIGURE 3: Example of Global Corneal Staining

FIGURE 4: Correlation of Global Corneal Staining (Worst Eye) and Age



- There was **no significant correlation** between grade of corneal staining worst eye and patient age (n = 119, r = -0.17, p = 0.065).

FIGURE 5: Correlation of Global Corneal Staining (Worst Eye) and Years Since Diagnosis



- There was also **no significant correlation** between grade of corneal staining worst eye and years since diagnosis (n=71, r = 0.048, p = 0.691).

** Our original analysis showed a correlation with corneal staining and years of disease. However, after reassessment of the data, no correlation was present.

CONCLUSIONS

These results suggest that Sjogren's related dry eye, as defined by corneal fluorescein staining of the worst eye is unrelated to patient age or time with disease.

- Further longitudinal review of these charts will establish other risk factors for progression and severity of dry eye in SS patients.
- The importance of co-management between rheumatology and optometry is significant in the diagnosis and management of SS patients.

SUPPORT

Funding Sources: Canadian Sjogren's Syndrome Society, Labtician Resources: Fellows Doing Research SIG of the American Academy of Optometry
Guidance: Peter Bergenske OD, FAAO, Robin Chalmers OD, FAAO

DISCLOSURES

Each author has no disclosure.

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Kathryn, 58 year old Caucasian Female

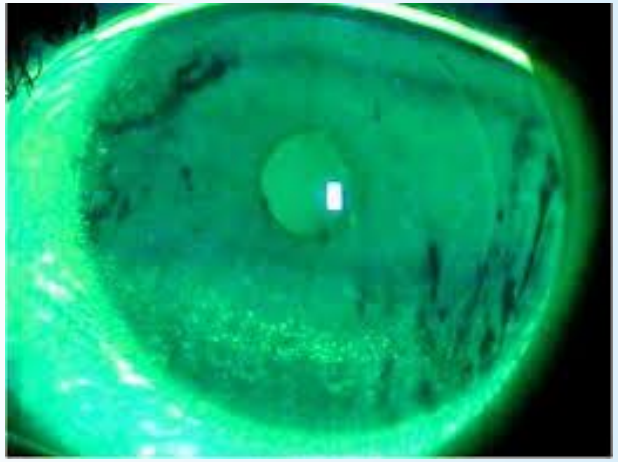
- Eyes hurt, ache, feel sandy, feel swollen
- Needs to blink to see better
- Hard to read small print
- No eyedrops used

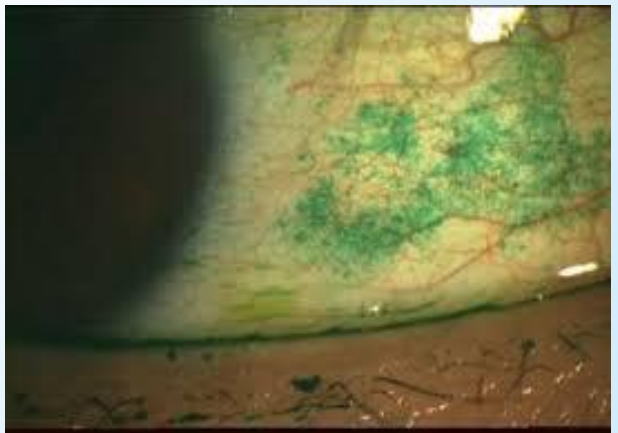
- Medical history significant for Sjögren’s disease
- Referred by rheumatology for evaluation

- Corrected VA
- OD 20/20
- OS 20/20

Kathryn Examination

- 1+ ptosis OU
- OD 2+ nasal, 1+ temp NaF stain, 1+ nasal and temporal LG
- OS 2+ nasal, 1+ temp NaF stain, 3+ nasal, 1+ temporal LG stain
- OD trace inferior PEK
- OS 1+ inferior PEK
- Reduced tear meniscus OU
- TBUT OD 3 seconds OS 4 seconds
- Map dot fingerprint dystrophy OU
- Normal intraocular pressures and retinal exam OU

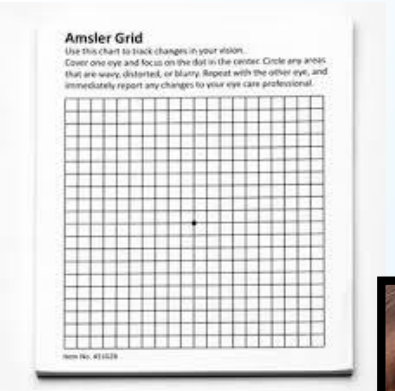


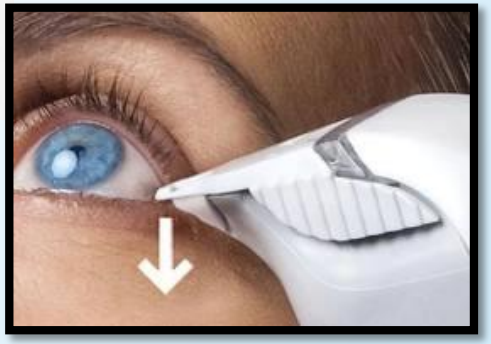


Kathryn Examination

- Normal color vision OU
- Normal Amsler grid OU
- Normal OCT of macula OU
- Normal 10-2 visual field OU

- Tear Lab OD 318, OS 299
- Normal intraocular pressures
- Normal dilated examination OU





Kathryn Treatment

- Monitor ptosis – not interested in surgical correction at this time
- Eyelid hygiene including warm compresses

- Cyclosporine 0.05% bid OU
- Non-preserved Optive and Oasis artificial tears as needed
- Lubricant ointment at night
- Frequent breaks on the computer
- HydroEye Omega 3 fatty acids
- Monitor cataracts yearly

Kathryn

- With time, added punctal plugs
- Moisture goggles at night
- Humidifier at night and near desk at work

- Eyes much more comfortable
- No dryness, no pain, no ache
- Resolved sandy and swollen sensation
- Vision improved

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

Odaka A, Toshida H, Ohta T, et al. Efficacy of retinol palmitate eye drops for dry eye in rabbits with lacrimal gland resection. Clin Ophthalmol. 2012;6:1585-93.
Ubels JL, Dennis MH, Rigatti BW, et al. Nuclear retinoic acid receptors in the lacrimal gland. Curr Eye Res. 1995 Nov;14(11):1055-62.
Ubels JL, MacRae SM. Vitamin A is present as retinol in the tears of humans and rabbits. Curr Eye Res. 1984 Jun;3(6):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

OD staphyloma OS leukoma

Ocular sequelae of vitamin A deficiency. Sunil Karande, Sujit Jagtap and Richard T Le Mesurier Med J Aust 2008; 188 (5): 308. | | doi: 10.5694/j.1326-5377.2008.tb01628.x

Vitamin B6

- One of the nutrient co-factors required to push the metabolic pathway conversion of GLA to DGLA.[1,2]
- Required for the neuronal blink response.[3]

- Sources of Vitamin B6
- Nuts, bananas, and beans

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2. Bordoni A, Hrelia S, Lorenzini A, et al. Dual influence of aging and vitamin B6 deficiency on delta-6-desaturation of essential fatty acids in rat liver microsomes. Prostaglandins Leukot Essent Fatty Acids. 1998 Jun;58(6):417-20.
3. Berman BD, Horovitz SG, Morel B, Hallett M. Neural correlates of blink suppression and the buildup of a natural bodily urge. Neuroimage. 2012 Jan 16;59(2):1441-50.

Vitamin B 12

- Also called cobalamin
- Water-soluble vitamin
- Involved in the metabolism of every cell of the human body
- Cofactor in DNA synthesis, and in fatty acid and amino acid metabolism

- Sources
  - Fish, meat, poultry, eggs, milk
  - Clams, sardines, tuna

Yamada K (2013). "Chapter 9. Cobalt: Its Role in Health and Disease". In Sigel A, Sigel H, Sigel RK. Interrelations between Essential Metal Ions and Human Diseases. Metal Ions in Life Sciences. 13. Springer. pp. 295–320. doi:10.1007/978-94-007-7500-8_9. ISBN 978-94-007-7499-5. PMID 24470095.

Vitamin B12 deficiency and neuropathic ocular pain (NOP)

- Study of vitamin B12 deficiency on NOP and symptoms in patients with DED
- 90 patients with severe DED without using ATs
- Group 1 (n =45)
- Severe DED and vitamin B12 deficiency
- Received parenteral vitamin B12 supplement + topical treatment (ATs + cyclosporine)
- Group 2 (n =45)
- Severe DED and normal serum vitamin B12 level
- Received only topical treatment (ATs + cyclosporine)

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

- 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 DF, 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;6(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. Bosetti M, Sabbatini M, Calarco A, et al. Effect of retinoic acid and vitamin D3 on osteoblast differentiation and activity in aging. J Bone Miner Metab. 2016 Jan;34(1):65-78.
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3. Haq A, Svobodová, Imran S, et al. Vitamin D deficiency: A single centre analysis of patients from 136 countries. J Steroid Biochem Mol Biol. 2016 Nov;164:209-213. doi: 10.1016/j.jsbmb.2016.02.007. Epub 2016 Feb 11.
4. Forrest KY, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. Nutr Res. 2011 Jan;31(1):48-54. doi: 10.1016/j.nutres.2010.12.001.

Vitamin E

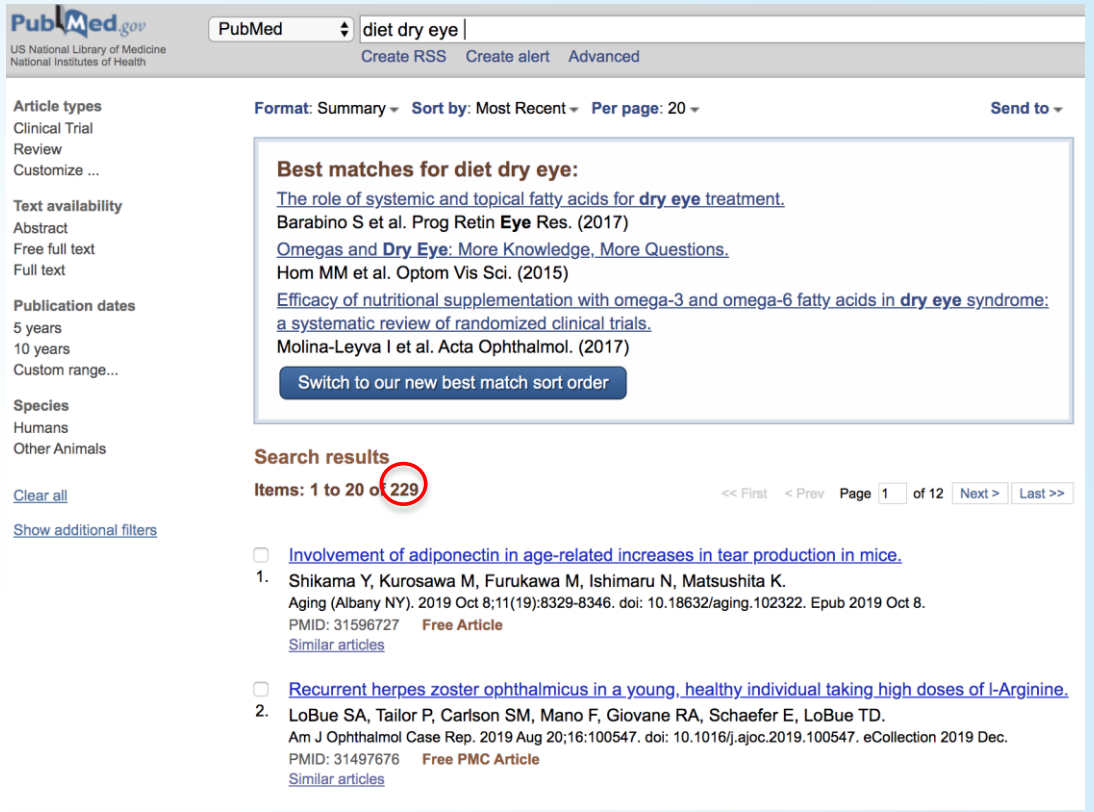
- Helps prevent or slow lipid oxidation
- Recommend to include in all fatty acid-based formulations including any formulation that includes flaxseed oil or fish oil

- Sources of Vitamin E
  - Cooking oils, nuts, sunflower seeds, almonds, hazelnuts, abalone, pine nuts, salmon, peanuts, avocado, raw peppers, mango

Jiang Q, Elson-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):11494-9.

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

J Occup Health. 2018 Jul 25;60(4):281-288. doi: 10.1539/joh.2017-0191-OA. Epub 2018 Apr 4.

Impact of lifestyle intervention on dry eye disease in office workers: a randomized controlled trial.

Kawashima M[1], Sano K[1], Takechi S[2], Tsubota K[1].

- 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.

J Occup Health. 2018 Jul 25;60(4):281-288. doi: 10.1539/joh.2017-0191-OA. Epub 2018 Apr 4.

Impact of lifestyle intervention on dry eye disease in office workers: a randomized controlled trial.

Kawashima M[1], Sano K[1], Takechi S[2], Tsubota K[1].

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

Tumeric and Dry Eye

- Curcumin properties
  - anti-oxidant, anti-inflammatory, anti-angiogenic and wound-healing
  - anti-tumor (breast, prostate, lung, pancreas, ovary, bladder, cervix, head and neck, brain, kidney and skin)
- Curcumin can help prevent corneal neovascularization
  - Curcumin blocks various growth factors and cytokines which can lead to nv
- Curcumin helps wound healing on the cornea
- Curcumin inhibits inflammatory cytokines which can then decrease the feedback loop which causes dry eye disease

Front Pharmacol. 2017 Feb 14;8:66. doi: 10.3389/fphar.2017.00066. eCollection 2017.

Curcumin, A Potential Therapeutic Candidate for Anterior Segment Eye Diseases: A Review.

Liu XF[1], Hao JL[1], Xie T[2], Mukhtar NJ[1], Zhang W[3], Malik TH[4], Lu CW[1], Zhou DD[5].

Cent Eur J Immunol. 2019;44(2):181-189. doi: 10.5114/ceji.2019.87070. Epub 2019 Jul 30.

Therapeutic potential of curcumin in eye diseases.

Radomska-Leśniewska DM[1], Osiecka-Iwan A[1], Hyc A[1], Góźdź A[1], Dąbrowska AM[2], Skopiński P[1].

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

Osei KA, Ovenseri-Ogbomo G, Kyei, et al. The effect of caffeine on tear secretion. Optom Vis Sci. 2014 Feb;91(2):171-7. doi: 10.1097/OPX.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

Osei KA, Ovenseri-Ogbomo G, Kyei, et al. The effect of caffeine on tear secretion. Optom Vis Sci. 2014 Feb;91(2):171-7. doi: 10.1097/OPX.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.

Osei KA, Ovenseri-Ogbomo G, Kyei, et al. The effect of caffeine on tear secretion. Optom Vis Sci. 2014 Feb;91(2):171-7. doi: 10.1097/OPX.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, artherosclerosis, and diabetes.

1. Peterson CT, Sharma V, Elmen L, Peterson SN. Immune homeostasis, dysbiosis and therapeutic modulation of the gut microbiota. Clin Exp Immunol. 2015;179:363–77.
2. Sender R, Fuchs S, Milo R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. Cell. 2016;164:337–40.
3. Viaud S, Daillere R, Boneca IG, et al. Gut microbiome and anticancer immune response: really hot Sh*t! Cell Death Differ. 2015;22:199–214.
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5. Sanz Y, Olivares M, Moya-Perez A, Agostoni C. Understanding the role of gut microbiome in metabolic disease risk. Pediatr Res. 2015;77:236–44.
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"What are the characteristics of the healthy ocular microbiota and how do they change during disease?"

- Healthy conjunctiva, lid margins, and tears
- Fewer microbial species than other mucosal sites like oral mucosal surfaces
- Most common species from conjunctival surfaces in humans
  - *Coagulase Negative Staphylococcus sp (CNS sp)*, including *Staphylococcus epidermidis*
- Isolated from
  - 20–80% of conjunctival swabs
  - 30–100% of lid margin swabs
- Less frequently present microbial species
  - *Propionibacterium sp(P. acnes)*, *Corynebacterium sp*, *S. aureus*, *Streptococcus sp*, *Micrococcus sp, Baccilus sp,* and *Lactobacillus sp*

Campos MS, Campos e Silva Lde Q, Rehder JR, et al. Anaerobic flora of the conjunctival sac in patients with AIDS and with anophthalmia compared with normal eyes. Acta Ophthalmol. 1994;72:241–5. Elander TR, Goldberg MA, Salinger CL, et al. Microbial changes in the ocular environment with contact lens wear. CLAO J. 1992;18:53–5.
Graham JE, Moore JE, Jiru X, et al. Ocular pathogen or commensal: a PCR-based study of surface bacterial flora in normal and dry eyes. Invest Ophthalmol Vis Sci. 2007;48:5616–23.
Willcox MD. Characterization of the normal microbiota of the ocular surface. Exp Eye Res. 2013;117:99–105.
Hsu HY, Lind JT, Tseng L, Miller D. Ocular flora and their antibiotic resistance patterns in the midwest: a prospective study of patients undergoing cataract surgery. Am J Ophthalmol. 2013;155:36–44 e2.
Ozkan J, Zhu H, Gabriel M, et al. Effect of prophylactic antibiotic drops on ocular microbiota and physiology during silicone hydrogel lens wear. OptomVis Sci. 2012;89:326–35.

Proteomic analysis of tear fluid in DED

- Showed specific alterations in the protein signature
- Several downregulated proteins had bactericidal activities
  - Lactotransferrin
  - Lysozyme
  - Polymeric immunoglobulin receptor
  - Lacritin
- Is there a connection between the ocular commensal microbiota and the state of the ocular surface barrier?
- Only few studies to date

Karnati R, Laurie DE, Laurie GW. Lacritin and the tear proteome as natural replacement therapy for dry eye. Exp Eye Res. 2013;117:39–52.

Association between ocular microbiota and OSD

- More extensive bacterial loads in patients with Sjogren Syndrome than healthy controls.[1]
- Increased bacterial presence of *CNS* species in addition to other common commensals such as *Corynebacterium* and *Propionibacterium* in non-autoimmune dry eye disease.[2]
- The expanding applicability of deep sequencing approaches will provide insights to whether alterations of ocular surface microbiota correlate with the development of DED.[3]

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2. Graham JE, Moore JE, Jiru X, et al. Ocular pathogen or commensal: a PCR-based study of surface bacterial flora in normal and dry eyes. Invest Ophthalmol Vis Sci. 2007;48:5616–23.
3. Narayanan S, Redfern RL, Miller WL, et al. Dry eye disease and microbial keratitis: is there a connection? Ocul Surf. 2013;11:75–92.

- 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!