A Nutritional Approach to Treating Dry Eyes

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  - Primary Care Optometry News
  - Optometric Office
  - Review of Optometry
Dry Eye Syndrome

What is Dry Eye Syndrome

Dry Eye Syndrome (DES) is a disorder of the tear film due to either diminished tear production or excessive tear evaporation.
What is Dry Eye Disease

Dry Eye Disease (DED) is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.

DEWS II, 2017

Dry Eye Population

- Estimated about 30-33 million in U.S.
- About 14% of adult population and between 20-53% of diabetic patients.
- The DED market is estimated to be $3.84 billion and is expected to grow about $4 billion through the next decade.
- 75% of Americans over 65 years old
Why is Dry Eye Important for Optometric Practices?

- Frequent complaint
- Contact lens success
- Digital display use
- Post-LASIK complication
- Cataract patients
- Improve practice reputation

Dry Eye Disease Process
Current Theory

Tear Film

Destabilization (Loss of Protection) **Cause?**

Desiccation of Ocular Surfaces

Inflammation

Cytokines
  - Ocular Surfaces
  - Epithelium
  - Lacrimal Gland

Injurious Agents
  - Free Radicals
  - Toxins
  - Microbes
  - Allergens
The Healthy Tear Film
A Delicate Balance

- Lipid, aqueous and mucin components
- Outer lipid layer prevents evaporation
  - Secreted by meibomian glands
- Aqueous component – a complex mixture of proteins, mucins, electrolytes
  - Secreted by main & accessory lacrimal glands
- Mucins provide viscosity and stability during the blink cycle
  - Mucin gel decreases in density toward tear film surface

Altered Tear Composition
in Dry Eye

- Alterations in mucins, proteins, lipids
  - Decreased soluble mucin concentration
  - Decreased antibacterial proteins
  - Balance between immunosuppressive cytokines and their antagonists disrupted
  - Protease activity increased
- Increased osmolarity
  - From 296 (normal) to 325 mEq/L (Ogasawara et al., 1996)
Causes of Dry Eyes

- Environment
- Age/Gender
- LASIK
- Post LASIK Corneal Edema Syndrome
- Systemic Medications
- Chronic Diseases
- Contact Lens

Environment

- Air conditioning/Heating
- Smoke
- Airplanes
- Geography
- Computer-based offices
Causes of Dry Eyes

Age/Gender

- **Hormones**
  - Androgen receptors are in the lacrimal glands.
  - Decrease levels in menopausal women & elderly.

- **Oil content**
  - At 65 years old we have 60% less oil in our bodies than we did at 18 years old.

Causes of Dry Eyes

Surgery

- **Neural feedback loop** - Sever LPC nerves that innervate cornea.
- **Thinner lipid layer** - poorer quality lipid layer may predispose to dry eyes
- **Over 50% of cataract patients have dry eyes.**
Causes of Dry Eyes

Lid Abnormality

- **Lid deformities** - Entropian, Extropian, etc.
- **Cosmetics** - Can plug up meibomian gland ducts.

“Meibo-Makeup”

Causes of Dry Eyes

Computer Vision Syndrome (Digital Eyestrain) is “the complex of eye and vision problems related to near work which are experienced during or related to computer use”

-American Optometric Association
Causes of Dry Eyes

Systemic Medications
- Anti-histamines - for allergies and stomach disorders
- Psychotropic drugs - Prozac, Valium, Lithium, etc.
- Hormones - Birth control pills, HRT
- Scopolomine - motion sickness
- Diuretics - hypertension
- Beta-blockers - Glaucoma; Cardiac disease

Causes of Dry Eyes

Chronic (auto-immune) Diseases
- Sjögrens Syndrome - .5% of population
- Lupus
- Rheumatoid Arthritis
- Grave’s Disease
- Sarcoid Disease
- 5th Nerve Disease
Causes of Dry Eyes

Contact Lenses

- Makes existing condition worse
- Soft vs. RGP
- Fitting concerns
- Wearing schedules
- Is Daily Disposable the answer?

Meibomian gland dysfunction and dry eye are similar, but different…

- The age-specific prevalence of MGD and DE differed, and analysis for 16 parameters showed that MGD and DE had independent hidden sources
- Although their ocular symptoms were similar, the pathogenesis of MGD differed from that of DE.

Tests for Dry Eyes

- Tear Breakup Time (TBUT) - tear film integrity
- Zone Quick (Phenol Thread) - tear volume
- Blink Rate - evaporation rate
- Tear Osmolarity - “salt concentration”
- Shirmer’s Test - tear volume
- Rose Bengal - devitalized conjunctival cells
- Lissamine Green - devitalized goblet cells
- Lid Wiper Epitheliopathy - symptom differential
- Micro-assay - lactoferrin levels

Multiple tests needed to diagnose dry eyes

DED Diagnostic Tests

Foundational tests to make differential diagnosis

<table>
<thead>
<tr>
<th>Bio-marker</th>
<th>Measurement</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Lactoferrin</td>
<td></td>
<td>Aqueous deficiency</td>
</tr>
<tr>
<td>Immunoglobulin E [IgE]</td>
<td></td>
<td>Allergy</td>
</tr>
<tr>
<td>Osmolarity</td>
<td></td>
<td>Stability of tear film</td>
</tr>
<tr>
<td>Matrix metallopeptidase 9 [MMP9]</td>
<td></td>
<td>Inflammation</td>
</tr>
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</table>

Point-of-Care [POC] Tests currently available

<table>
<thead>
<tr>
<th>Technology</th>
<th>Lactoferrin</th>
<th>IgE</th>
<th>Osmolarity</th>
<th>MMP9</th>
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<tbody>
<tr>
<td>Currently Marketed</td>
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<tr>
<td>Lateral Flow</td>
<td></td>
<td></td>
<td></td>
<td>GUIDET</td>
</tr>
<tr>
<td>ElectroChemical</td>
<td></td>
<td></td>
<td></td>
<td>TearLab</td>
</tr>
</tbody>
</table>
Lactoferrin

- Lacto (milk sourced); Ferrous (iron-related)
- Is the main glycoprotein component of tears
- Has multiple functions, including anti-inflammatory effects and the promotion of cell growth.
- It has antimicrobial activity and is part of the innate defense, mainly at mucosal tissue.

Lactoferrin

- The replication and biofilm formation of fungi, bacteria and viruses in mucosal tissues are iron-dependent.
- Growth of these pathogens becomes almost impossible if adequate amounts of lactoferrin, are concentrated in these mucosal fluids.
- Adequate levels of tear lactoferrin are particularly important for the eye surgery or contact lens patient with an increased risk of infection.
Association between severe MGD and tear lactoferrin concentration

- Meibomian gland activity/dysfunction may be associated with increased inflammation on the ocular surface.
- The inflammation may be sufficient to reduce tear lactoferrin production from damage to accessory lacrimal glands and/or Meibomian gland and result in increased symptoms.
- A lower lactoferrin concentration was found in eyes with reduced Meibomian gland expressability.

Tear Lactoferrin and Features of Ocular Allergy in Different Severities of Meibomian Gland Dysfunction.
Chao C Tong L

Immunoglobulin E (IgE)

- IgE is a type of antibody that has only been found in mammals.
- Synthesized by plasma cells.
- Is utilized during immune defense against certain parasites.
- Differentiate dry eye from allergy.
Immunoglobulin E (IgE)

- Elevated tear film IgE values indicate an ocular allergy.
- Because total ocular IgE increases with the severity of allergic response, determination of total tear IgE levels are useful in confirming a clinical diagnosis of allergic conjunctivitis and assessing the level of severity.

Dietary Lactoferrin Alleviates Age-Related Lacrimal Gland Dysfunction in Mice

Oral lactoferrin administration preserves lacrimal gland function in aged mice by attenuating oxidative damage and suppressing subsequent gland inflammation.

Differentiation of Dry Eye and Allergy

Clinical Signs- DES
- Dryness
- Grittiness
- “Tired eyes”
- Sporadic tearing
- Flaking lid crusting
- Ocular fatigue
- Blepharitis

Clinical Signs- Allergy
- Itchiness
- Swelling
- Puffiness
- Constant tearing
- Crusting w/mucous
- Nasal congestion
- Sneezing
- Itchy throat

A.G. Kabat, OD

A study published in the Annals of Allergy, Asthma and Immunology suggests a clinically significant overlap between the symptoms of dryness (45.4%) and itch (57.7%).

Allergy and immunology interfaces with ophthalmology and optometry
Leonard Bielory, MD, Milton M. Horn, OD, FAAO
December 2014 Volume 113, Issue 6, Pages 582–583
Dry Eye Jeopardy?

- In the past month, how often did your eyes feel discomfort?
- How intense was this feeling of discomfort at the end of the day, within two hours of going to bed?
- During a typical day, how often did your eyes feel dry?
- How intense was this feeling of dryness at the end of the day?
- How often did your eyes feel excessively watery?
- Does your vision change throughout the day?
- Do your eyes become tired in the afternoon?
- Have your eyes become red while wearing contacts?
- Do you use lubricating drops during the day?
- How many hours a day do you use a computer?
- Do you experience any itching of your eyes?
- Do you incorporate any fish in your diet?

TearScan 300™ Lactoferrin Diagnostic Test

- Painless, non-invasive tear sample
- Correct diagnosis and treatment can be prescribed on first visit
- More targeted and effective treatment for eye discomfort
TearScan 300™ Lactoferrin Diagnostic Test

- Improved and more efficient patient care
- Simple, accurate, rapid, inexpensive and **reimbursable**
- Assess lacrimal gland function and aid the assessing etiology of DED
- May indicate the cause of contact lens intolerance
- May help identify risk factors prior to ophthalmic surgical procedures
- Can be performed by a technician
- Platform is a Class II, moderate complexity lab system
- Low equipment & set up expense

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**Low Lactoferrin Levels**

- Dry Eye Disease - Aqueous deficient dry eye, allows for quantitative grading of severity
- Contact Lens - May have increased risk of hypoxia and dehydration
- Ophthalmic Surgery - May have increased risk of post operative DES
- Immunology – Compromised ocular immune system

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**Elevated IgE Levels**

- Dry Eye Disease - Allows assessment of allergic component of dry eye etiologies, secondary dry eye
- Contact Lens - May have increased risk of GPC and contact lens intolerance
- Ophthalmic Surgery – May have increased risk of corneal haze and DLK
TearScan™ Diagnostic Tear Tests
TearScan300™ Diagnostic Tear Test

Dry Eye by the Numbers

<table>
<thead>
<tr>
<th>Lactoferrin</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.9 mg/mL</td>
<td>Aqueous deficient</td>
</tr>
<tr>
<td>&gt;0.9 mg/mL</td>
<td>Normal range</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IgE</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80 ng/mL</td>
<td>Allergy</td>
</tr>
<tr>
<td>&lt;80 ng/mL</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Lemp, MA. Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes. CLAO J 1995;21(4):221-32
Income Per Patient

- Ocular Lactoferrin: (cpt 83520) $17.27
- Ocular IgE: (cpt 82785) $18.29
  Per Eye $35.56
  Per Patient $71.12
- Cost per patient tested: $42.12
- Net income per patient: $30.00

Buying DED Devices

- **Footprint**- make sure it fits
- **Patient Base**- If you build it, they will come
- **Ease of Use**- Easy to incorporate into patient flow
- **The “Right” Staff**- Someone to take charge
- **Cost**- Value to practice and reputation

Whitney Hauser, OD
What are your objections to incorporating advanced tear film diagnostics into your practice?

- None, I use advanced tear film diagnostics in my practice: 10%
- Limited access to technologies: 22%
- Practice flow disruption: 14%
- Increases my chair time: 22%
- Technologies not paid for by health system: 41%
- Cost to me: 35%
- Safety and efficacy – I do not see any differences: 17%

Figure 1. 2018 ESCRs Clinical Trends Survey Results: Key objections to including advanced tear film diagnostics in a practice.

Reimbursements

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Instrument Cost</th>
<th>Code Reimbursement*</th>
<th>Break Even Point</th>
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</thead>
<tbody>
<tr>
<td>OCT</td>
<td>$60,000</td>
<td>92133 (optic nerve) $38</td>
<td>1,578 (not counting anterior seg or macula)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>92134 (macula) $38</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td></td>
<td>92132 (anterior seg) $32</td>
<td>--</td>
</tr>
<tr>
<td>Visual Field</td>
<td>$30,000</td>
<td>92083 $65</td>
<td>461</td>
</tr>
<tr>
<td>Fundus Camera Tear Scan</td>
<td>$40,000</td>
<td>92250 $58</td>
<td>689</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8320/82785 ($30.00)</td>
<td>168</td>
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<tr>
<td>Pachymeter</td>
<td>$2500</td>
<td>76514 $15</td>
<td>166</td>
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<tr>
<td>Gonioscopy Lens</td>
<td>$400</td>
<td>92020 $27</td>
<td>15</td>
</tr>
</tbody>
</table>

*Based on Medicare reimbursement averages

@ 6 patients/day: paid for in under 2 months
Treatments for Dry Eyes
Developments

Anti-Inflammatory

- Steroids (Alrex / Lotemax / Velox) - cytokine inhibitors
- Restasis (Cyclosporine A; Allergan)- immunosuppressant
- Xiidra (Lifitegrast; Spire)- anti-inflammatory
- Cequa (cyclosporine ophthalmic 0.09%; Sun Pharma)
- Essential Fatty Acids (EFA) – natural source

“What we really want is a treatment that can break the inflammatory cascade without side-effects”

Stefano Barabino, MD, PhD.
University of Milan, Italy
2018 Cornea Subspecialty Day
36th Congress of the ESCRS, Vienna
Natural Anti-Inflammatories

- **Quercetin**: Down regulates COX-2 expression
- **Ginger**: gingerols (COX-2 inhibitor); anti-inflammatory
- **White Willow Bark**: Extracted as salicin
- **Curcumin**: (Turmeric); suppresses over-proliferation of lymphocytes and the cytokine cascade
- **Omega-3 EFAs**: Fish oils
New Developments for Dry Eyes

Orals

- Hydro-Eye
- TheraTears Nutrition
- BioTears
- PRN De
- Nordic Naturals
- EyePromise EZ Tears

Randomized Clinical Trials on Treatment of Dry Eyes with Omega-3


Lipid Layer Enhancement

Corneal Epithelium Surface
Metabolic Pathways of Omega-3 and Omega-6 Fatty Acids

**Omega-6**
- Linoleic Acid (LA)
  - Polyunsaturated oils, including flax, corn and safflower
  - Delta-6-desaturase
  - Gamma-Linolenic Acid (GLA)
    - Black Currant, EPO, Borage (18-24% GLA)
    - Dihomo-Gamma-Linolenic Acid (DGLA)
      - Delta-5-desaturase
      - Arachidonic Acid (AA)
        - Lipoxigenase
        - Cylooxygenase (COX2)
  - LBT—4
    - Pro-inflammatory
  - PGE—2
    - Pro-inflammatory
  - PGE—3
    - Anti-inflammatory
  - LBT—5
    - Anti-inflammatory

**Omega-3**
- Alpha-Linolenic Acid (ALA)
  - Black Currant (15%) Flax (85%)
  - Delta-6-desaturase
  - Steridonic Acid (SDA)
    - Eicoestatrienoic Acid (ETA)
    - Delta-5-desaturase
    - EPA/DHA
      - Fish Oil & Cod Liver Oil
      - Series One Prostaglandin
        - Anti-inflammatory
  - EPA appropriately blocks Omega 6 delta-5-desaturase downstream conversion

Delta-6 enzymes impaired by aging, alcohol and nutrient deficiencies, trans fatty acids and elevated cholesterol.
Prostaglandins

**PGE1**

- Reduces inflammation and inhibits blood clotting.
- Capable of reducing pain, swelling and redness associated with inflammation, particularly in mucosal tissues, which includes the eyes.
- Can only be produced by Omega-6 fatty acids.

Prostaglandins

**PGE2**

- Are opposite of PGE1s but can only be produced by Omega-6 fatty acids.
- Are pro-inflammatory mediators that constrict blood vessels, increase body temperature, and encourage blood clotting.
- These events are lifesaving when the body suffers a wound or injury, for without PGE2s, a person could bleed to death.
- However in excess this type of prostaglandin is harmful because it sets up a chronic inflammatory condition in the body.
Prostaglandins

**PGE3**

- Are available from Omega-3 fatty acids.
- The Omega-3 fatty acid, EPA, also plays an important anti-inflammatory role.
- It appropriately blocks the release of Omega-6 arachidonic acid.
- Without sufficient Omega-3s in the diet, chronic inflammation becomes one of the problems now linked to many degenerative diseases of the eye.

Is dry eye an indicator of systemic essential fatty acid deficiency or imbalance?
Flax Seed Oil

- Does contain a large amount of Omega-3 EFA
- Highly unstable, must be refrigerated
- Contains none of the nutrient co-factors necessary to ensure conversion to PGE1 anti-inflammatory
- **Does not enhance production of lactoferrin**
- Excess now linked to cortical opacities and prostate cancer.
- May cause intestinal blockage, thyroid problems and reduce platelet aggregation.
- Poor conversion to longer chain fatty acids

Vitamin A

- Vital for the health of epithelial cells of the cornea and conjunctiva, as well as the function of the immune system.
- It is also necessary for goblet cell and lacrimal gland production of the large variety of mucins now associated with the base layer of the tear film.
Vitamin B6

- One of the nutrient co-factors required to push the metabolic pathway conversion of GLA to DGLA.
- Required for the neuronal blink response.

Vitamin C

- *Absorbil palmitate* (fat-soluble) modulates PGE1 synthesis due to the extended half-life of the fat-soluble vitamin C over ascorbic acid.
- This vitamin C combination also 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.
Vitamin D

- This study demonstrates that vitamin D deficiency is associated with tear hyperosmolarity and tear film dysfunction.
- Patients with vitamin D deficiency may be prone to dry eye

Dry eye assessment in patients with vitamin D deficiency.
Eye & Contact Lens. 2018 Sep;44

Vitamin E

- Vitamin E should be included in all fatty acid-based nutraceutical formulations to help prevent or slow lipid oxidation.
- This particularly includes any formulation that includes flax seed oil or any type of fish oil.
**Turmeric**

- Member of Ginger family
- Powerful anti-inflammatory effects and is a very strong antioxidant.
- Poor bioavailability but it helps to consume black pepper with it, which contains piperine, a natural substance that enhances the absorption of curcumin by 2,000%.

**Additional Tear Support**

- **Minerals**—important in immune functions
  - Zinc
  - Magnesium
- **Mucin Enhancers**
  - Aloe Vera Oil
  - Hyaluronic Acid
Nutritional Support

Nutritional supplements can play an important role in the management of inflammation associated with dry eye by enhancing the body's natural defense system, and the protection provided by nutritional therapy may be better than after-the-fact treatment by pharmaceuticals.

A Nutritional Approach to Treating Dry Eyes

Thank you

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