

Dry Eye: Natural History, Diagnosis and Treatment

By Jeffrey P. Gilbard, M.D.

Our understanding of dry eye disorders has improved dramatically over the past several years, enhancing our ability to diagnose and treat patients who have these challenging conditions.

Here, we'll look at the natural history, diagnosis and treatment of dry eye disorders. But first, let's review the mechanisms underlying these conditions.

Classifying dry eye disorders

Virtually all dry eye disorders are related to an increase in tear film osmolarity above the normal limit of 311 mOsm/L. Osmolarity increases when water is lost from the tear film without an accompanying decrease in solutes, such as sodium and potassium. Increased osmolarity may result from any condition that decreases tear production or increases tear evaporation. See "Mechanisms That Increase Osmolarity" for a list of these conditions.

Everyone experiences a gradual decline in tear function as they age, usually secondary to an associated decline in corneal sensation and meibomian gland function. However, in most people, physiologic reserve along with some ptosis is adequate to prevent symptoms and disease.

Milestones of dry eye

We now know that dry eye disorders evolve through a sequence of four milestones. For a list of these milestones, diagnostic tests and treatment options, see "Diagnosing and Treating Dry Eye."

In dry eye, decreased tear production or increased tear evaporation rapidly raises tear osmolarity and decreases goblet cell density. Goblet cell loss is significant because these cells produce mucus, the major lubricant in the tear film. An increase in the osmotic gradient between the tear film and the ocular surface also pulls water between conjunctival epithelial cells, as illustrated on the cover, breaking the delicate inter-cellular attachments. The result of this process is increased conjunctival cell desquamation, revealing conjunctival cells on the surface without cell surface glycoproteins.

At this stage of dry eye, corneal morphology remains normal. Tight corneal junctions make the cornea more resilient to increased tear osmolarity than the conjunctival epithelium. Nevertheless, decreased corneal glycogen, the energy source for the sliding step of corneal wound healing, can be detected at this stage.

But the cornea doesn't stay unaffected. Much later in the natural history of the disease, water movement breaks the attachments between corneal cells, causing an increase in corneal desquamation. As corneal desquamation proceeds, immature cells without cell surface glycoproteins appear on the corneal surface, resulting in destabilization of the cornea-tear interface.

If we want to interpret and evaluate diagnostic tests and appreciate treatment advances, it's crucial that we understand the natural history of dry eye disorders.

MECHANISMS THAT INCREASE OSMOLARITY

Increased tear film osmolarity, the first milestone in the development of dry eye disease, occurs in the presence of:

1. Damaged lacrimal glands caused by:
 - Autoimmune disease
 - Cicatricial ocular surface conditions.
2. Normal lacrimal glands with decreased corneal sensation from:
 - Herpes zoster
 - Long-term contact lens wear
 - Surgical ablation or interruption of corneal nerves
 - Diabetes.
3. Increased tear evaporation associated with:
 - Long-standing posterior blepharitis leading to meibomian gland dysfunction.
 - Large palpebral fissure width, occurring either naturally, secondary to cosmetic surgery or with thyroid eye disease.

Eventually, chronic meibomian gland inflammation leads to dysfunction. At this stage, dryness caused by increased evaporation produces a second symptom peak toward the end of the day. Finally, when inflammation and secondary fibrosis obliterate the meibomian glands, the morning symptoms resolve and patients are left with symptoms of sandy-gritty irritation that worsens as the day progresses.

Diagnosing dry eye disorders

When beginning an evaluation for dry eye, you should:

- Look for facial telangiectasias that may presage meibomitis or meibomian gland dysfunction associated with rosacea.
- Measure palpebral fissure width, as evaporation increases as width increases.
- Determine if meibomian gland orifices are patent, stenosed or closed.

Next, examine the patient's tear film by touching a wet fluorescein strip to the inferior tarsal conjunctiva. A lack of spontaneous fluorescence indicates decreased tear volume. In more severe situations, you'll detect debris or precipitated mucus in the inferior fornix.

Why dry eye

In most cases, you can diagnose dry eye based on a patient's history. Then, why bother to examine the patient? Because we want to determine why the patient has dry eye disease.

Patients with dry eye disorders complain of chronic sandy-gritty irritation that worsens as the day progresses. The eyelids form a watertight seal over the eyes during sleep, giving the ocular surfaces a chance to recover. However, once the patient opens his eyes in the morning, evaporation begins and tear film osmolarity increases as the day goes on.

Patients with meibomitis (posterior blepharitis) also complain of chronic sandy-gritty eye irritation, but in these patients, the symptoms are worse upon awakening. Morning irritation occurs because tear production decreases during sleep, and eye closure brings the inflamed lids against the eye where inflammatory mediators act on the cornea. When these patients awaken, tear flow increases, the lids pull away from the cornea and symptoms improve.

Relatively early changes associated with dry eye disorders can be evaluated clinically with vital stains such as lissamine green and rose bengal. These dyes stain the ocular surface once cell surface glycoproteins are lost. The value of this test lies in the pattern of corneal staining, which is more diagnostic than the overall amount of staining. With dry eye, the nasal conjunctiva stains more than the temporal conjunctiva, and the resilient cornea stains less than the conjunctiva. The conjunctiva always stains more than the cornea because desquamation with loss of cell surface glycoproteins occurs earlier in the conjunctiva than in the cornea.

Tear film instability can be detected by the rapid development of randomly located dark spots in the tear film after the instillation of fluorescein dye. This finding has been used to measure tear breakup time. As many as 50% of patients with dry eye have normal tear film stability because the corneal epithelial changes that cause tear film instability -- loss of corneal cell surface glycoproteins -- occur late in the natural history of dry eye disease.

Targeted treatment

Previous treatments for dry eye disorders targeted the late milestones, in part because they're easier to spot. But as our knowledge and understanding of dry eye disease has improved, we've developed better treatments that address earlier milestones in the disease progression.

Modern dry eye treatment began with preserved tear solutions. Demulcents in these products mimicked mucus and transiently improved tear film stability by temporarily stabilizing the cornea-tear interface.

The next treatment advance -- preservative-free demulcent solutions -- occurred about 15 years ago, shortly after researchers recognized that preservatives increase corneal desquamation. Preservative-free solutions diminished iatrogenic corneal desquamation, but left disease-based desquamation untouched.

Considering what we now know about the natural history of dry eye, it's logical that the next treatment advance would address the increase in tear film osmolarity that drives ocular surface disease. The first eye drop hypotonic enough to lower elevated tear film osmolarity is TheraTears. Continued treatment with this agent osmotically rehydrates the tear film-ocular surface system and causes a progressive, significant and sustained decrease in elevated tear osmolarity. In addition, TheraTears has been shown to restore corneal glycogen levels and conjunctival goblet cells by decreasing elevated tear osmolarity and providing a patented electrolyte balance that matches the human tear film.

A recent clinical study found that TheraTears helps restore conjunctival goblet cells in patients with post-LASIK dry eye. At 1 week and 1 month after surgery, respectively, 87.5% and 100% of dry eye patients who received TheraTears were free of dry eye symptoms, whereas only 12.5% and 20% of patients in the control group were symptom-free. In addition, goblet cell density measured by impression cytology 1 month after treatment showed that TheraTears significantly restored conjunctival goblet cell density, whereas the control treatment didn't. Two subsequent studies have found that patients who start using TheraTears about 1 week before LASIK surgery see better faster and feel more comfortable than patients who don't use this agent.

Punctal occlusion also helps lower tear film osmolarity, reduce rose bengal staining and improve overall symptoms. But controlled studies indicate that punctal occlusion has no effect on goblet cell density because simply adding more moisture to the tear film can't correct the disproportionate increase in tear sodium that depletes goblet cells.

DIAGNOSING AND TREATING DRY EYE		
The natural history of dry eye disease dictates the sensitivity of diagnostic tests and the efficacy of treatment. The most efficacious treatment now addresses all four milestones of dry eye disease.		
Milestone	Diagnostic Tests	Eye Drops
Increased tear osmolarity	Patient history Tear osmolarity	Sufficiently/optimally hypotonic (Preservative-free TheraTears, TheraTears in a bottle, TheraTears Liquid Gel)
Decreased goblet cell density Decreased corneal glycogen	Conjunctival staining Impression cytology	Tear-matched electrolyte balance (Preservative-free TheraTears, TheraTears in a bottle)
Increased corneal desquamation	Corneal staining	Preservative-free lubricants of various viscosities (Refresh Plus, Bion Tears, Tears Naturale Free, GenTeal, GenTeal Gel, Refresh Endura)
Decreased corneal cell surface glycoproteins	Tear film breakup time	Preserved lubricants of various viscosities (Refresh Tears, Tears Naturale II, Systane)

Omega-3 revolution

Oral supplementation for dry eye began with the introduction of products such as HydroEye and BioTears. The disadvantage of these supplements is that they add to the already excessive amount of omega-6s in the average American diet. Omega-6s increase serum levels of arachidonic acid (AA) and promote heart disease, stroke and other degenerative diseases.

Research presented at the 2003 annual meeting of the Association for Research in Vision and Ophthalmology showed that high dietary intake of omega-3 essential fatty acids decreases the risk of developing dry eye disease. Using the Women's Health Study Database at the Harvard School of Public Health, investigators examined the dietary intake of essential fatty acids in 32,470 health professionals. They found that a higher dietary ratio of omega-3 to omega-6, as well as a higher omega-3 intake, decreases the likelihood of developing dry eye. Americans, in general, have a dietary omega-3 deficiency.

This landmark study contributed to the switch to omega-3s started by TheraTears Nutrition, an omega-3 supplement with flaxseed oil, fish oil and vitamin E. TheraTears Nutrition is formulated to address both meibomitis and the underlying causes of dry eye.

Omega-3s decrease inflammation

Once consumed, enzymes elongate dietary omega-3s to produce the anti-inflammatory agents prostaglandin E₃ (PGE₃) and leukotriene B₅ (See "Metabolic Pathways of Essential Fatty Acids" for details). Even more importantly, eicosapentaenoic acid (EPA), a long-chain omega-3 available from fish oil, blocks the gene expression of the pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α), interleukin-1* (IL-1*), IL-1 β , proteoglycan degrading enzymes (aggrecanases) and cyclooxygenase (COX-2).

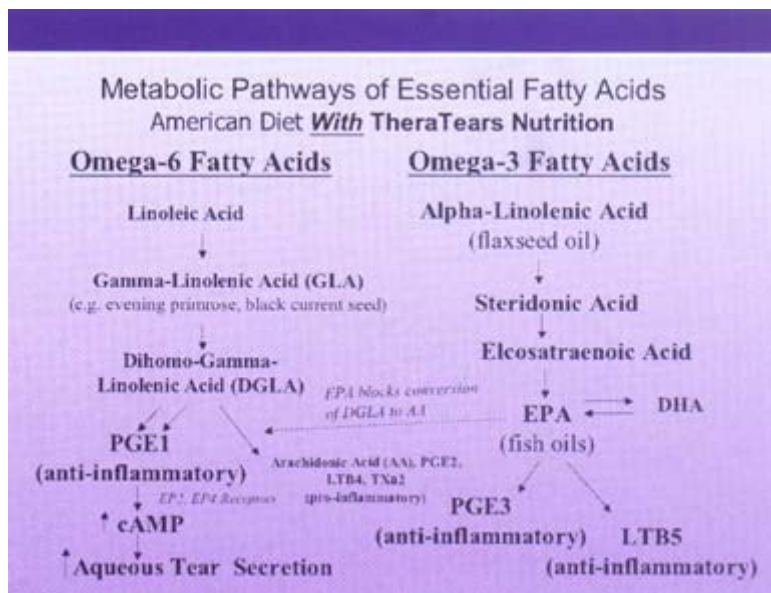
The anti-inflammatory effects of omega-3s explain why these fatty acids are useful for treating patients with meibomitis. I've even begun prescribing omega-3s in place of systemic tetracyclines to treat early morning eye irritation in patients with meibomitis. However, the benefits of omega-3 fatty acids go far beyond relieving the symptoms of meibomitis.

Omega-3s decrease apoptosis

In Sjögren's syndrome, TNF-^{*} accelerates lacrimal gland apoptosis, contributing to the decrease in tear production and the increase in tear film osmolarity that drives dry eye disease.

Meanwhile, increased tear film osmolarity increases the expression of TNF-^{*} on the ocular surface, which in turn promulgates the inflammatory cascade and increases apoptosis on the ocular surface in dry eye disease. Topical cyclosporine ophthalmic emulsion 0.05% (Restasis) also inhibits TNF-^{*} production by monocytes. Although this agent achieves good concentrations on the eye surface, it probably doesn't reach the orbital lacrimal gland. When taken by mouth, omega-3 supplements, such as TheraTears Nutrition, reach the lacrimal gland via the blood supply and the ocular surface via meibum. Cyclosporine and omega-3 supplements appear to inhibit pro-inflammatory cytokines, but differ in their ability to reach relevant target tissues. It's interesting to note that cyclosporine has no effect in patients with punctal occlusion. Punctal occlusion lowers elevated tear osmolarity, presumably by blocking the expression of pro-inflammatory cytokines on the ocular surface.

Whereas EPA decreases the gene expression of TNF-^{*}, deosahexaenoic acid (DHA) protects cells from TNF-^{*}-induced apoptosis. Yano and coworkers have demonstrated that vitamin E works synergistically with DHA to protect cells from TNF-^{*}-induced apoptosis.



Omega-3s stimulate tear secretion

The effects of suppressing pro-inflammatory cytokines aren't limited to decreased apoptosis. We now know that the pro-inflammatory cytokines TNF-^{*}, IL-1^{*} and IL-1 β impair tear secretion in lacrimal gland disease-based dry eye by inhibiting the release of neurotransmitters from neural synapses and interfering with the secretory response of lacrimal gland acinar cells.

A recent study demonstrated that blocking TNF-^{*} gene expression reversed autoimmune lacrimal disease, restored tear secretion and reduced corneal staining in an animal model. Clinical studies have found that Sjögren's patients have a lower dietary intake of omega-3s, including EPA and DHA, than age-matched controls.

In addition, research has shown that DHA dietary supplementation restores DHA levels in neural synapses and improves age-related declines in synapse function. DHA may reduce the ability of pro-inflammatory cytokines in the lacrimal gland to inhibit signal transduction at the

synapse. Lending credence to this hypothesis is the finding that severity of dry eye in Sjögren's patients is inversely proportional to membrane and serum levels of DHA.

Omega-3s affect the lacrimal gland in another way. EPA competitively inhibits the conversion of omega-6s to AA, thereby promoting the conversion of dihomo-gamma-linolenic acid to PGE₁. PGE₁ also has anti-inflammatory properties and acts on the E-prostanoid (EP) receptors EP2 and EP4 to activate adenylate cyclase, increasing cyclic AMP (cAMP). PGE₁ and cAMP have been shown to stimulate aqueous tear secretion.

Omega-3s, the meibomian gland oils

Meibomian glands use essential fatty acids to synthesize meibum. Dietary intake of omega-3s in general, and EPA and DHA in particular, has been shown to affect the polar lipid profiles of meibum as observed by high performance lipid chromatography. Indeed, Carol Boerner, M.D., has observed the clearing and thinning of meibomian gland secretions with omega-3 supplementation. Further studies are needed to determine whether these effects are sufficient to bolster the ocular tear film oil layer and retard tear film evaporation.

Customized care for dry eye disorders

Our improved understanding of the natural history of dry eye has enhanced our ability to diagnose this condition, as well as appreciate the outcome of patient examination and clinical testing. With this information, we can better implement various treatments at our disposal and offer patients the best care possible.

Dr. Gilbard practices with Tallman Eye Associates in North Andover, Mass., and is founder, CEO and Chief Scientific Officer of Advanced Vision Research. He maintains an active research and teaching program.

References are available at www.dryeyeinfo.org/Dry_Eye_In_Depth.htm