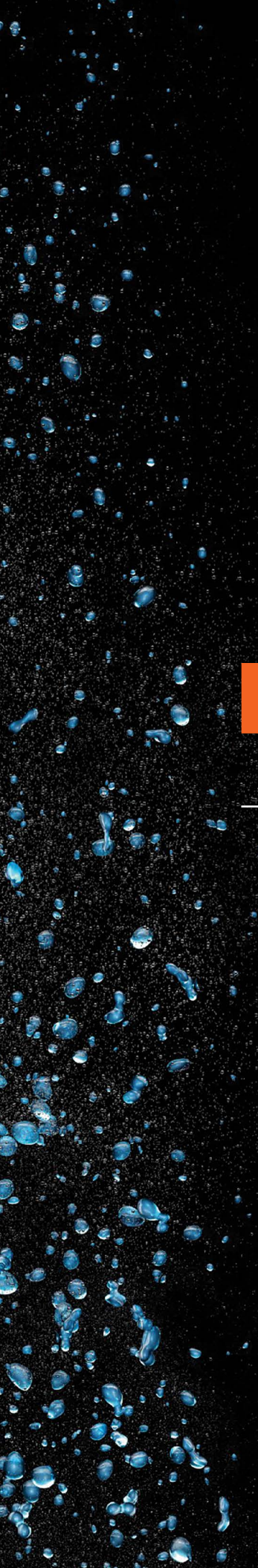


DELVING INTO THE CORE MECHANISM:

Evaporation in Dry Eye Disease

Paul Karpecki, OD, FAAO

BAUSCH + LOMB

RETHINKING THE "VICIOUS CYCLE" OF DRY EYE DISEASE

As eyecare practitioners who diagnose and treat dry eye disease (DED), we are continually updating our understanding of the condition. As articulated in the seminal Dry Eye Workshop (DEWS) II report of the Tear Film and Ocular Surface Society (TFOS), it is well established that DED is a multifactorial process involving a loss of tear film homeostasis.[1] Tear film instability, tissue damage, and inflammation are all connected and play self-reinforcing roles, keeping patients stuck in the DED cycle. While this cycle has multiple potential points of entry, evaporation-related tear film instability and hyperosmolarity are central, upstream mechanisms.[1]

Whether due to intrinsic or extrinsic causes, excessive tear evaporation leads to hyperosmolarity and desiccation stress, which trigger an inflammatory cascade within ocular surface epithelial cells, leading to cell damage and death. The release of inflammatory mediators from activated T-cells reinforces the damage, further contributing to tear film instability and amplifying the cycle of events that result in the symptoms and signs of DED (**Figure 1**).[1]

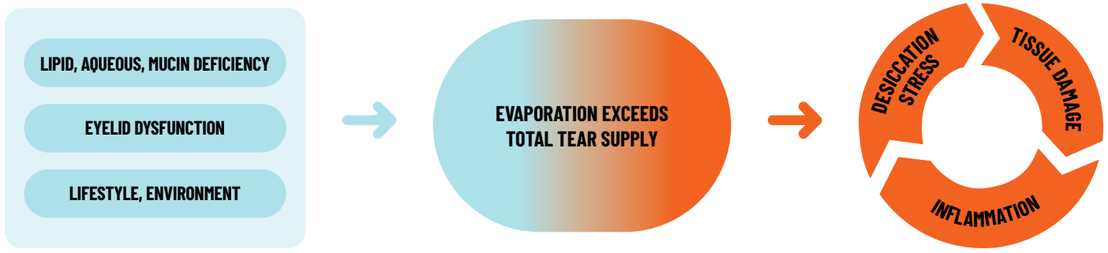
ZOOMING IN ON EVAPORATION

With each blink, the tear film is distributed across the ocular surface; the thin lipid layer spreads over the mucoaqueous component of the tear film and helps maintain its stability between blinks.[2] The meibomian glands are the main source of lipids for the tear film,[3] and deficiency in meibomian gland function leads to increased tear evaporation.[4] Indeed, perhaps the most common cause of excessive tear evaporation is a deficient lipid layer due to meibomian gland dysfunction (MGD).[5,6]

In the frequently cited study by Lemp and colleagues, about 86% of participants had signs of evaporative DED due to MGD (either "purely" evaporative, 50%, or with a mixed aqueous-deficient/evaporative presentation, 36%).[5] Subsequent studies have confirmed both the high prevalence of MGD and its key contribution to DED.[6,7] MGD prevalence was 92% among patients treated for glaucoma with prostaglandin analog therapy,[8] 76% among patients with diabetes,[9] and 52% among those presenting for cataract surgery.[10] Additionally, a number of studies show an association between MGD and contact lens wear,[11] and one study found 59% of contact lens wearers had abnormal meibum quality.[12]

EXCESSIVE EVAPORATION IS OFTEN AT PLAY AND CAN CONTRIBUTE TO TEAR FILM INSTABILITY EVEN AMONG PATIENTS WITHOUT OVERT MGD

Figure 1. Tear evaporation that exceeds supply may be due to deficiencies in tear quantity or quality, anatomical eyelid issues, and/or lifestyle or environmental factors. [2,13-14,18,28-35]



A multitude of factors can contribute to excessive tear evaporation and may also exacerbate MGD:[1] reduced frequency and completeness of blinking (often associated with digital device use),[13] inadequate lid seal,[14] environmental challenges[1] (low humidity, pollution, wind, ceiling fans, continuous positive airway pressure therapy),[15] hormonal issues, and certain medications (botulinum toxin injections around the eye,[16] oral antihistamines,[2] and oral isotretinoin).[17]

Excessive evaporation is often at play and can contribute to tear film instability even among patients without overt MGD. For example, in cases of primary aqueous deficiency DED and a "normal" lipid layer, tear film integrity may be disrupted between blinks due to an inadequate reserve of aqueous tears.[18] Whether hyperosmolarity occurs due to reduced tear production, poor tear quality, or both, it is ultimately caused by evaporation exceeding tear supply. In this sense, evaporation is a key common denominator in all forms for DED.[1]

CURRENT THINKING ON DED TREATMENT

Although excessive evaporation is a central mechanism in DED, currently available prescription treatments do not target evaporation directly. Over-the-counter artificial tears, which are common first-line approaches, can provide temporary relief, but do not address the underlying pathophysiology keeping many patients stuck in the dry eye cycle.[19,20]

Since 2003, four topical drops and one nasal spray have been FDA-approved and are on the market to treat DED. These treatments can be classified into one of two mechanisms: immunomodulating/anti-inflammatory or tear stimulating. While each can play an important role in managing symptoms of DED, minimizing ocular damage by decreasing inflammation, and/or increasing tear production in patients with aqueous deficiency, there is data to suggest that long-term adherence to some current prescription treatments is limited. In a retrospective study involving patients with DED treated with immunomodulatory prescription eye drops, over 60% of patients discontinued treatment within 12 months of initiation.[21]

FOR THE MAJORITY OF PATIENTS WITH AN EVAPORATIVE DED COMPONENT, TREATMENT THAT DIRECTLY TARGETS TEAR FILM EVAPORATION MAY BE NECESSARY TO FULLY INTERRUPT THE VICIOUS CYCLE OF DED AND PROVIDE LONG-TERM RELIEF

As an important piece of the pathophysiological puzzle, non-pharmacological therapies aimed at the meibomian glands are often a part of DED treatment. For the majority of patients with an evaporative DED component, treatment that directly targets tear film evaporation specifically may be necessary to fully interrupt the vicious cycle of DED and provide long-term relief.

NON-PHARMACEUTICAL APPROACHES TO MGD IN EVAPORATIVE DED[19,20]

- Education on MGD and contributing lifestyle factors (diet, work/home environments, medications)
- Eyelid hygiene and warm compresses
- Lipid-based over-the-counter eye drops
- Thermal/mechanical and/or light therapy

PATIENT CASE – LARA

Lara is a 62-year-old white woman who presented to our clinic complaining of severe dry eye symptoms in both eyes, which worsened as the day progressed. She routinely used lipid-based artificial tears throughout the day in addition to saline eye drops BID. She said she had previously tried cyclosporine 0.5% (dosed BID), but felt it didn't help relieve her symptoms and burned on instillation.

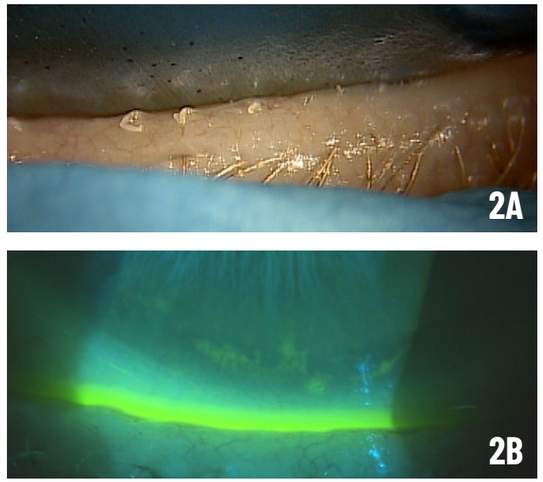
Upon examination, her corrected visual acuity was 20/30 OD and 20/30+2 OS, and her tear osmolarity readings were 318 and 312 mOsm/L, respectively (full findings summarized in **Table 1**). At the slit lamp, external examination was noteworthy for mild dermatochalasis OU. Lid margin findings included trace blepharitis and grade 3 MGD (ie, paste-like secretion on diagnostic expression) (**Figure 2a**). She had trace conjunctival injection and inferonasal staining, and showed grade 2 inferior corneal fluorescein staining (**Figure 2b**).

We diagnosed Lara with evaporative DED and blepharitis and prescribed a treatment plan of hydrating compresses (once a day for 10 minutes), eyelid scrubs, oral omega-6 (gamma-linoleic acid [GLA]) and omega-3 (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) supplementation, and continued use of lipid-based tears.[20,22,23] She returned in 6 weeks for a follow-up exam.

Upon follow up, Lara reported continued dryness symptoms, which she characterized as "constant" and "moderately bothersome." She liked the hydrating compresses, but said the symptom relief only lasted for a short time. Notably, at this visit, her corrected visual acuity had improved to 20/25 OD and 20/25+1 OS. At the slit lamp, dermatochalasis and blepharitis remained, and MGD improved to grade 2+ OU. There was grade 1+ conjunctival injection and corneal staining OU.

At this point, the exam findings suggested that inadequate lid seal should be added to Lara's

Figure 2a. Meibomian gland expression revealing thickened meibum; 2b. fluorescein staining of the inferior cornea. ***Images courtesy Paul Karpecki, OD.***



diagnoses. To address her symptoms, we recommended that she continue with the compresses, eyelid hygiene, and GLA/EPA/DHA supplements, and added a 2-week regimen of topical loteprednol etabonate ophthalmic suspension 0.25% for short-term management of inflammation.[24] We also prescribed overnight wear of a non-latex, hypoallergenic, oxygen permeable eyelid seal and scheduled an intense pulsed light (IPL)/low-level laser therapy (LLLT) procedure.[25,26]

When Lara returned in 2 months, she reported mild and substantially less frequent DED symptoms, saying she had noticed improvement for the first time in as long as she could recall.

At this visit, her tear osmolarity had reduced to 306 mOsm/L OD and 308 mOsm/L OS. Slit-lamp findings were also largely improved, with trace blepharitis and MGD, little to no conjunctival staining and grade 1+ injection, and a clear cornea, save for mild epithelial basement membrane dystrophy (**Figure 3**).

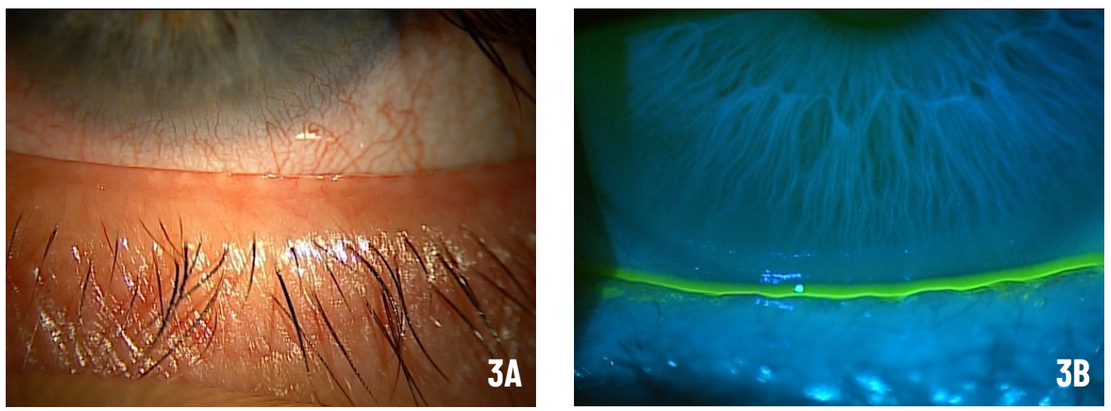
At this third visit, I counseled Lara to continue with the nighttime eyelid seals, warm compresses, eyelid hygiene, and GLA/EPA/DHA supplementation.

Table 1. Examination Findings

	VISIT 1	VISIT 2 (6 WEEKS LATER)	VISIT 3 (2 MONTHS LATER)
VISUAL ACUITY WITH CORRECTION	OD: 20/30 OS: 20/30+2	OD: 20/25 OD: 20/25+1	OD: 20/25 OD: 20/25+1
EXTRAOCULAR MOVEMENT	Full OU	Full OU	Full OU
CONFRONTATION VISUAL FIELD	FTFC	FTFC	FTFC
PUPILS	PERRLA (-) APD	PERRLA (-) APD	PERRLA (-) APD
INTRAOCULAR PRESSURE	OD: 18 mmHg OD: 18 mmHg	OD: 17 mmHg OS: 19 mmHg	OD: 20 mmHg OS: 19 mmHg
TEAR OSMOLARITY (normal osmolarity is ≤308 mOsm/L)[2]	OD: 318 mOsm/L OS: 312 mOsm/L	OD: 314 mOsm/L OS: 312 mOsm/L	OD: 306 mOsm/L OS: 308 mOsm/L
CORNEA	Grade 2 inferior corneal fluorescein staining	Grade 1+ corneal staining	Mild EBMD
LID MARGIN/ MEIBOMIAN GLAND FINDINGS	Trace blepharitis Grade 3 MGD	Trace blepharitis Grade 2+ MGD	Trace blepharitis Trace MGD

APD, afferent pupillary defect; **EBMD**, epithelial basement membrane dystrophy; **FTFC**, full to finger count; **OD**, right eye; **OS**, left eye; **OU**, both eyes; **PERRLA**, pupils equal, round, reactive to light and accommodation; **MGD,** meibomian gland dysfunction; **mmHg**, millimeters of mercury; **mOsm/L**, milliosmoles per liter

Figure 3a. Improved meibomian expression, with trace blepharitis; 3b. inferior cornea cleared of staining. ***Images courtesy Paul Karpecki, OD.***



A MULTIFACETED APPROACH

As Lara's case illustrates, the excess tear evaporation, tissue damage, and inflammation that characterize DED can arise from multiple interrelated factors. In this case, eyelid laxity contributed to inadequate lid seal, leaving the inferior ocular surface exposed to evaporation.[14] Hyperkeratinization of the meibomian glands, resulting in thickened meibum, obstruction, and a poor-quality lipid layer, likewise contributed to excessive tear film evaporation.[27] This situation may have amplified bacterial growth on the lid margin and the inflammatory changes associated with blepharitis. Given these factors and the fact that Lara had been experiencing symptoms for some time, it is little wonder that she found incomplete relief from artificial tears and a short course of immunomodulatory therapy. While these treatments have a place in minimizing the downstream effects of inflammation and a disrupted tear film, significant improvement for this patient only resulted once treatments that targeted the cause of evaporative dry eye were initiated. By addressing the MGD, inadequate lid seal, and associated blepharitis with appropriate currently available treatment options (warm compresses, essential fatty acid supplementation, and lid hygiene), improvements in both signs and symptoms manifested.

THE EXCESS TEAR EVAPORATION, TISSUE DAMAGE, AND INFLAMMATION THAT CHARACTERIZE DED CAN ARISE FROM MULTIPLE INTERRELATED FACTORS

In most cases in medicine, understanding the pathophysiology of a disease precedes development of effective treatments, and clarifying the complexities of diseases like DED is often an ongoing process. Looking at the DED treatment landscape, significant strides have been made in the development of pharmacotherapies targeting inflammation and non-pharmaceutical approaches to MGD. Given the complex, multi-factorial nature of DED, a multifaceted treatment approach may be warranted in a majority of cases. This is similar to other complex, chronic conditions such as diabetes, hypertension, and hypercholesterolemia, which often involve a combination of prescription therapies that work through different mechanisms, with each playing a vital role to provide patients effective control of their condition. The prevalence of MGD and its role in the etiology of dry eye prompt a reconsideration of the importance of controlling evaporation in DED management.[27]

GIVEN THE COMPLEX, MULTIFACTORIAL NATURE OF DED, A MULTIFACETED TREATMENT APPROACH MAY BE WARRANTED IN A MAJORITY OF CASES

BIO

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