DRY EYE DISEASE

What We Know About It Today and Its Importance for Optometry

Arthur B. Epstein, OD, FAAO

Paul M. Karpecki, OD, FAAO

Katherine M. Mastrota, MS, OD, FAAO

Walter O. Whitley, OD

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INTRODUCTION

Although critically important to the practice of optometry, a sophisticated understanding of dry eye disease (DED) is a relatively recent development. Just 20 years ago, DED was a poorly understood entity for which there was a significant controversy with respect to diagnosis.[1]

This picture began to change with the publication of the "Report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes."[1] Like the subsequent DEWS Report, the NEI/Industry Workshop brought together and gave structure to our then-current knowledge of DED and laid the groundwork for future research and understanding. Thanks to significant interest—including commercial interest—the field has grown rapidly. So much has happened that a second DEWS Report (DEWS II) is now being undertaken.

Arthur B. Epstein, OD, FAAO, FABCO, FBCLA, DPNAP, is co-founder of Phoenix Eye Care, PLLC, where he heads the Ocular Surface Disease Center and serves as the Center's director of clinical research.

Paul M. Karpecki, OD, FAAO, heads the Advanced Ocular Surface Disease Center and is director of clinical research at the Koffler Vision Group, Lexington, KY.

Katherine M. Mastrota, MS, OD, FAAO, is Regional Practice Ambassador/ Director, Omni Eye Surgery New York Dry Eye/Ocular Wellness Center.

Walter O. Whitley, OD, is Director, Optometric Services at Virginia Eye Consultants, Norfolk, VA.

TOWARDS A NEW UNDERSTANDING

So how far have we come? And what does a new understanding mean for optometric practice? We can start by looking back. In 1995, the NEI/Industry Workshop defined dry eye as "a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort."[1] This definition recognized two primary etiologies (aqueous deficiency and excessive evaporation), a sign (ocular surface "damage," primarily detectable by staining [Figure 1]), and a symptom (discomfort) but was otherwise silent with respect to causes, effects, or corollaries of the condition.[1]

Twelve years after the NEI/ Industry Workshop, the DEWS Report was able to offer a more robust definition:

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.[2]

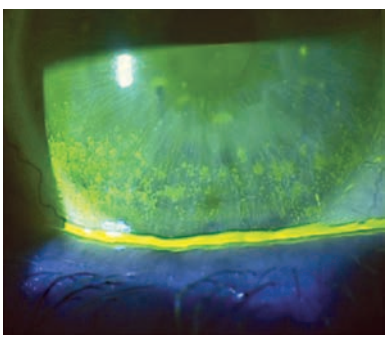

FIGURE 1 Fluorescein stain shows inferior corneal staining suggestive of DED tissue damage. *(Photo courtesy Dr. Karpecki.)*

This definition makes clear that inflammation and hyperosmolarity are hallmarks of the condition and that visual disturbance, tear film instability, and ocular surface damage are characteristic clinical findings of DED. The inclusion of visual disturbance and the emphasis on tear film instability brings the definition closer to our current understanding. While much has been learned since its publication, the DEWS Report gave us a useful platform for thinking about the diagnosis of DED. The DEWS Report has been enormously influential in shaping both research and clinical practice.

In the following pages, we'll look at advances in understanding DED since the DEWS Report was published, and its impact on diagnosis and day-in, day-out optometric practice. While still incomplete, our knowledge has significantly expanded.

PREVALENCE

We have said that DED is critically important to optometry, and part of what makes DED so important is the sheer number of people affected. To put DED prevalence in perspective, we normally think of glaucoma as a highly prevalent eye disease. In quantitative terms, the prevalence of open-angle glaucoma in the US is approximately 3 million (almost 2% of the US population).[3]

How prevalent is DED? Although studies vary based on the definition of DED and a population studied, the recently published report on DED prevalence among 3257 participants in the long-term, ongoing Beaver Dam Offspring Study (BOSS) provided a baseline for estimating the level of DED in the general population of US adults.[4]

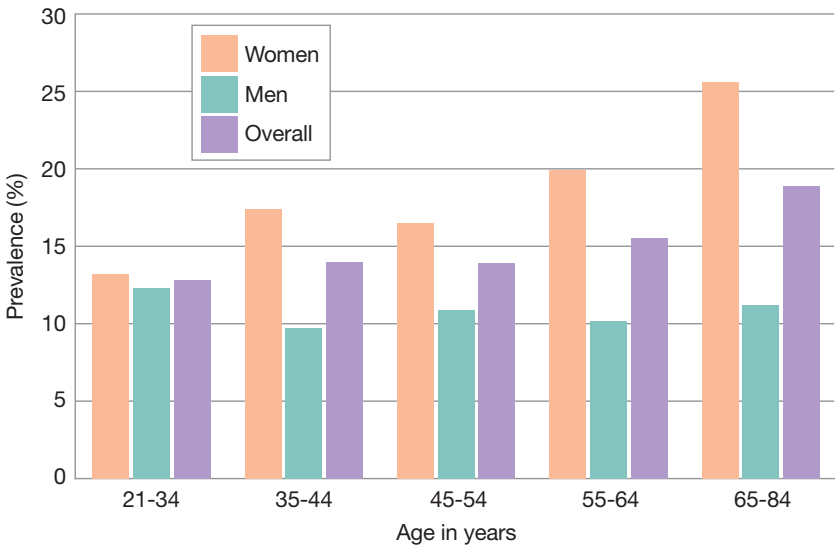

FIGURE 2 Prevalence of dry eye symptoms found in the Beaver Dam Offspring Study 2005–2008. *(Adapted from Paulsen Reference 4.)*

In that study, baseline data were collected between 2005 and 2008 from BOSS participants aged 21 to 84 years via a questionnaire on health history, medication use, risk factors, and quality of life. Whether a BOSS subject had DED was determined by self-report of symptom frequency and intensity or reported use of artificial tears.

In an initial publication of these baseline data, Paulsen and coworkers reported an overall prevalence of DED symptoms of 14.5%—or nearly 30 million people—with rates significantly higher in women than men (17.9% vs. 10.5%, $P < 0.0001$) (Figure 2).[4] Interestingly, although DED has traditionally been associated with aging, in the overall BOSS group, symptoms were also prevalent among younger subjects.[4]

When stratified by sex, the effect of age on dry eye differed between men and women in BOSS. In men, the estimated prevalence was similar among all age groups and there was no observed effect of age ($P = 0.91$);

"As we have learned from the BOSS data and from experience in our own clinics, a DED diagnosis should not be ruled out simply because a patient is young—particularly if the patient is a contact lens wearer."

—PAUL M. KARPECKI, OD, FAAO

while in women, prevalence increased with age ($P = 0.02$), although this interaction was not significant (Figure 2).[4] Using

different criteria, Schaumberg and coworkers' important work found an age-adjusted prevalence of dry eye syndrome of 7.8% in women 50 and older in a study population between 49 and 89 years of age.[5] In a separate study, Schaumberg and colleagues also reported that dry eye was common in men (aged 50 to 99 years), with an age adjusted prevalence of 4.34% in men 50 and older.[6]

So, clearly, DED prevalence rates vary depending on the study population and criteria, but our clinical experience (which admittedly is skewed by our status as clinicians with an interest in DED) is that the 14.5% prevalence rate in the BOSS is a reasonable estimate and possibly even an underestimate of the number of Americans affected. The BOSS data also conform to another aspect of our clinical experience: that a DED diagnosis should not be ruled out simply because a patient is young—particularly if the patient is a contact lens wearer.

> **"The impact of dry eye on an individual's perception of their health is substantial and of importance as a public health problem."**
>
> —JA PAULSEN AND COLLEAGUES, 2014

IS THE DED POPULATION CHANGING?

DED was once commonly talked about as largely a disease of perimenopausal women. Perimenopausal women weren't the only patients, but if you asked a fellow clinician to describe the typical DED patient, that was what you were likely to hear. The BOSS data also aligns well with our clinical impression that, although perimenopausal women still make up a significant fraction of DED sufferers, younger women and men of all ages are increasingly susceptible (Figure 2).

Although the evidence is still largely anecdotal, it is no longer considered unusual to encounter 20-somethings with DED. Whether this is because there is more DED at younger ages or because we are more conscious of DED and therefore more willing to diagnose it in younger patients is an open question. But there is precedent for large scale social/environmental changes to impact vision. Consider, for example, the enormous increase in myopia in young people that we have witnessed over the last 2 generations.[7]

DED AND OPTOMETRIC PRACTICE

DED can produce a range of negative impacts on the patients whom optometrists see every day. The typical optometric practice is likely to offer contact lenses, and for many practices, contact lenses are central to their success. Changes to the tears, ocular surface, and lid margin can reduce wearing time—and may even lead to contact lens drop out.[8]

For optometrists who either work in a surgical practice or comanage surgical patients, DED can compromise critical preoperative measurements and affect postoperative outcomes.[9]

And of course, there is the medical aspect of DED. Patients come to us with DED because they are uncomfortable and/or unable to achieve clear, stable vision, impacting productivity and some visual-related activities of daily living (e.g., reading and driving).

It's also important to recall that DED can be a side effect of ocular surgery or topical medications. It no longer surprises an eye care physician when DED crops up following ocular surgery[10] or in medically treated glaucoma patients, where Baudouin and others have shown that preservatives—particularly benzalkonium chloride (BAK)—used in intraocular pressure-lowering medications can produce significant damage to the ocular surface.[11] And diabetes, a growing threat to global health, can produce ocular surface changes as well as the better known retinal complications.[12]

Whether the patient initially presented for spectacles, contact lenses, surgery, a glaucoma check, or any other medical condition, what matters in the end is how well the patient can see—and vision starts with the ocular surface. Because it impacts both vision and comfort, DED can be the enemy of patient satisfaction and optometric success—or it can be an opportunity for practice growth.

BURDEN OF DISEASE

Leaving aside its potential effects on contact lens wear and surgical outcomes, DED itself can be a very unpleasant condition. The BOSS looked closely at DED's impact on some visual-related activities of daily living and found that while ocular pain was the most serious impact of DED, dry

eye could also be associated with disruptions in daily function, and the effects of DED were similar across all age groups—it is not just older adults who are impacted by DED.[4] In the words of the current report on the BOSS: "The impact of dry eye on an individual's perception of their health is substantial and of importance as a public health problem."

This impact on patients was often overlooked in the past. Since DED may be chronic and patients often have been to multiple doctors, an optometrist who takes their complaints seriously earns their gratitude and respect. Often these patients are vocal about this with their friends, which can provide word of mouth to grow the practice.

As we continue to better understand DED, changes in practice may be called for. For example, when a contact lens patient complains of end-of-day discomfort, our reflex has been to change the lens and/or solution. Similarly, we have all encountered patients who present with complaints of blurred vision, thinking they need new glasses when the problem may be DED.

DIAGNOSTIC CHALLENGES

Despite enormous progress in DED diagnostic technology, challenges in DED diagnosis remain. One challenge derives from the well-known but still frustrating lack of concordance between DED signs and symptoms[13] and the overlap of DED signs and symptoms with signs and symptoms of other ocular surface inflammatory disorders, including allergic conjunctivitis and blepharitis.

As Nichols has pointed out, patients may have signs of DED with few symptoms, or vice versa; and Sullivan has shown us that standard tests for dry eye often produce contradictory results. As clinicians, we want information to be straightforward—we want tests to tell us unambiguously whether to monitor or dismiss the patient. That said, one of the great understandings that has been achieved in DED is that it is a condition where that level of certainty can't be expected from any single test (except, perhaps, with results that are clearly normal or markedly abnormal).[14] In fact, it is the very variability of the results that often points to dry eye disease.[14]

One approach to the problem of poor correlation between signs and symptoms has been to make a diagnosis solely on symptoms. Yet in a major review for *The Ocular Surface,* Bron and coworkers make the following assertion:

> **While symptoms are thought to be characteristic of DED, recent studies have shown that less than 60% of subjects with other objective evidence of DED are symptomatic. Thus the use of symptoms alone in diagnosis will likely result in missing a significant percentage of DED patients, particularly with early/mild disease. This could have considerable impact in patients undergoing cataract or refractive surgery, as patients with DED have less than optimal visual results.[14]**

According to Bron and coworkers, basing DED diagnosis on symptoms alone could result in missing as many as 40% of patients with DED—imagine an optometric practice that got 40% of its spectacles prescriptions wrong! The other side of the coin is that among patients who report typical dry eye symptoms—burning and a dry, gritty feeling with ocular fatigue and irritation especially late in the day or after intense visual tasks—not all of them will have DED. Some may turn out to have other conditions, the symptoms of which overlap with DED.

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NEW TECHNOLOGY AND DIAGNOSTIC STRATEGY

We now have a spate of new diagnostic and therapeutic technologies that can help us help our patients. Major advances include easy-to-use point-of-care tests for osmolarity and detection of the inflammatory marker matrix metalloproteinase-9 (MMP-9). Other devices enable practitioners to visualize meibomian glands or use topography to measure tear film indices, while still other instruments measure blink and lipid layer thickness. We have also

come to appreciate how much can be learned from something as simple and low tech as meibomian gland expression. Not all of these testing modalities are equally valuable, but all add to our knowledge.

The best strategy is not to depend on any single test or marker. As in glaucoma diagnosis, no single test tells us everything we need to know. To continue the analogy, although elevated IOP is often a sign of glaucoma, it is not diagnostic when taken in isolation. Now we have quantifiable biochemical and anatomical markers to break the complex conundrum of DED into manageable entities. It's very useful to look at multiple markers.

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But one need not go to the other extreme and use every available test. The key is to have a panel of tests (that may be used serially) that will provide adequate information about tear production, degree of ocular surface damage, and meibomian gland status. The goal is to balance diagnostic efficacy with efficiency, so that an accurate diagnosis can be made without unnecessary expenditure of time or dollars.

THE LID MARGIN AND A CHANGE IN THINKING

Over the last decade, an enormous amount of information has come to the fore detailing the role of the lid margin and the meibomian glands in the pathogenesis of DED; in parallel with this, a number of therapeutic measures aimed at MGD have been developed. This has given rise to a broad rethinking about DED. To give an idea of how far the pendulum has swung, in the 1995 NEI/Industry Workshop report, the expert panel, led by Michael Lemp, stated without qualification: "Tear-deficient dry eye is the largest category of dry eye."[1]

Fast forward to 2011 and we find the following statement in an article by Lemp and coworkers describing a multicenter study of aqueous deficiency vs meibomian gland dysfunction (MGD) in 224 patients diagnosed with DED: "159 [of the 224 DED patients could be] classified into 1 of 3 categories: 79 were classified with only MGD, whereas only 23 were classified as purely aqueous deficient, and 57 showed evidence of both MGD and aqueous deficiency. Overall, 86% of these qualified DED patients demonstrated signs of MGD."[15] The conclusion: in a typical patient population, the great bulk of DED is either the result of MGD or has a demonstrable MGD component. Evolving science led by top researchers in the field continues to shape our understanding of this disease, and it is imperative that we keep pace with new knowledge to best serve our patients.

Following this logic, much attention has been given to the diagnosis of obstructed meibomian glands. That is entirely appropriate, but is it the end of the story? It shouldn't be. First, even if the majority of DED has an MGD component, there remains a subset of DED patients with minimal or no meibomian gland involvement—and a much larger set of patients with meibomian gland involvement that also have inflammation, biofilm formation, and tear film instability. More important is to ask: what is the symptom driver in DED?

DED: A TEAR FILM ABNORMALITY

DED has been described as a tear film abnormality in which tears no longer provide adequate support to the ocular surface.[16] Tear dysfunction occurs when the lacrimal functional unit (consisting of the lacrimal glands, conjunctival goblet cells, meibomian glands, and their neural and hormonal support structures) is unable to maintain a stable tear layer. A broad range of environmental and endogenous factors can trigger dysfunction of the lacrimal functional unit, but in all cases, once triggered, there is a chronic inflammatory reaction that sets in motion an immune reaction that produces the condition we recognize as DED.[16]

Once triggered, ocular surface inflammation can contribute to sustained dysfunction of the lacrimal functional unit. The result is a lacrimal functional unit that cannot produce tears of adequate quantity or quality. Without an adequately protective tear film, there is continued stress on the ocular surface, leading to a cycle

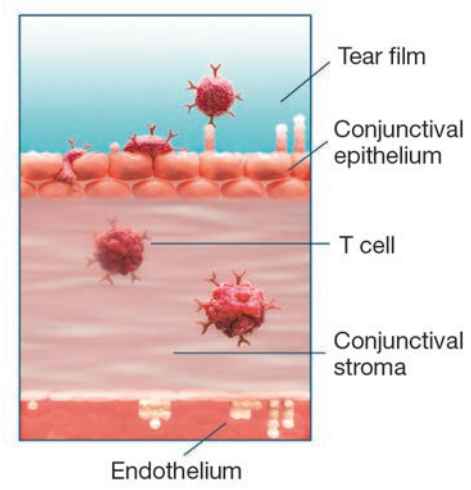

FIGURE 3 T cells infiltrating the ocular surface.[18]

of DED in which inflammation produces tissue damage, which in turn causes cytokine release. Resultant inflammation then leads to further cytokine release—an ongoing cycle that, in some patients at least, can continue, with the DED becoming progressively worse.[2] Even if the inciting cause was meibomian gland obstruction that led to evaporative dry eye, an inflammatory cycle has been initiated.

THE ROLE OF T CELLS AND MEDIATORS

In this process, T cells play an important role by contributing to ocular inflammation through production and release of proinflammatory cytokines.[17] This can be shown in histopathology studies, where DED is characterized by T cell infiltration of the lacrimal gland and conjunctiva (Figure 3).[18]

To make the process comprehensible and clinically meaningful, let us drill down a bit and look at some of the specific mediators, how they are produced, and how they function. In the early 1980s, T cell target recognition was shown to occur through a complex reaction in which a T cell surface receptor called lymphocyte function-associated antigen-1 (LFA-1) was able to bind to a ligand on the target cell (Figure 4). This ligand is intercellular adhesion molecule-1 (ICAM-1), which plays an important role in inflammation.

As evidence of this role, ICAM-1 is normally expressed in low levels on epithelial and endothelial cells of ocular tissues as well as on antigen presenting cells. ICAM-1 is overexpressed in patients with DED, and this ICAM-1 overexpression can be demonstrated in DED patients' ocular surface and lacrimal tissues.[18]

The binding of ICAM-1 to LFA-1 integrin on the surface of T cells plays an important role in the inflammatory process of

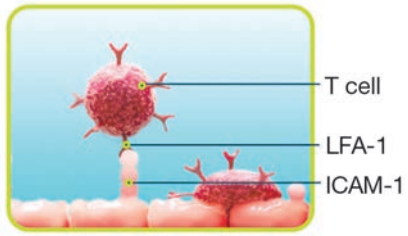

FIGURE 4 LFA-1/ICAM-1 adhesion, an important event in the inflammatory cycle of DED. ICAM-1 is a protein found on ocular epithelial and endothelial tissues. ICAM-1 mediates the inflammatory response by binding to the LFA-1 receptor on the T cell surface.

DED.[18] When ICAM-1 binds to LFA-1, it sets in motion three key components of the inflammatory response: T cell activation, recruitment and cytokine release (Figure 5).[18-20]

Let us look at this cycle of mediator release, inflammation, and mediator release. In the first phase of the cycle, *expression*, a triggering event leads to increased expression of ICAM-1 on epithelial and endothelial cells in ocular tissues as well as on antigen-presenting cells (APCs), with eventual overexpression of

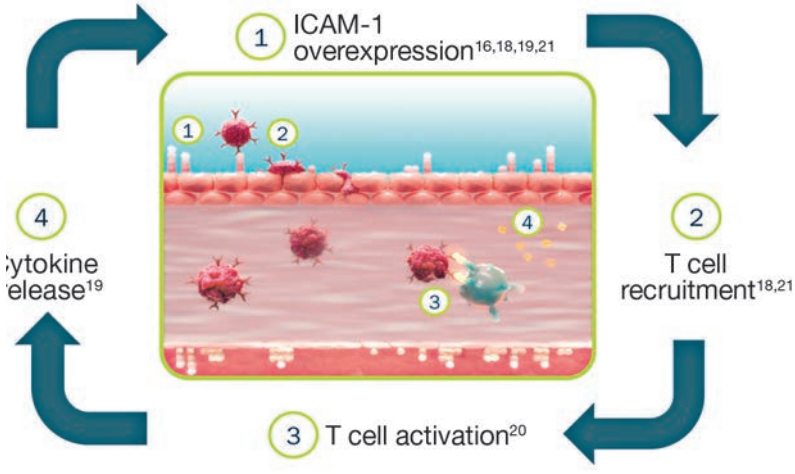

FIGURE 5 ICAM-1 binding initiates a self-perpetuating inflammatory cycle.[16,18-21]

ICAM-1 on the ocular surface.[18,21] In the next phase, *activation*, ICAM-1 binding to LFA-1 on T cells contributes to their activation.

Continuing the cascade, in the third phase, *recruitment*, ICAM-1 binding to T cell LFA-1 facilitates recruitment of additional immune cells to the ocular surface from the tear film and blood vessels.[21] The ICAM-1/LFA-1 interaction becomes a key component of the continued migration of T cells to target tissues.[18]

The final step—and the step that perpetuates the cycle—is *cytokine release*: ICAM-1 binding stimulates cytokine release that further increases ICAM-1 expression, leading to tissue damage and another round of the cycle.[19] (These numbered steps are included for educational purposes. Due to the multifactorial nature of DED and the complexity of inflammation, there are many different entry points to the cycle and simultaneous processes; therefore, the cycle may not follow these linear steps in exact order.)

MAKING CLINICAL SENSE OF DED

The pathogenesis of DED is complex. One can't simply treat the lid margin and leave it at that.

Today, we know a considerable amount about the processes that can cause the lacrimal functional unit to produce too few and poor quality tears. We know too that there is much more to be learned, and that while our tools for diagnosing DED are good, there are still gaps in our understanding.

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This educational program was developed in conjunction with and sponsored by Shire, based on interviews with Arthur B. Epstein, OD, FAAO, Paul M. Karpecki, OD, FAAO, Katherine M. Mastrota, MS, OD, FAAO, and Walter O. Whitley, OD.

Dr Epstein, Dr Karpecki, Dr Mastrota, and Dr Whitley each received a fee for participation in this program.

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