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Modern Perspectives on Dry Eye Disease

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Expert Review: Maurizio Rolando, Michael E Stern and Margarita Calonge

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Dry eye disease (DED), a disease of the lacrimal functional unit, is a complex autoimmune-based chronic inflammatory condition that can have a significant negative impact on quality of life and the patient's ability to effectively carry out everyday activities. Further, DED may lead to contact lens intolerance, and may adversely affect refractive surgical outcomes and be associated with post-ocular surgery complications. The ocular surface system is in constant dynamic equilibrium; however, if damage is severe or too prolonged, repair mechanisms can fail, initiating a feedback loop of increasing inflammation known as the 'vicious cycle'. Stress to the ocular surface triggers the initial inflammatory events that lead to autoimmunity; autoantibodies may contribute to complement-dependent ocular surface pathology. With an aging population and with lifestyles becoming increasingly dependent on screen technology, the burden of DED is likely to escalate in the future. There are multiple challenges in the management of DED, not least the lack of medications for chronic use.

Keywords

Dry eye disease (DED), ocular surface system, immunopathogenesis, anti-inflammatory therapy

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The Changing Landscape of Dry Eye Disease in Europe

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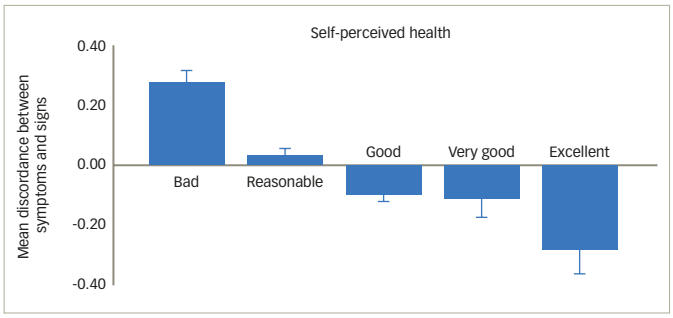
The latest model of dry eye disease (DED) states that: 'Dry eye is a multifactorial disease of the ocular surface characterised by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.'[1] The ocular surface system is in a constant dynamic equilibrium, always adapting to changing environmental and external insults. However, if the initial damage is severe or too prolonged, repair mechanisms can fail, ultimately resulting in a feedback loop of escalating inflammation termed the 'vicious cycle'.[2] Once the cycle is initiated, the continuous environmental challenge acting on a compromised ocular surface allows the vicious cycle to perpetuate, even if the initial cause has been removed or reduced.[3–5] The most frequent results of the vicious cycle are: tear instability, epithelial malfunction/damage and inflammation.[6] Tear film abnormalities are associated with hyper-evaporation and reduced tear clearance.[7] The resulting increased osmolarity leads to eye irritation, which, if persistent, causes production of pro-inflammatory cytokines on the ocular surface to be upregulated. The result is a chronic immuno-inflammatory condition, with the recruitment, activation and involvement of regulators, helper and killer lymphocytes. Pathophysiological factors that contribute to this immune-mediated disorder include: aqueous deficiency, mucin abnormalities, and evaporation (as occurs in Meibomian gland disease [MGD] or when the blink rate exceeds the tear film break-up time [TBUT]).[7] There are multiple causes and contributors to an abnormal tear film, which include ageing, dry environment, hormonal changes, medications, blepharitis, surgery (laser-assisted *in situ* keratomileusis [LASIK]) and autoimmune disease.[7]

The prevalence estimates of DED in Europe[8–11] are consistent with global data, which indicate a prevalence of between 7% and 30%.[12] The exact prevalence is difficult to accurately determine due to a lack of consensus on diagnostic methods, a mismatch between signs and symptoms, and the use of restricted cohorts that have traditionally excluded younger individuals with multiscreen lifestyles. While the typical patient seen in the past might have been female and aged over 50 years,[4] modern patients may be younger contact lens wearers.[13] With the average UK adult now spending more time using digital media than sleeping,[14] lifestyle-driven DED is set to increase. This increase is in combination with the rise due to the ageing population.

DED can have a substantial effect on general quality of life (QoL) and health-related QoL.[4] In fact, a utility assessment of 44 patients in the UK with DED found that severe DED may impact a patient's life to a similar extent as dialysis and severe angina.[15] This impact can be on everyday activities such as reading, working, computer use, watching television and daytime or night-time driving, and as such is an important public health problem.[16] It can also result in contact lens intolerance and discontinuation.[4] In general, the impact of DED persists over long periods of time and increases with disease progression and/or severity.[17] DED is often chronic and progressive. In a study of 398 men and 386 women who reported they had DED and responded to a questionnaire, those who reported severe symptoms of DED in the past were more likely to report worsening odds ratio (OR) 1.79 (1.07–3.00).[18]

Figure 1: Discordance between symptoms and signs in dry eye disease



Reproduced with permission from Vehof J, et al., Ophthalmology, 2017;124:280–86.[19]

An analysis of data from 648 patients with DED (82.7% female; mean age 55.8 year, standard deviation: 15.6 years) from the Groningen LOngitudinal Sicca StudY (GLOSSY), found that greater symptoms versus signs were highly associated with lower self-perceived health (p<0.001; *Figure 1*).[19] This discrepancy highlights the importance of accounting for both signs and symptoms in DED. Significant predictors of greater symptoms than signs were: chronic pain syndrome; atopic diseases; a known allergy, use of antihistamines; depression; use of antidepressants; and osteoarthritis.

DED can adversely affect refractive surgery outcomes and may be associated with increased risk of infection/post-ocular surgery complications.[4] Further, cataract surgery in patients with DED can be associated with ocular morbidity.[4] The risk for refractive regression after LASIK has been shown to increase in patients with chronic dry eye (27% of patients [12/45] with chronic DED versus 7% of patients [35/520] without DED [p<0.0001]).[20] In a Korean study, 48 eyes of 34 patients who underwent uncomplicated phacoemulsification were divided into two groups: those with pre-existing DED before cataract surgery and those without. Compared with the non-DED group, the DED group had significantly higher ocular symptom scores, lower TBUT, higher lid margin abnormalities, meibum quality and expressibility scores after cataract surgery.[21] There were also significant correlations between interleukin (IL)-6 and parameters of DED. Furthermore, the presence of dry eye-related changes in osmolarity is a significant cause of error in the measurement of the intraocular lens to be implanted.[22]

Summary

The prevalence of DED in Europe is consistent with global estimates: 7–22%. The burden of DED is likely to escalate in the future, with an ageing population and as lifestyles become increasingly dependent on multiscreen technologies. DED is often a chronic disease that can impact everyday activities and could lead to contact lens intolerance. In addition, DED may adversely affect refractive surgical outcomes and may be associated with post-ocular surgery complications. ❑

Immunopathogenesis of Dry Eye Disease and its Clinical Relevance

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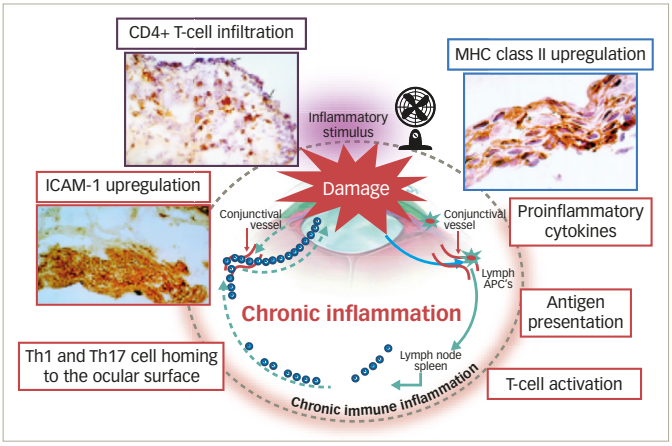
DED is a disease of the lacrimal functional unit;[23] which, in the normal individual provides a homeostatic environment to the ocular surface through its regulation of tear film composition.[24] The three main tear film components are, firstly, the mucins (secreted in soluble form by the conjunctival goblet cells and expressed as transmembrane entities across the ocular surface epithelium). This provides viscosity and stability during blink cycle. Secondly, the aqueous consists of a complex mixture of proteins, mucins, electrolytes etc., and, thirdly, the lipid layer (secreted by the Meibomian glands along the lid margin) that helps to maintain a smooth optical surface and prevent evaporation.[24] New research suggests that mixing of the mucin and aqueous layer occurs, which forms a hydrated gel that is then covered by the lipid layer.[24] In a typical patient with chronic DED, the tear film features both aqueous deficiency and an altered lipid layers and mucin profile.[25]

One of the most common mucins in humans, soluble mucin 5AC is greatly decreased in DED due to a loss of goblet cells and this impacts on viscosity of the tear film.[25] Antimicrobial proteins such as lactoferrin and lysozyme are lower in concentration while pro-inflammatory cytokines such as IL-1 and tumour necrosis factor (TNF)-α are increased and proteases are activated, which in addition to eliciting a pro-inflammatory environment on the ocular surface, degrade extracellular matrix and epithelial tight junctions.[24] Finally, increased electrolyte concentrations such as sodium ions elevate tear osmolarity. Patients with DED display an array of inflammatory markers such as pro-inflammatory cytokine/chemokine expression, upregulation of human leukocyte antigen (HLA) expression, elevated expression of adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and infiltration of inflammatory cells.[26]

In a comparison of cytokine/chemokine levels in 23 patients with DED versus nine control subjects, levels of the following were significantly ($p<0.05$) elevated in the patients with DED: epidermal growth factor (EGF); fractalkine (CX3CL1), IL-1 receptor antagonist (IL-1Ra), interferon (IFN) inducible protein 10 (IP-10); and vascular endothelial growth factor (VEGF).[27] This acute inflammation leads to self-antigen-driven autoimmunity (*Figure 2*).[23,28] Induction of pro-inflammatory factors may be initiated by stress-induced signal transduction pathways or aberrant Toll-like receptor (TLR) signalling.[28] Antigen-presenting cells (APCs) internalise autoantigens, process and present immunogenic epitopes and upregulate expression of costimulatory molecules. C-C chemokine receptor type 7 (CCR7), which is expressed on APCs, directs trafficking to the draining cervical lymph node, activating pathogenic lymphocytes.[29] The local cytokine milieu, produced by mature APCs, influence activation and differentiation of autoreactive T-helper 1 (Th1 cells), which mediate immunity against intracellular pathogens and secrete, among other cytokines, IFN-gamma. Th17 cells, which are involved in several inflammatory diseases, are also activated; these secrete IL-17 and promote elevation in proinflammatory cytokine and chemokine production in a variety of cell types as well as contributing to the regulatory T cell (Treg) defect in DED.[30]

Figure 2: Inflammatory circle of chronic dry eye disease



APC = antigen-presenting cells; CD4 =cluster of differentiation 4; ICAM = intercellular adhesion molecule 1; MHC = major histocompatibility complex; Th = T helper. Figure adapted from: Stern M et al., International Reviews of Immunology 2013;32:19–41.[23]

Autoreactive lymphocytes potentiate the chronic autoimmune response and mediate different pathological consequences on the ocular surface.[28] IFN-gamma, derived from Th1 cells, alters mucins on corneal epithelial cells and has devastating effects on the integrity of the ocular surface.[31,32] These include epithelial cell apoptosis in both the conjunctiva and lacrimal glands, reduced goblet cell density and squamous metaplasia.[33] IL-17 increases matrix metalloproteinase (MMP) 3/9 expression and induces corneal epithelial barrier dysfunction.[30,32] Th17-related cytokines have been shown to correlate with disease severity.

Summary

DED is a complex autoimmune-based chronic inflammatory disease.[28] Stress to the ocular surface triggers the initial inflammatory events that lead to autoimmunity.[28] Cytokines present within ocular surface tissues affects T cell differentiation into Th1 and Th17 cells.[28] Autoantibodies derived from autoreactive B cells appear to contribute to complement-dependent ocular surface pathology.[28] ❑

Challenges in the Management of Dry Eye Disease

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General therapeutic schemes are laid out by the Dry Eye Syndrome Preferred Practice Patterns of the American Academy of Ophthalmology;[34] the 2006 International Task Force (ITF) Delphi Panel Guidelines for Dry Eye[35] and the 2007 Report of the International Dry Eye Workshop (DEWS).[4] An update of the Report of the International DEWS (DEWS II) is expected in July 2017 but was not available at the time of writing. Disease severity is considered to be the most important factor for treatment decision-making and has been categorised into four levels (*Table 1*).[36]

Inflammation is always present in DED, regardless of the type of DED.[4] Anti-inflammatory agents used to tackle this are all off-label and include topical steroids, topical azithromycin and oral tetracyclines (doxycycline). Topical steroids most frequently utilised in the short-term therapy for DED are loteprednol etabonate,[37–39] fluorometholone[40,41] and glucocorticoid.[42,43] In a randomised, vehicle-controlled trial, three-week topical 0.1% fluorometholone therapy was shown to be effective not only in reducing ocular surface signs in patients with DED but also in preventing exacerbation by exposure to desiccating stress.[41]

Immunomodulatory agents used in DED include topical cyclosporin A, tacrolimus and lifitegrast. Cyclosporin A has restricted availability worldwide whereas lifitegrast is not approved yet outside the US.[44] Topical cyclosporin A inhibits T-cell-mediated inflammation and activation and has anti-inflammatory, anti-apoptotic and immunomodulatory effects.[45] Its use also brings about an increase in lacrimal gland production of tears.[45] Topical 0.05% unpreserved cyclosporin A is not approved in the European Union while 0.1% topical unpreserved cyclosporin A has recently become available in some EU countries.[46] Clinical trials have shown that topical cyclosporin A decreased lymphocyte infiltration and activation, and markers of apoptosis and proinflammatory cytokines.[45] In general, improved symptom scores, decreased ocular staining, and increased Schirmer scores were observed with cyclosporin A treatment.[47] Goblet cell density, tear meniscus height and volume and corneal sensitivity have also been shown to improve,[47] as well as decreased use of artificial tears.[48] Topical tacrolimus, an immunomodulatory macrolide, has a similar mechanism of action to cyclosporin A with 10- to 100-times more potency.[49] It inhibits calcium-dependent events such as IL-2 gene transcription, nitric oxide synthase activation, cell degranulation and apoptosis.[49] Topical tacrolimus suppresses the immune response by inhibiting the release of other inflammatory cytokines (IL-3, 4, 5 and 8, IFNα, TNFα).[49] Topical lifitegrast targets ICAM-1/ lymphocyte function-associated antigen (LFA)-1,[50,51] interrupting the inflammatory cycle.[52] 5% topical lifitegrast solution is currently approved only in the US.[53] Clinical trials of the potential benefits of lifitegrast showed reduced signs of DED as measured by corneal and conjunctival staining, and reduced symptoms of eye dryness and discomfort.[54–58] In addition, it was generally well tolerated, as evidenced by short-term (84 day) clinical trials and a longer term (360 day) safety study.[54–58]

Table 1: General therapeutic scheme for dry eye disease by staging

Level	Presentation	Management
1	Mild-to-moderate symptoms but no corneal signs No or mild conjunctival staining Unstable tear film	Education and environmental/dietary modifications (e.g. increase in omega-3 fatty acids) Elimination of systemic or topical medications contributing to dry eye Artificial tear substitutes, gels, ointments Improved eyelid hygiene
2	Visual signs as shown by mild corneal punctate and/or conjunctival staining	Anti-inflammatory therapies Oral tetracyclines and derivatives Secretagogues (not available in Europe) Punctal plugs Moisture chamber spectacles
3	Severe symptoms with marked corneal punctate staining, central corneal staining and filamentary keratitis	Autologous serum (PRP, PRGF) Contact lenses Permanent punctal occlusion
4	Severe corneal staining, erosions, conjunctival scarring	Systemic anti-inflammatory agents Surgery (including: lid surgery, tarsorrhaphy, surgery of the mucus membrane or salivary gland, and amniotic membrane transplantation)

PRP = platelet rich plasma; PRGF = platelet rich growth factor. Information sourced from Behrens A et al.[36]

Summary of challenges in the management of dry eye disease

- Lifestyle modifications (e.g. environmental, nutritional, omega 3 supplements).
- Withdraw any non-required topical/systemic medications.
- Treat MGD aggressively.
- Artificial tear substitutes are always indicated.
- Autologous serum and derivatives are very useful when indicated.
- Tear drainage blockade is controversial.
- Doxycycline oral/azithromycin topical or oral, for eyelids and cornea.
- Topical steroids short-term are essential, though an improved safety profile is needed.
- Topical cyclosporin: prepare ocular surface for tolerance.
- Topical lifitegrast: limited real-world experience in the US, no experience elsewhere.
- Systemic immunosuppressants: Sjögren's syndrome, graft-versus-host disease.
- The most significant challenge is the scarcity of medications available for chronic use. ❑

Discussion

Q: Are there any notable trends with respect to prevalence of DED?

We are observing a rise in prevalence owing to MGD. We are now seeing more young people with DED due in part to over-use of screens and the effect of pollution on the ocular surface.

Q. What are the three top biomarkers for DED?

IL-6, which is a precursor of Th 17-mediated inflammation; epidermal growth factor receptor; and MMP9 are the most studied although the biomarker may vary depending on the drug.

Q. What in general drives patients to your office: signs, symptoms or both?

Most patients present because of their symptoms and the impact they have on their lives, for example, their ability to work and drive.

Q. If inflammation is under control, do we break the vicious cycle and restore ocular surface heath?

Resolution of the disease or at least disease control is possible with long-term suppression of inflammation. For optimal results, we need an anti-inflammatory agent for chronic use (many years).

Q. What antigen plays a key role in the vicious cycle?

There are two hypotheses: destroyed pathogenic bacteria may release antigens; or TLRs may be activated by DNA segments shredded from apoptosis.

Q. When are punctal plugs useful?

These can be harmful in that they can maintain the inflammatory soup present on the ocular surface. They should not be used in the case of MGD or blepharitis in general and whenever improvement is not observed, the plugs should be removed. ❑

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