

Dry Eye: Diagnosis and Current Treatment Strategies

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One in four patients attending ophthalmic clinics report symptoms of dry eye, making it one of the most common complaints seen by ophthalmologists. Aqueous-layer deficiency is the most common form of dry eye and is frequently caused by decreased secretion of tears by the lacrimal glands. Evaporative dry eye is often secondary to meibomian gland disease and results in a defective lipid layer. Tear replacement or preservation using artificial tears and/or punctal occlusion are the mainstay of treatment. Newer forms of therapy were designed to modify the underlying disease process. These include the use of topical cyclosporin A, autologous serum, and sodium hyaluronate drops, which suppress underlying inflammation, provide growth factors, and prevent the onset of squamous metaplasia in ocular surface epithelium. Hormonal therapy might have a role in the future of dry eye therapy.

Introduction

Dry eye refers to a group of disorders of the tear film caused by reduced tear production or excessive tear evaporation that is associated with symptoms of ocular discomfort and might cause damage to the ocular surface. A recent population-based prevalence study found that nearly 15% of subjects aged 65 years and older reported that symptoms suggestive of dry eyes were present often or all of the time [1]. The prevalence of dry eye has increased in recent years, owing to the general aging of the population, as well as the increased use of certain medications [2]. Up to 25% of patients visiting ophthalmic clinics report dry eye symptoms [3], making dry eye disease one of the most common complaints seen by ophthalmologists. A diagnosis of dry eye is made after careful analysis of subjective complaints, objective signs, and abnormal results of dry eye tests.

The pre-ocular tear film is essential in maintaining a normal functioning ocular surface. It serves to smooth out irregularities in the cornea, contributing to the optical properties of the eye and also plays a role in regulating the hydration and nutrition of the cornea. In conditions in

which there is a significant decrease in aqueous tear production (eg, keratoconjunctivitis sicca [KCS]), the normal ocular surface defense mechanisms are compromised, rendering the external eye more prone to infections [4]. Sjögren established the term KCS in 1933, and attributed the dryness and symptoms of dry eye to a reduction of the aqueous component of the tears. Knowledge of the properties of the tear film and ocular surface helps us understand the mechanisms of disease and, in turn, helps the clinician devise a specific treatment plan for patients with dry eye.

The Tear Film and Ocular Surface

The tear film is composed of an external lipid layer, an aqueous layer, a semi-solid conjunctival goblet cell mucus layer, and the epithelial mucin layer (the glycocalyx). The lipid layer is produced by the meibomian glands in the upper and lower lids, and its principal roles are to slow the evaporation of tears, lubricate the action of the lids over the cornea and conjunctival surfaces, and thicken and stabilize the tear film. The aqueous layer contains antibacterial substances, vitamin A, electrolytes, oxygen, glucose, and growth factors (including epidermal growth factor [EGF] and transforming growth factor [TGF- α]) and is secreted primarily by the lacrimal gland. The inner layer of the tear film is composed of mucin secreted by the goblet cells, which are distributed throughout the bulbar and palpebral conjunctiva. The superficial epithelial cells have microvilli and microplicae that are covered by glycocalyx, which is a nongoblet cell mucin synthesized at the apical surface of the epithelium. The inner layers of aqueous and mucin probably combine to form a hydrated gel. This gel is anchored by chemical bonds to the underlying glycocalyx on the corneal epithelium [5]. The glycocalyx renders the hydrophobic ocular surfaces more wettable by the overlying tears and might facilitate tear-film stabilization by reducing the surface tension of tears. Without it, tears do not properly adhere to the eye, and epithelial damage might occur, despite the presence of normal tear production. It also prevents adhesion of foreign debris, cells, or pathogens to the ocular surface. In severe cases of aqueous-tear deficiency, such as KCS, the ocular surface epithelium undergoes squamous metaplasia, with a resultant loss of goblet cells and absence of mucin expression. This, in turn, leads to a further destabilization of the tear film.

Table 1. Diagnostic classification for dry eye proposed by the National Eye Institute/Industry Workshop

Decreased aqueous production
Sjögren's syndrome
Primary or secondary
Non-Sjögren's
Lacrimal gland disease
Lacrimal duct obstruction
Medication side effects
Evaporative dry eye
Meibomian gland disease
Blepharitis
Rosacea
Exposure
Thyroid eye disease
Ectropion/entropion
Contact lens/allergy

Adapted from Lemp [6].

Causes of Dry Eyes

The National Eye Institute/Industry Workshop on clinical trials in dry eyes [6] has recommended a revision of the classification of dry eye, given its multifactorial nature. The major dry eye categories proposed were tear-deficient dry eye and evaporative dry eye (Table 1).

Aqueous-layer deficiency is the most common cause of dry eye and is usually caused by decreased tear secretion from the lacrimal glands. Causes of reduced tear secretion include Sjögren's syndrome (SS), senile hyposcretion, lacrimal gland excision, lacrimal-duct scarring secondary to ocular cicatricial pemphigoid or chemical burns, and immune lacrimal gland damage, as seen in sarcoidosis or lymphoma. Causes of evaporative forms of dry eye include lipid layer deficiency (usually the result of meibomian gland dysfunction); lid anomalies, such as retraction or exophthalmos in thyroid eye disease; chronic allergy/toxicity, which results in chronic stimulation of the local immune system; and cicatricial ocular surface diseases, such as pemphigoid or Stevens-Johnson syndrome, which produce tear deficiency due to conjunctival inflammation, scarring, and goblet-cell destruction.

Pflugfelder *et al.* [1] reported that 3.6% of a large study population had blepharitis associated with meibomianitis. Patients with meibomian gland dysfunction were twice as likely to have dry eye symptoms as those without signs of meibomianitis. These patients often show a shorter tear break-up time (TBUT), rapid tear evaporation rate, high osmolarity, and positive dye-staining tests. Acne rosacea is associated with both posterior and anterior blepharitis. Stagnation of meibomian gland lipids gives bacterial lipase an opportunity to break down meibomian lipids into free fatty acids, which results in increased tear evaporation and an unstable tear film. Control of meibomian gland disease, with vigorous lid hygiene and a lid-massage regimen, and

treatment of concurrent blepharitis, often provides effective relief for the symptoms of dry eye, particularly in the patient with mild aqueous deficiency. If the meibomian gland disease is resistant to mechanical therapy alone, oral tetracycline and its derivatives (doxycycline 100 mg/d orally) will often lead to the success of lid massage [7].

Symptoms caused by dry eye might be exacerbated by the use of systemic medications that lead to decreased aqueous production. Common drugs with such effects include diuretics, antihistamines, β -blockers, anti-Parkinson's drugs, anticholinergics, and tricyclic antidepressants (such as amitriptyline). In addition, environmental conditions, such as reduced humidity and evaporative loss from wind, air conditioning, or heating might exacerbate the ocular discomfort of patients with dry eye. For those cases induced or worsened by medications and adverse environmental factors, elimination of the offending drug or modification of the patient's home or work environment might be curative.

Systemic diseases causing severe aqueous deficiency include SS, which is a chronic, generalized, systemic disorder characterized by the clinical findings of KCS, xerostomia, and an autoimmune disorder. This disease has a prevalence of approximately 1%, mostly female. Primary SS is characterized by KCS and xerostomia without an associated autoimmune disease, whereas secondary SS is characterized by KCS and xerostomia associated with an autoimmune disease (commonly rheumatoid arthritis, lupus erythematosus, or scleroderma). The main histopathologic change in the lacrimal gland of patients with SS is an inflammatory cellular infiltration that leads to destruction of the glandular structures. Lacrimal gland infiltration with inflammatory cells also occurs in patients with sarcoid, lymphoma, and HIV infection.

Although most forms of dry eye cannot be completely prevented, appropriate treatment often reduces symptoms and signs while preventing permanent sequelae. Many other ocular-surface diseases produce symptoms, including foreign body sensation, irritation, and soreness that are similar to the symptoms associated with dry eye. Characteristics of the causative factors, such as exacerbating conditions (*eg*, reading or sitting near air conditioning) or ameliorating circumstances (relief with the use of artificial tears) help the clinician make the correct diagnosis of dry eye.

Clinical Assessment of Dry Eye

Several clinical tests are used to support the diagnosis of dry eye. Unfortunately, there is often poor correlation between reported symptoms and clinical signs as well as relatively poor specificity and/or sensitivity of clinical tests in mild cases. For patients with severe dry eyes, the diagnosis is usually supported by one or more of the following tests: fluorescein TBUT, ocular surface dye staining pattern (rose Bengal, fluorescein, or lissamine green), and the Schirmer test. TBUT is a good measure of tear-film stability



Figure 1. Rose Bengal 1% staining typically seen in patients with dry eye.

and is determined by instilling fluorescein in the inferior cul-de-sac and then evaluating the stability of the pre-corneal tear film after 1 to 2 minutes, using a broad beam of the slit lamp with a blue filter. TBUT is rapid for both aqueous-tear deficiency and meibomian gland disease. The time lapse between the last blink and the appearance of the first randomly distributed dry spot is the TBUT. Dry spots that appear before 10 seconds are considered abnormal. Rose Bengal drops can be painful after instillation and should, therefore, be preceded by a drop of topical anesthetic. Areas of the ocular surface are stained where tear mucus is discontinuous. Mucin normally forms a diffusion barrier to prevent rose Bengal staining. Debris in the tear film is also stained. The specific pattern of corneal and conjunctival staining in the interpalpebral fissure area might be very helpful in establishing the diagnosis of aqueous-tear deficiency (Fig. 1).

Fluorescein stains corneal and conjunctival epithelial cells where there is sufficient disruption of intercellular junctions to allow access to the dye. An exposure-zone fluorescein staining pattern is observed in dry eye, and it is usually more obvious in the cornea than the conjunctiva. Lissamine green has a staining profile similar to that of rose Bengal, but causes much less ocular irritation.

Schirmer testing is useful to differentiate Sjögren-type dry eye from non-Sjögren-type dry eye. No topical anesthetic is instilled prior to insertion of the filter paper when measuring the reflex tear secretion. However, anesthetic should be applied before measuring basal secretion. The loss of reflex tearing is correlated with severe lacrimal gland destruction by lymphocytic infiltration [8]. A topical anesthetic drop is instilled (if measuring basal tearing), and the inferior conjunctival fornix is dried using a cotton bud. After 2 minutes, standard Whatman no. 41 filter paper is placed between the lower eyelid and the globe at the junction of the middle and lateral thirds of the eyelid and examined after 5 minutes. Although no cut-off has been established, less than 10 mm of wetting in 5 minutes is suggestive of a diagnosis of dry eye or aqueous deficiency (less than 5 mm of wetting, if no anesthetic is used). A new

1-minute Schirmer test has been shown to be an equally reliable and faster alternative [9]. That study replaced the 5-minute Schirmer test with anesthesia with the 1-minute test and used 2 mm of wetting as a cut-off for severe dry eye and 6 mm as a cut-off for mild/moderate dry eye. Newer tests of tear-film integrity include the measurement of tear-film osmolarity, tear-fluid protein assays, and fluorescein tear clearance. These tests are more frequently performed in a research setting, and are less commonly used clinically.

Dry Eye Treatments

The primary aim of dry eye treatment should be to improve symptoms, improve tear-film stability, and reverse ocular surface damage. The most common mode of therapy for dry eye patients is the application of artificial tear supplements. Although this form of therapy is only palliative, in that its purpose is to replace tears without correcting the underlying disease process, it is often effective for the patient with mild to moderate dry eye. Any patient who requires the application of tear substitutes more than four times daily should be commenced on preservative-free formulations (unit-dose) because preservatives such as benzalkonium chloride and cetrimide can be toxic to the cornea. Dry eye subjects with inadequate tear secretion are more susceptible to the toxic effects of topical medication due to inhibited tear clearance resulting in prolonged residence time of potential toxins on the ocular surface. The goal of using tear substitutes is to increase humidity at the ocular surface and to improve lubrication, with subsequent secondary benefits. Numerous artificial tear preparations are readily available. A recently launched emulsion lubricant (Refresh Endura; Allergan, Irvine, CA), which was initially developed to serve as a vehicle for cyclosporin in clinical trials, was found to have an intrinsic beneficial effect on dry eye disease. The possible mode of action of the emulsion is to stabilize the tear film and prevent evaporation. Some patients with KCS have very viscous mucus, which forms filaments on the ocular surface. These filaments can be a cause of severe discomfort [10]. We feel that the use of topical mucolytic agents (*eg*, 10% acetylcysteine) in such patients can be very beneficial and often helps to relieve their irritation. Unfortunately, instillation of these drops can be temporarily painful for the patient.

Punctal occlusion is frequently used to help retain and preserve tears. To minimize the risk of epiphora following punctal plug insertion, most clinicians perform temporary occlusion with absorbable or removable plugs before proceeding to permanent occlusion. The nasolacrimal duct should be patent prior to plug insertion to lower the risk for acute dacryocystitis following insertion. Usually occlusion of the inferior punctum in each eye provides sufficient relief from symptoms, but occasionally occlusion of both inferior and superior puncta might be necessary in severe cases. There are several methods of punctal occlusion. The most common include thermal occlusion using cautery,

diathermy, or laser and tamponade using absorbable inserts (hydroxypropyl cellulose or collagen plugs) initially, followed by permanent tamponade using silicone or Teflon-collared plugs inserted into the vertical portions of the canaliculus. Occasionally, patients complain of irritation due to friction between the tip of the punctal plug and the underlying conjunctiva. If epiphora occurs, the collared plug allows easy removal from the punctum. Intracanalicular, collarless silicone plugs are also available and can be easily inserted into the horizontal portion of the canaliculus. They do not protrude from the punctum, and, therefore, rarely cause conjunctival irritation. If epiphora does develop, the intracanalicular plugs can be irrigated down through the lacrimal system. Occasionally, the collarless plugs are impossible to remove by simple irrigation and might cause permanent, irreversible, symptomatic lacrimal drainage system obstruction [11].

Other methods of tear preservation include the use of room humidifiers, which are a simple, noninvasive way to reduce the evaporation of tears. Tarsorrhaphy can substantially reduce the exposed area of the cornea, leading to a reduction in the evaporation of tears. This is usually reserved for patients with exposure keratopathy secondary to lid abnormalities and persistent corneal epithelial defects.

Newer Strategies

Recognition of the role of inflammation in the production of dry eye by the suppression of secretion and damaging effects on the lacrimal glands and ocular surface led to the recommendation of anti-inflammatory therapy for dry eye disease. Unpreserved topical corticosteroids have proven to be effective by reducing inflammation and improving ocular surface health in patients with dry eye [12]. Unfortunately, several unwanted side-effects, such as an increased risk for glaucoma, premature cataract formation, and susceptibility to corneal infection, preclude its long-term use.

More encouraging for long-term therapy is the use of topical cyclosporin A (CsA). Evidence suggests that chronic dry eye disease is the result of an underlying cytokine and receptor-mediated inflammatory process that affects the lacrimal gland, leading to abnormalities in the tear film and ultimately disrupting the homeostasis of the ocular surface [13,14]. Most conventional treatments for dry eye disease focus on tear replacement or tear preservation therapies that do not affect these causative inflammatory processes. Cyclosporin is a potent immunomodulatory agent that inhibits T-cell activation and downregulates the production of many inflammatory cytokines. Topical treatment with CsA has been shown to reduce cell-mediated inflammatory responses associated with inflammatory ocular surface diseases [15]. Other studies have demonstrated that 6 months of therapy with topical CsA resulted in: an increase in goblet cell numbers in patients with non-Sjögren's keratoconjunctivitis sicca (NSS-KCS) and Sjögren's syndrome keratoconjunctivitis sicca (SS-KCS) [16]; significantly reduced the

numbers of activated lymphocytes within the conjunctiva [17]; and showed a decrease in interleukin (IL)-6 levels in the conjunctival epithelium of moderate-to-severe dry eye patients [18]. Stevenson *et al.* [19••] showed that treatment with topical CsA ophthalmic emulsions (using doses ranging from 0.05% to 0.4%) significantly improved the ocular signs and symptoms of moderate-to-severe dry eye disease and that these improvements resulted in a significant decrease in the effect of the disease on vision-related functioning. They also demonstrated, using blood analysis, that even the highest concentrations of topical CsA produced minimal systemic absorption. Significantly, no patients reported complaints, such as ocular discomfort, burning, or itching, following instillation of drops, implying that this treatment was well-tolerated. CsA 0.1% produced the most consistent improvement in objective and subjective endpoints (such as superficial punctate keratitis and rose Bengal staining), and CsA 0.05% produced the most consistent improvements in patient symptoms. Topical CsA 0.05% received approval from the US Food and Drug Administration (FDA) in December, 2002, as Restasis (Allergan, Irvine, CA). It is not yet licensed for use in Europe.

In 1984, Fox *et al.* [20] reported the beneficial effects of autologous serum application to dry eye in SS. Tears normally contain several essential growth factors, such as EGF and vitamin A, which are important in regulating the proliferation and maturation process of the epithelium. These same growth factors are also present in serum. The application of autologous serum (including growth factors) offers an advantage over artificial tears, which lack such essential components. Tsubota *et al.* [21••] demonstrated that the use of serum drops in patients with dry eye in SS resulted in a significant upregulation of mucin expression and a corresponding beneficial effect on the improvement of rose Bengal staining noted clinically. They also showed that components (EGF, vitamin A, and TGF- β) present in autologous serum (20%) drops remained stable in the refrigerator for 1 month and in the freezer for 3 months. No significant complications have been reported with the use of serum drops. In another study [22], the benefit in patients with KCS using serum drops was shown to begin within 48 hours of commencing treatment. Additionally, this study demonstrated a faster healing time in cases of persistent corneal epithelial defects treated with serum drops. Autologous serum drops are now a crucial adjuvant in ocular surface reconstruction in diseases such as Stevens-Johnson syndrome, ocular cicatricial pemphigoid, and chemical burns [23]. In our experience, serum drops are especially helpful in cases of persistent neurotrophic keratitis. In such cases, in which decreased corneal sensation is the hallmark, there is a reduction in the level of aqueous production [24]. The main drawback associated with the use of serum drops is the fact that they are very time consuming to prepare. For this reason, as well as the obvious risks inherent when handling blood from patients with transmissible diseases, such as HIV, another group has suggested the use of albumin eye drops

[25]. They hypothesized that some of the therapeutic effects of serum drops could be reproduced by artificial protein solutions applied to the ocular surface. In their clinical case series, they noted that all patients treated with albumin drops (5%) used six times daily showed a significant improvement in both objective signs (fluorescein staining, TBUT, and rose Bengal staining) and subjective symptoms after only 4 weeks of therapy.

Topical application of sodium hyaluronate has been shown to confer both subjective and objective improvement in patients with dry eye syndrome or KCS [26•]. This study presented impression cytology scores that showed a significant improvement of ocular surface features after treatment with sodium hyaluronate compared with saline. The exact mechanism of action of hyaluronate is unknown, but it might increase corneal tear-film stability and ocular-surface wettability, and also reduce the tear-evaporation rate and the healing time of the corneal epithelium. In patients with severe dry eye, an increased tear osmolarity might lead to desiccation of the ocular surface and, therefore, also play a role in the pathogenesis of the ocular surface damage. The treatment of patients with SS using hypotonic sodium hyaluronate was recently demonstrated to be more beneficial than isotonic sodium hyaluronate at the same concentration [27].

Future Developments

It is known that healthy individuals produce anti-inflammatory androgens, and, as long as this hormone is maintained at normal circulating levels, the lacrimal glands and ocular surface remain in a noninflammatory state. When circulating androgen levels fall, for example, with age, during certain autoimmune diseases such as SS [28], or at menopause, a precipitating stimulus, such as an infection or a dry environment, can allow an inflammatory immune response to occur on the ocular surface or in the lacrimal glands. Another study has shown that androgen insensitivity might promote meibomian gland dysfunction and, in turn, lead to an increase in the signs and symptoms of dry eye [29]. Androgen receptor protein exists within epithelial cell nuclei of the human lacrimal gland, meibomian gland, conjunctiva, and cornea [30]. Therefore, topical androgen administration might serve as an effective therapy for the treatment of both aqueous-deficient and evaporative dry eye in androgen-deficient people.

P₂Y₂ purinergic receptor agonists, similar to those found in the human lung, stimulate mucin secretion from goblet cells of rabbits in vivo [31]. The same P₂Y₂ receptors are also found in human conjunctival cells [32] and, therefore, might be suitable targets for the treatment of patients with dry eye syndrome. Results from rabbit studies have shown that treatment with a P₂Y₂ agonist (INS365) was associated with significantly less corneal damage in a rabbit dry eye model [33]. INS365 has also been shown to stimulate lacrimal gland function in humans [34].

Oral pilocarpine (10 mg once daily) has produced an improvement in subjective symptoms and rose Bengal staining in patients with SS-KCS [35], without showing evidence of an increase in tear production measured by the Schirmer test. Commonly reported side effects include increased sweating, headache, nausea, and vomiting.

Conclusions

Recent advances in the understanding of the pathogenesis of dry eye have helped in the development of new therapeutic agents with promising effectiveness. Disease-modifying therapy with combinations of CsA, autologous serum drops, albumin, and sodium hyaluronate might reduce the severity of pathologic changes on the ocular surface as well as dramatically improving patient symptoms. The clinical efficacy of some evolving treatment strategies for dry eye patients promises much, but still remains to be categorically proven. Those with chronic dry eye symptoms can now look to the future with great hope and optimism.

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