Dry Eye Disease: Pathophysiology, Classification, and Diagnosis

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Abstract

Dry eye disease (DED) is a multifactorial disorder of the tear film and ocular surface that results in eye discomfort, visual disturbance, and often ocular surface damage. Although recent research has made progress in elucidating DED pathophysiology, currently there are no uniform diagnostic criteria. This article discusses the normal anatomy and physiology of the lacrimal functional unit and the tear film; the pathophysiology of DED; DED etiology, classification, and risk factors; and DED diagnosis, including symptom assessment and the roles of selected diagnostic tests.

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For author information and disclosures, see end of text.

Definition

Dry eye disease (DED)—also called keratoconjunctivitis sicca or, more recently, dysfunctional tear syndrome[1]—has been defined in various ways that have changed over time as understanding of the disease process has evolved. For example, in 1995 the National Eye Institute defined DED as "a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort."[2] In 2007, the International Dry Eye WorkShop defined it as "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."[3] The newer definition emphasizes symptoms and global mechanisms (to be discussed below), while recognizing the multifactorial nature of DED.

Normal anatomy and physiology

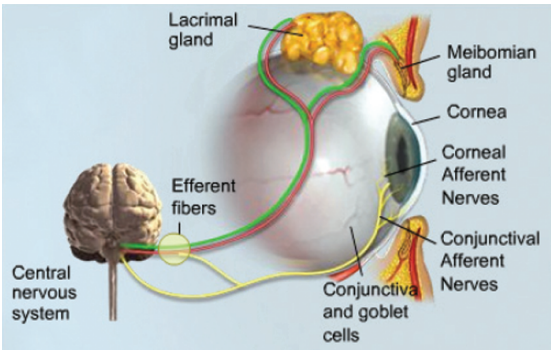
The lacrimal functional unit (LFU) includes the lacrimal glands, ocular surface (cornea and conjunctiva), eyelids, meibomian glands, and associated sensory and motor nerves.[3] Figure 1 also notes the goblet cells in the conjunctiva that contribute to the tear film.

The tear film consists of 3 components or layers: mucous, aqueous, and lipid. Functions of the tear film include lubricating the ocular surface and eyelids[4]; providing a smooth, regular optical surface for the eye[4,5]; supplying nutrients to the ocular surface[4]; removing foreign material and microbes from the ocular surface[4]; protecting the ocular surface against pathogens by means of antibacterial substances[4]; and promoting tissue maintenance and wound healing of the ocular surface.[6]

Blinking spreads the tear film over the ocular surface toward the medial canthus. There the tears are drawn into the superior and inferior puncta (one punctum in each eyelid) to enter the lacrimal canaliculi. The canaliculi convey the tears to the lacrimal sac, the upper end of the nasolacrimal duct, which drains into the nose. (See Figure 2.)

The *mucous component* is the innermost layer of the tear film. The mucous layer contains multiple mucins, some of which are anchored to the ocular surface epithelium.[7,8] Mucins are produced by conjunc-

Figure 1. Lacrimal Functional Unit



tival goblet cells[9] and by stratified squamous cells of the cornea and conjunctiva.[7] Laboratory experiments suggest that conjunctival $P2Y_2$ nucleotide receptors may play a role in regulating mucin secretion.[10] Functions of the mucous layer include lubricating the ocular surface[9] and providing an adsorbent interface between the aqueous layer and the hydrophobic ocular surface epithelium.[8] It also traps foreign particles, cellular debris, and microbes which, with blinking, are moved to the medial canthus where they exit the eye.[9]

The *aqueous component*, the main portion of the tear film, lies on top of the mucous layer. It is produced by the lacrimal glands, which include: (1) the main lacrimal gland (located in the superior temporal region of the orbit) and its palpebral lobe (extending into the upper eyelid), and (2) the accessory lacrimal glands of Krause and Wolfring (located in the conjunctival fornices [ie, where the conjunctiva is reflected from the eyelid to the eyeball]).[9]

Aqueous tear secretion appears to have 2 modes, basal and stimulated. A major portion of tear production is reflexive via stimulation of the ocular surface and nasal mucosa[11]; this reflexive secretion is thought to arise primarily from the main lacrimal gland and its palpebral lobe.[12] Basal secretion (ie, occurring in the absence of neural stimulation) is believed to come from the accessory lacrimal glands[13]; however, some experts have questioned whether basal tear secretion exists.[14] It has been proposed that so-called basal tearing may result from continuous corneal stimulation that is below the threshold of perception.[15] On the other hand, some laboratory experiments suggest that basal tearing may be nonglandular, arising from active transport of fluid and chloride across the conjunctival epithelium. This active transport is mediated by $P2Y_2$ receptors; whether it also occurs in response to neural stimulation is unknown.[12]

The composition of the aqueous component includes water and electrolytes[4]; antibacterial proteins such as lysozyme, lactoferrin, and immunoglobulins (especially IgA)[4]; vitamins, particularly vitamin A (retinol, which is required for corneal maintenance)[16]; and growth factors (eg, epidermal growth factor, hepatocyte growth factor).[6] Functions of the aqueous layer include hydrating the mucous layer[9]; supplying oxygen and electrolytes to the ocular surface[9]; antibacterial defense[8,17]; maintenance and renewal of the ocular surface[6]; and promotion of wound healing via proliferation and differentiation of ocular surface epithelial cells.[6]

The *lipid component* covers the aqueous layer and is the outermost layer of the tear film. It is produced by the meibomian (tarsal) glands, located in the tarsal plates of the eyelids, which open onto the lid margin just posterior to the eyelashes.[8,9] There is also a small contribution from the glands of Zeis, which open into the eyelash follicles.

Functions of the lipid layer include slowing tear evaporation,[8,9,18,19] enhancing tear film spreading,[18] providing a smooth optical surface,[18,19] preventing contamination of the tear film by skin lipids,[19] preventing overflow of tears (in the absence of excessive reflex tearing),[19] and sealing the apposed lid margins during sleep.[18]

Pathophysiology

DED is a multifactorial disorder involving multiple interacting mechanisms. Dysfunction of any LFU component can lead to DED by causing alterations in the volume, composition, distribution, and/or clearance of the tear film. Two mutually reinforcing global mechanisms, tear hyperosmolarity and tear film instability, have been identified.[3]

- *Tear hyperosmolarity* can arise from either low aqueous flow or excessive tear film evaporation. Hyperosmolar tears can damage the ocular surface epithelium by activating an inflammatory cascade, with release of inflammatory mediators into the tears. While acute inflammation may initially be accompanied by increased reflex tearing and blinking, chronic inflammation may result in reduced corneal sensation and decreased reflex activi-

ty, leading to increased evaporation and tear film instability. Inflammation can also result in goblet cell loss and decreased mucin production, which further contributes to tear film instability.[3]

- *Tear film instability* can arise secondary to hyperosmolarity, or can be the initiating event (eg, lipid layer abnormalities in meibomian gland disease). Tear film instability results in increased evaporation, which contributes to tear hyperosmolarity.[3]

Regardless of the initiating event or etiology, inflammation is usually a key factor in perpetuating DED.[1] Chronic DED may result in further pathologic changes. For example, patients with moderate to severe DED may develop reversible squamous metaplasia and punctate erosions of the ocular surface epithelium.[20] DED is also the most common cause of filamentary keratitis (FK), a condition characterized by strands of degenerated epithelial cells and mucus attached to the cornea. Friction between the filaments and the eyelid during blinking can result in further epithelial damage, inflammation, and filament formation; thus, FK often becomes chronic, and is a common finding in severe DED.[21,22] Rarely, severe DED may lead to complications such as ocular surface keratinization; microbial keratitis; corneal neovascularization, ulceration, perforation, and scarring; and severe vision loss.[20]

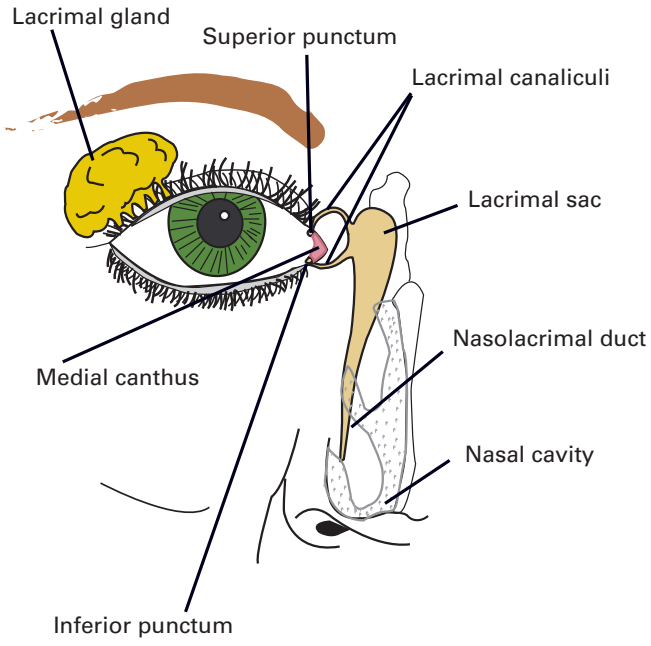
Etiology and classification

There are 2 major etiologic categories of DED: aqueous-deficient and evaporative.[3]

Aqueous-deficient DED is classified as either Sjögren or non-Sjögren. Primary Sjögren syndrome is an autoimmune disorder in which the lacrimal and salivary glands are infiltrated by activated T-cells, resulting in symptoms of dry eye and dry mouth. Secondary Sjögren syndrome is Sjögren syndrome associated with other autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus.[3] Non-Sjögren aqueous-deficient DED can result from lacrimal gland insufficiency (various etiologies), lacrimal duct obstruction, or reflex hyposecretion (Table 1).[3]

Evaporative DED also has various causes, including meibomian gland disease, eyelid aperture disorders or lid/globe incongruity, blink disorders, and ocular surface disorders (Table 1).[2,3] The most common cause is meibomian gland dysfunction (MGD; also called posterior blepharitis), a condition of meibomian gland obstruction.[3,18]

Figure 2. Tear Drainage System



Although these major categories seem clear-cut, in reality there is considerable overlap between them. First, any form of dry eye may be associated with any other form.[2] Second, because of the interaction (described above) between the 2 global DED mechanisms, tear hyperosmolarity and tear film instability, the differentiation between aqueous-deficient and evaporative DED is often unclear. Third, certain DED etiologies involve multiple mechanisms. For example:

- Contact lens wear may result in decreased corneal sensitivity, with reflex sensory block leading to aqueous deficiency.[3] At the same time, contact lens wear may also result in increased evaporation due to a reduced blink rate and/or incomplete lid closure during blinking.[23,24] In addition, poor lens wettability may also contribute to increased evaporation.[3,23]
- Vitamin A deficiency can cause xerophthalmia, due to both impaired goblet cell development and lacrimal gland damage.[3]
- Sjögren syndrome is considered primarily an aqueous-deficient disorder; however, increased evaporation due to meibomian gland destruction is also common in this disease, and may be a contributing factor.[25]

Table 1. Etiologic Categories of Dry Eye Disease

Aqueous-deficient

- **Sjögren**

  Primary—autoimmune disease affecting lacrimal and salivary glands[3]

  Secondary—associated with other autoimmune diseases (eg, rheumatoid arthritis or systemic lupus erythematosus[3])

- **Non-Sjögren**

  Lacrimal gland insufficiency

  Primary—eg, congenital alacrima; familial dysautonomia; age-related[3]

  Secondary

  - o *Lacrimal gland infiltration*—eg, in sarcoidosis, lymphoma, AIDS, graft-versus-host disease[3]
  - o *Lacrimal gland ablation*[3]
  - o *Lacrimal gland denervation*[3]

  Lacrimal duct obstruction—can be caused by any kind of cicatrizing conjunctivitis (eg, trachoma, cicatricial pemphigoid, erythema multiforme, chemical or thermal burns[3])

  Reflex hyposecretion

  Sensory block—can be secondary to anything that decreases corneal sensation, including corneal surgery (eg, LASIK), contact lens wear, diabetes (possibly due to sensory neuropathy), infection (eg, herpes simplex keratitis; herpes zoster ophthalmicus)[3]

  Motor block—eg, secondary to cranial nerve VII damage, multiple neuromatosis, anticholinergic medications[3]

Evaporative

- **Meibomian gland disease**—causes include:

  Meibomian gland dysfunction (MGD)—a result of, eg, local disease, systemic dermatoses (eg, acne rosacea, seborrheic dermatitis), drug toxicity (eg, isotretinoin)[3]

  Congenital aplasia[3]

  Distichiasis (growth of aberrant eyelashes from the meibomian gland orifices)[3]

- **Eyelid aperture disorders or lid/globe incongruity**—causes include exophthalmos (eg, in thyrotoxicosis), eyelid deformity, poor lid apposition[3]
- **Blink disorders**—infrequent blinking (eg, in Parkinson's disease[2])
- **Ocular surface disorders**—eg, allergic conjunctivitis[3]

Risk factors

Older age[3,26] and female sex[26] are well-known risk factors for DED. Other risk factors include:

- *Environmental conditions*. Low humidity, high temperature, and wind or high air velocity increase evaporation.[3,26,27] Poor air quality or air pollution (eg, tobacco smoke)[27] may cause irritation, worsening DED symptoms.[26]
- *Occupational factors*. Tasks requiring sustained visual attention (eg, working at a microscope or computer) result in a reduced blink rate and increased evaporation.[3,26-28] Visual tasks performed with upward or even horizontal gaze (eg, computer use) may also contribute, because upgaze widens the palpebral aperture, exposing more of the ocular surface to evaporation.[27,28]
- *Nutritional factors*. A diet low in omega-3 fatty acids, or with a high ratio of omega-6 to omega-3 fatty acids, may contribute to DED.[26,29] Low vitamin A intake can predispose to DED (see also above under **Etiology and classification**).[26]
- *Hormonal status*. Several lines of evidence suggest that androgens regulate meibomian gland function, and that androgen deficiency promotes MGD and evaporative DED.[30] Androgens also appear to influence the structure and function of the lacrimal glands.[31] Women with Sjögren syndrome have been found to be androgen-deficient. Androgen deficiency also may be a contributing factor in DED associated with aging (in both sexes) and menopause.[30] However, postmenopausal hormone replacement therapy has also been associated with an increased risk of DED.[26]
- *Systemic medications*. Drugs that have been associated with DED include anticholinergics (eg, antihistamines, antispasmodics, tricyclic antidepressants, diphenoxylate/atropine),[3,20,26,32] beta-blockers,[3,20,26] diuretics,[3,20,26,32] systemic isotretinoin,[33,34] amiodarone,[35-37] interferon,[38,39] postmenopausal hormone replacement therapy (estrogen alone more so than estrogen plus progestin),[26,40] and antiandrogenic agents.[26,30] In contrast, one population study found that angiotensin-converting enzyme inhibitors were associated with a lower risk of DED.[32]
- *Topical ophthalmic medications*. Frequent use (>4-6 times daily) of preserved eye drops (including glaucoma medications and artificial tears) may contribute to DED. The toxicity of benzalkonium chloride (the most widely used preservative) to the ocular surface epithelium

is well established; however, other preservatives also can have irritating effects.[41]

- *Contact lens wear* (see above under **Etiology and classification**).
- *Refractive surgery*, for example, laser-assisted in situ keratomileusis (LASIK) and, to a lesser extent, photorefractive keratoplasty.[26] Refractive surgery disrupts corneal innervation and can contribute to aqueous deficiency. A common complication of LASIK, DED can become chronic in some cases. In turn, chronic DED after LASIK is a risk factor for poor refractive outcome.[42]
- *Parkinson's disease*. Reduced blink rate is a common feature of this disease, resulting in increased evaporation.[3,26]
- *Diabetes mellitus*,[3,26,43,44] autoimmune disease,[26] hepatitis C,[26] human immunodeficiency virus (HIV) infection,[26] radiation therapy,[26] and bone marrow transplantation[26] have all been associated with an increased risk of DED.

Diagnosis

Currently, there are no uniform criteria for the diagnosis of DED. Traditionally, combinations of diagnostic tests have been used to assess symptoms and clinical signs.[45]

Common DED symptoms are listed in Table 2. Symptoms tend to be worse later in the day,[20,46] and may also be exacerbated by factors such as low humidity, smoky environments, and prolonged use of the eyes.[46] In addition to the clinical history, use of a validated symptom questionnaire is helpful.[2,45] A number of questionnaires are available for evaluation of various aspects of DED symptomatology, including severity, effect on daily activities, and quality of life.[26] Some widely used DED symptom questionnaires are listed in Table 3.

Physical examination includes visual acuity measurement, external examination, and slit-lamp biomicroscopy.[20] Additional diagnostic tests may be performed to assess tear film instability, ocular surface damage, and aqueous tear flow.

Tear film instability is commonly evaluated by performing a tear breakup time (TBUT) test. A widely used method involves instillation of fluorescein dye into the eye. After the dye has been distributed throughout the tear film by blinking, the patient is asked to stare straight ahead without blinking. Under slit-lamp examination, the time between the last blink and the appearance of the first break in the fluorescent tear film is measured.[2,45] Values of <10 seconds have traditionally been considered abnormal; however, more recently, cutoffs as low as <5 seconds have been recommended.[45]

Table 2. Common Symptoms of Dry Eye Disease

Dry, scratchy, gritty, or sandy feeling[8,46,47]
Foreign body sensation[20,46]
Pain or soreness[20,46,47]
Stinging or burning[8,20,46,47]
Itching[20,46]
Increased blinking[20]
Eye fatigue[47]
Photophobia[20,46]
Blurry vision[20,46] (may be related to tear film irregularity,[5] and may clear temporarily with blink[26])
Redness[20,47]
Mucous discharge[20]
Contact lens intolerance[20]
Excessive tearing (may paradoxically occur due to corneal irritation with reflex tearing)[46]

Ocular surface damage is commonly assessed by staining with rose bengal, lissamine green, or fluorescein dye. Abnormal corneal and/or conjunctival staining patterns, observed on slit-lamp examination, are a sign of damage. The staining pattern can be photographed and graded using one of several scoring systems. Fluorescein dye is well tolerated, but results may be variable. Rose bengal produces more consistent results, but is irritating to the eye. Lissamine green is similar to rose bengal in its staining characteristics, and is as well tolerated as fluorescein.[2,45]

Aqueous tear flow is commonly assessed by performing a Schirmer test. In this test, a specified type of paper strip is placed over the lower lid margin, in contact with the ocular surface. This can be done either without topical anesthesia (to measure reflex tearing) or with anesthesia (to measure basal tearing by minimizing ocular surface reflex activity). To measure maximal reflex tearing, the test without anesthesia can be performed with stimulation of the nasal mucosa by means of a cotton swab.[65] The paper strip is removed after 5 minutes, and the amount of

Table 3. Selected Dry Eye Disease Symptom Questionnaires

Questionnaire	Use	Content Information in Reference
Ocular Surface Disease Index (OSDI)[48,49]	Measurement of symptom severity, frequency, and impact on functioning	49
McMonnies Dry Eye Questionnaire[50]	Screening	50
Canadian Dry Eye Epidemiology Study (CANDEES) Questionnaire[51]	Screening	51
Dry Eye Epidemiology Projects (DEEP) Questionnaire[52]	Screening	52
Women's Health Study Questionnaire[53]	Screening	53
National Eye Institute Visual Function Questionnaire (NEI-VFQ),[54] 25-item version (VFQ-25)[55,56]	Measurement of vision-targeted HRQOL (not DED-specific)	55, 56
Dry Eye Questionnaire (DEQ) and Contact Lens Dry Eye Questionnaire (CLDEQ)[57-61]	Measurement of symptom frequency, diurnal intensity, and intrusiveness	57 (DEQ) 59 (CLDEQ)
Dry Eye Disease Impact Questionnaire (DEDIQ)[62,63]	Measurement of symptom severity and impact on lifestyle	63
Ocular Comfort Index (OCI)[64]	Measurement of symptom frequency and intensity	64

DED indicates dry eye disease; HRQOL, health-related quality of life.

wetting is measured. Wetting of ≤5.5 mm has traditionally been considered abnormal, and a cutoff no lower than ≤5 mm is currently recommended.[45]

Other diagnostic tests that may be performed include:

- *Fluorescein clearance*. This test measures tear clearance or turnover. Delayed clearance has been associated with increased tear cytokine concentration, which may contribute to chronic inflammation.[66]
- *Corneal topography*. A number of noninvasive techniques are available for evaluating the shape of the corneal surface. For example, in videokeratography, an illuminated pattern (usually a series of concentric rings) is focused on the cornea and reflected back to a camera. The shape of the reflected pattern reveals the corneal shape. Computerized algorithms are used to create a 3-dimensional topographical map of the corneal surface. Studies suggest that videokeratography may be useful as an objective test for diagnosing and evaluating the severity of DED.[67,68] Videokeratography may also have prognostic value, for example, in screening patients prior to LASIK and determining their risk for post-LASIK chronic DED.[69]
- *Impression cytology*. This test serves as a minimally invasive alternative to ocular surface biopsy. Superficial layers of the ocular surface epithelium are collected (eg, by applying filter paper) and examined microscopically. Impression cytology is useful for detecting abnormalities such as goblet cell loss and squamous metaplasia.[70]

Although useful for confirming the diagnosis, diagnostic test results generally correlate poorly with symptoms.[1,26,47] This may be due, in part, to the subjective nature of symptoms.[26] However, other factors also may account for the poor correlation; for example, severe disease may result in relatively mild symptoms if corneal hypesthesia is present.[26] Patients with early or mild disease may have symptoms prior to the appearance of objective signs.[1,20] Conversely, some individuals may have objective signs without symptoms. (Although the latter do not meet strict criteria for DED—which is considered a symptomatic disease—it has been suggested that the diagnosis may nevertheless be extended to them.[45]) Diagnostic test results also tend to vary more from visit to visit than subjective symptoms, but may be more reliable in severe than in mild DED.[71]

Tear hyperosmolarity is a global mechanism of DED whose measurement could potentially provide a "gold standard" for DED diagnosis. Currently there is no simple, widely available tear osmolarity test; however, a practical clinical test may soon become available. Meanwhile, TBUT may be the best clinical alternative because it also measures a global mechanism, has good overall accuracy,[45] and

appears to be more repeatable (varies less from visit to visit) than many other diagnostic tests.[71]

Summary

The LFU includes the lacrimal glands, ocular surface (cornea and conjunctiva), eyelids, meibomian glands, and associated sensory and motor nerves. The tear film consists of 3 layers: mucous (produced by conjunctival goblet cells and by corneal and conjunctival epithelial cells), aqueous (secreted by the lacrimal glands), and lipid (secreted primarily by the meibomian glands).

DED is a multifactorial disorder of the tear film and ocular surface that results in eye discomfort, visual disturbance, and possible ocular surface damage. Dysfunction of any LFU component can lead to DED by altering the volume, composition, distribution, and/or clearance of the tear film. There are two major etiologic categories of DED: aqueous-deficient and evaporative. However, regardless of etiology, tear hyperosmolarity and tear film instability have been identified as global, mutually reinforcing mechanisms. In addition, inflammation is a key factor in perpetuating DED.

Currently there are no uniform diagnostic criteria. DED is considered a symptomatic disease; assessment of symptoms is considered of primary importance, and may be aided by use of a validated symptom questionnaire. Combinations of various diagnostic tests (including measurements of tear film instability, ocular surface damage, and aqueous tear flow) have been used to evaluate clinical signs, but although diagnostic tests are useful for confirming the diagnosis, they often correlate poorly with symptoms. Measurement of tear osmolarity might provide a "gold standard" of diagnosis, but a practical tear osmolarity test is not yet widely available. Measurement of tear film instability by means of a TBUT test has good overall accuracy and may be more repeatable than many other diagnostic tests.

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