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New York State Continuing Education Mail-In Course

Current Understanding of the Pathophysiology of Dry Eye Disease

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Our understanding of the pathophysiology and treatment of dry eye disease has been rapidly expanding in recent years. Dry eye disease, or *keratoconjunctivitis sicca*, a.k.a. *ocular surface disease (OSD)* is now considered a multifactorial disease with an inflammatory component. The term *dry eye* has been attributed to the Swedish ophthalmologist Henrik S.C. Sjögren (Brewitt), who in 1933 described a triad of disease involving dry eye, joint soreness and dry mouth, which is referred to as Sjögren's syndrome. The definition of dry eye has been expanded to include any chronic symptomatic external ocular disease in which there is increased tear osmolarity and tear film instability resulting in ocular surface damage. Environmental influences such as humidity and pollution, immune influences such as allergy and stress, local physical tissue influences such as contact lens wear and/or LASIK surgery, as well as systemic influences such as medications, age, sex and hormone levels can all individually or collectively affect the prevalence and severity of ocular surface disease. Ocular surface disease

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damages the ocular surface, which causes an inflammatory stimulus that damages the lacrimal glands in a vicious cycle. Dry eye disease is now categorized into two main divisions: tear-deficient and evaporative.

Incidence

The prevalence of dry eye disease remains only vaguely defined. One study from Japan (Hickichi) stated that of a 2,127-person sample 17% suffered from dry eye symptoms. An investigation of dry eye symptoms among the elderly (Schein) involving 2,520 residents of Maryland, ages 65 and over, reported an incidence of 15%. Another questionnaire study of 13,517 Canadians (Caffery), including all age groups, reported dry eye symptoms among 28.7% of respondents. The report included 60% women and 24% contact lens wearers. Symptoms were more frequent among individuals age 50 or greater. Among those reporting severe dry eye symptoms, women reported severe symptoms more often than men at a ratio of 46:1. Half, 50.1%, of the contact lens wearing group reported dry eye symptoms. Patients taking medications or reporting systemic allergies were more prone to report dry symptoms. Other studies report up to 20% of the population ages 45 years or greater report dry eye symptoms. Although the true incidence of dry eye disease may remain vague, it is a significant problem that we are now just beginning to understand.

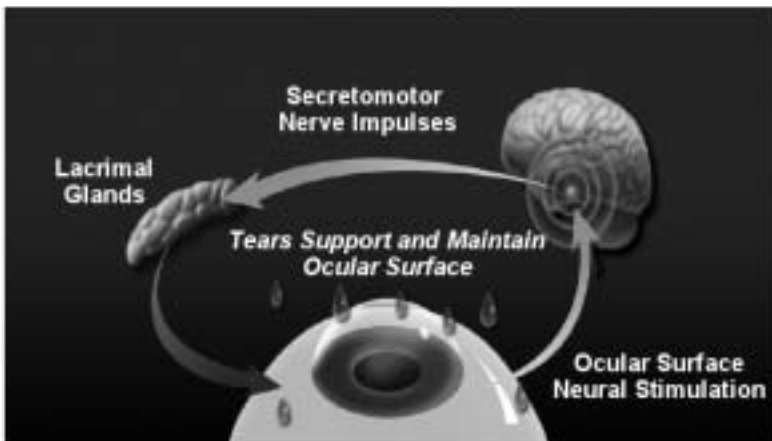


Figure 1: Through constant turnover, the tear film maintains a dynamic equilibrium of numerous chemical components to insure proper maintenance and stability of the ocular surface.

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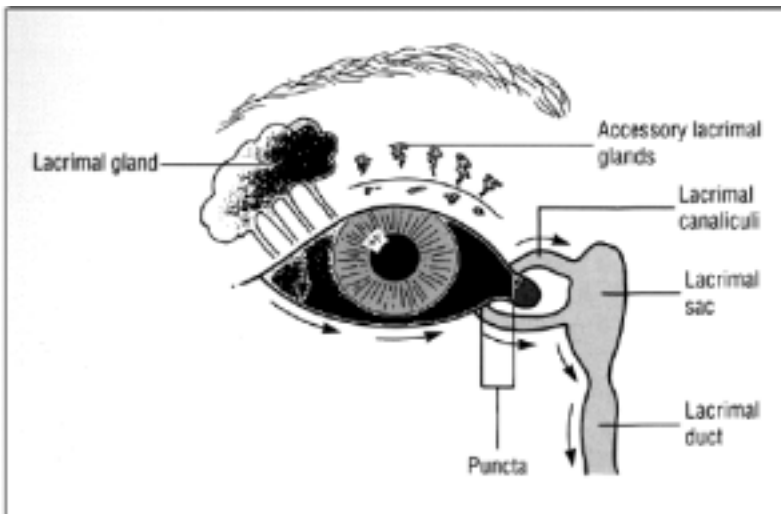


Figure 2: The lacrimal system.

The Tear Film

Tears nourish, cleanse and protect the outer ocular surface. Tears contain water, lipids, proteins, electrolytes, dissolved gases (O_2 , CO_2), immunoglobulins, and exfoliated epithelial cells in a dynamic balance. The tear film must maintain a dynamic equilibrium with constant turnover to insure proper maintenance and stability of the ocular surface. Tear film instability appears to be a component of all forms of dry eye disease and high tear osmolarity (increased viscosity due to low aqueous component) is consistently associated with ocular surface damage. Inflammatory components have been increasingly reported as both a cause and a consequence of the disease. Inflammation is part of an intricate and multifactorial feedback loop. The components participating in this functional unit are the lacrimal gland, corneal epithelium, conjunctival epithelium, tear film and eyelids. These structures communicate and are regulated through systemic hormones, cytokines and both sympathetic and parasympathetic branches of the central nervous system. Events that disrupt the homeostasis of this unit may lead to a cycle of disease; a single stimulus may create multiple and simultaneous reactions. For example, corneal epithelial cells can alter their migration rates from $17\mu\text{m}/\text{day}$ to $60\mu\text{m}/\text{hour}$ depending upon need.

The production of tears is regulated through a nervous reflex loop. Epithelial disruption leads to stimulation of the ocular surface, which sends a message to the trigeminal (CN.V) nerve, which in turn sends a message to the facial nerve (CN.VII), which stimulates the lacrimal glands to produce tears. Stress, hormones, humidity and temperature changes, epithelial disease, inflammations and even ultraviolet exposure can stimulate this reflex loop.

The tear film has classically been described as having three layers: lipid, aqueous and mucus. Although the boundaries and thicknesses of the layers remain under discussion, contemporary models describe two main layers: lipid layer and aqueous layer with the mucin creating a gel gradient as it attaches to the epithelial

microvilli. The main and accessory lacrimal glands produce the aqueous layer from various stimuli: sympathetic, parasympathetic and hormonal stimulation. The aqueous layer contains the oxygen and nutrients necessary to maintain normal epithelial metabolism. The lipid layer is produced from the meibomian glands of the eyelids. The primary function of the lipid layer is to prevent evaporation of the aqueous tears. A smooth, thin lipid layer floating on the aqueous layer provides a smooth anterior refractive surface for the eye; a smooth outer ocular surface is essential for good vision. Rapid and forceful blinking can increase the thickness of the lipid layer. A low blink rate can thin the lipid layer; this occurs when we stare while reading or using a computer.

Types of Tear Dysfunction

The National Eye Institute classifies tear deficiency states according to their main causative factors: *aqueous layer deficiency* and *evaporative deficiency*. These two states are not mutually exclusive. Aqueous layer deficiency is more common than evaporative deficiency. Causes of aqueous layer deficiency include age-related senile hypo secretion, vitamin A deficiency, Sjögren's syndrome, sarcoidosis, chemical burns, trauma and contact lens wear. The mucin component of the aqueous layer is produced by the conjunctival goblet cells; hence any damage to these cells will result in dry eye disease. Medications and preservatives can also damage the conjunctival goblet cells.

The lipid layer floats on the aqueous layer to prevent evaporation. An abnormal lipid layer causes evaporative tear deficiency. The main cause of evaporative tear deficiency is meibomian gland obstruction. This can occur due to inflammatory skin conditions such as blepharitis (staphylococcal or seborrheic), acne rosacea and others. Low androgen levels can contribute to evaporative tear deficiency. Androgen hormone receptors have been demonstrated in meibomian gland tissues. Androgens regulate meibomian gland function and secretion of lipids similarly as they do with other sebaceous glands. Other sex hormones, such as luteinizing hormone, follicles stimulating hormone, progesterone and estrogens also play a role in lacrimal gland function (Baudouin). Estrogens appear to promote lacrimal gland regression and therefore reduced tear production. Post-menopausal women tend to suffer from a decrease in tear production, however tear production is not stimulated by hormone replacement therapy (HRT). Rather, estrogen replacement alone tends to worsen dry eye states; androgens are apparently beneficial due to their immunosuppressive qualities. Androgen levels decrease with aging in both sexes and may lead to increased dryness and indirect inflammatory stimulation.

Nervous stimulation is necessary for normal tear production. Use of topical ocular anesthetics essentially

(Continued on Page 3)

stops tear production. Surgically induced ocular surface disease can be seen following LASIK surgery. In LASIK a horseshoe shaped incision is made by the microkeratome through the anterior cornea to create a flap. This cuts the corneal nerves along the incision line. This surgical denervation with an associated decreased blink rate plays a significant role in creating post-LASIK dry eye states. Dry eye symptoms tend to decrease with time as the corneal nerves regenerate; this may take 6-12 months or longer.

Chronic dryness and irritation of the ocular surface leads to inflammation, which leads to activation of T-lymphocytes and release of inflammatory cytokines, which in turn attack and damage the lacrimal glands. Once dry eye disease has developed, subsequent inflammatory processes become both the cause and consequence of cell damage (Baudouin). Dry eye disease is often associated with allergies and allergic conjunctivitis. Many of the same mediators are present in both dry eye disease and allergic states. Similarly, dry eye states often follow viral keratoconjunctivitis. A damaged cornea has reduced nervous sensation, therefore the system slows down and the eye is drier.

Contact lens wear can cause a decrease in conjunctival goblet cell concentration with an associated decrease in mucin production. Contact lens wear does not appear to alter tear protein levels. Dry eye-like symptoms can be produced by tight contact lenses and lens care product toxicities.

Treatment

In Sjögren's day, tear substitutes were developed using saline and later by adding gelatin and methylcellulose. Tear replacement therapy and punctal occlusion are the primary treatments today, but are only palliative in that they do not treat the underlying disease. Punctal occlusion remains controversial. Some studies have suggested that punctal occlusion can decrease tear production and decrease ocular surface sensation (Yen). Delayed tear clearance, through drainage or evaporation, can lead to increased concentrations of cytokines and other inflammatory mediators in a stagnant lacrimal pool. However, some patients receive significant relief from punctal occlusion; this argues toward our lack of understanding of the effects of this procedure.

Currently, preservative-free artificial tears are the recommended treatment for dry eye symptoms. Preservatives and other additives in medicated eye drops and artificial lubricants can damage the ocular surface and stimulate further inflammation. The cationic detergent and quaternary ammonium compound benzalkonium chloride (BAK) is especially damaging to the ocular epithelium. BAK emulsifies the cell membrane lipids and breaks down their intercellular junctions (Calonge). The use of preserved artificial tears in patients with closed puncta causes increased damage to the ocular surface due to the longer contact time (decreased tear

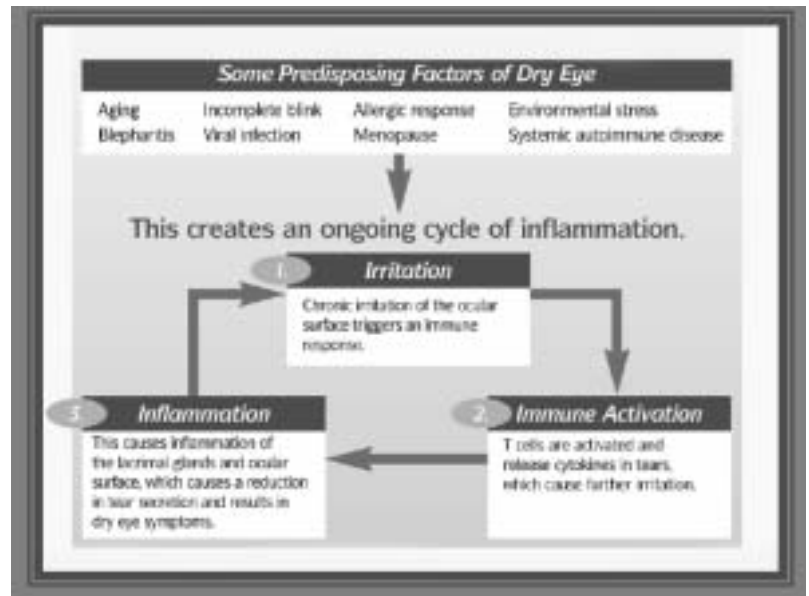


Figure 3: The inflammatory cycle of dry eye disease.

clearance) and undiluted preservative build up. In recent years relatively non-toxic preservatives have been developed that allow rapid breakdown of the preservative moiety without ocular irritation.

Artificial tear constituents that have shown particular promise in dry eye treatments include carboxymethylcellulose, hydroxymethylcellulose, polyvinyl alcohol and povidone. Petroleum-based ointments have received mixed reviews. Not only do they complicate contact lens wear, but also the oil-at-bedtime and water-during-the-day regimens may complicate each other. Concurrent treatment of eyelid disease is important. Most patients can benefit from judicious use of hot compresses and lid scrubs.

Environmental control with room humidifiers can also be helpful. Limiting exposure to environmental pollutants can also help. More aggressive therapies include moisture chamber goggles and tarsorrhaphies.

Anti-inflammatory and immunomodulating drugs are being developed for treatment of dry eye disease. Topical ocular steroids help to quell the active inflammatory state, but require careful monitoring for drug-induced complications and should not be used long term. A new ocular medication under clinical investigation is the immunomodulating drug Cyclosporin-A (Allergan) in eye drop form, which reduces inflammatory markers and symptoms. Other non-steroidal immunomodulating drugs will be available in the future.

Dry eye disease is a complicated entity that affects millions of people. It has been a nuisance diagnosis to physicians in the past, but is becoming more recognized and leading to more aggressive treatment modalities. Treatment of the ocular surface is necessary to prevent inflammatory mediators from damaging the lacrimal glands. Dry eye should be treated like dry skin: prophylactically-treat it before it cracks; if you wait for the pain, it is too late.

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Current Understanding of the Pathophysiology of Dry Eye Disease

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1. An abnormal lipid layer causes:

- a. Evaporative tear deficiency
- b. Sjogren's Syndrome
- c. Aqueous layer deficiency
- d. Hormonal imbalance

2. The contemporary model of the tear film describes two main layers: They are:

- a. Mucin and aqueous
- b. Mucin and lipid
- c. Lipid and aqueous
- d. None of the above

3. Dry eye disease can be categorized as:

- a. Systemic and non-systemic
- b. Aqueous and lipid
- c. Tear-deficient and evaporative
- d. Sjogren's and non-Sjogren's

4. Which of the following statements is true?

- a. Estrogens appear to increase tear production
- b. Post-menopausal women often suffer from decreased tear production
- c. Estrogen replacement alone will decrease dry eye symptoms
- d. Decreased androgen production has little effect on the tear film

5. The aqueous layer of the tear film is produced by:

- a. The main and accessory lacrimal glands
- b. The sympathetic and parasympathetic glands
- c. The meibomian glands
- d. Conjunctival goblet cells

6. Dry eye disease:

- a. Is easily cured with preservative-free drops
- b. Is a multifactorial disease with an inflammatory component
- c. Has been clearly understood for several centuries
- d. Shows a very well documented, consistent rate of incidence

7. Which of these is necessary for tear production?

- a. Nervous stimulation
- b. Adequate hormone levels
- c. Physical stimulation
- d. Emotional stimulation

8. In one study, women reported severe dry eye symptoms more often than men at a rate of:

- a. 4 to 6
- b. 46 to 1
- c. 6 to 4
- d. 60 to 24

9. The lipid layer is produced by:

- a. The main and accessory lacrimal glands
- b. The sympathetic and parasympathetic glands
- c. The meibomian glands
- d. The conjunctival goblet cells

10. Which of the following is *not* true regarding contact lenses and the dry eye state?

- a. Lens wear can cause a decrease in conjunctival goblet cell concentration
- b. Lens wear alters protein levels in the tears
- c. Tight lenses may produce dry eye symptoms
- d. Dry eye symptoms may result from lens care product toxicities

11. A systemic influence on the dry eye state may include:

- a. Humidity
- b. Pollution
- c. Medications
- d. Contact lens wear

12. The primary function of the lipid layer is to:

- a. Provide oxygen and nutrients
- b. Promote normal epithelial metabolism
- c. Prevent evaporation of the aqueous layer
- d. Create a hydrophilic corneal surface

13. Which is particularly damaging to the epithelium?

- a. Hydroxymethylcellulose
- b. Topical ocular steroids
- c. Carboxymethylcellulose
- d. Benzalkonium chloride

14. Which of the following appears to be a component of all forms of dry eye disease?

- a. Tear film instability
- b. Low tear osmolarity
- c. Decreased viscosity
- d. Sjogren's Syndrome

15. The mucin component is produced by:

- a. The main and accessory lacrimal glands
- b. The sympathetic and parasympathetic glands
- c. The meibomian glands
- d. The conjunctival goblet cells

16. Which of the following is the most practical treatment option for patients suffering from dry eye?

- a. Tarsorrhaphies
- b. Preservative-free artificial tears
- c. Hormone replacement therapy
- d. Moisture chamber goggles

17. Stress, temperature changes, and epithelial disease are examples of:

- a. Symptoms of dry eyes
- b. Causes of lipid layer deficiencies
- c. Types of tear dysfunction
- d. Stimulants to the ocular surface nervous system

18. Inflammation is:

- a. Both a cause and a result of dry eyes
- b. A cause of dry eyes, but not a result
- c. A result of dry eyes, but not a cause
- d. Neither a cause nor a result of dry eyes

19. Punctal occlusion has been shown to:

- a. Increase tear production
- b. Increase ocular surface sensation
- c. Increase inflammatory mediators
- d. Increase lipid layer production

20. BAK is a:

- a. Ocular steroid
- b. Immunomodulating drug
- c. Methylcellulose compound
- d. Quaternary ammonium compound

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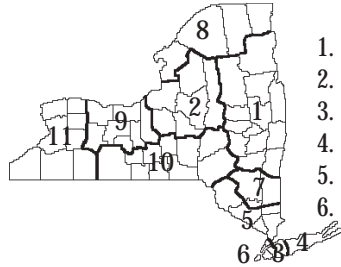
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