Dry Eye Disease

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Dry eye disease (DED) is one of the common disorders of the eye with an estimated prevalence of 5.5–33.7% worldwide. The Dry Eye Workshop (DEWS II) in 2017, defined dry eye syndrome (DES) as:

> A multifactorial disease of the ocular surface characterized 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.

Tear Film

The tear film is a simple fluid that coats the eye and protects the ocular surface. A healthy tear film is essential for normal functioning and health of the eye. Normal tear film consists of aqueous, mucin and lipid layers. Various epithelial and glandular tissues (cornea, bulbar and palpebral conjunctiva, and lacrimal and accessory eyelid glands) of the ocular surface, contribute in the secretion of tear film.

Dry eye disease can occur due to the following mechanisms:

1. Reduced tear production
2. Increased tear film evaporation
3. Mixed mechanism

The dry eye disease spectrum can be classified as:

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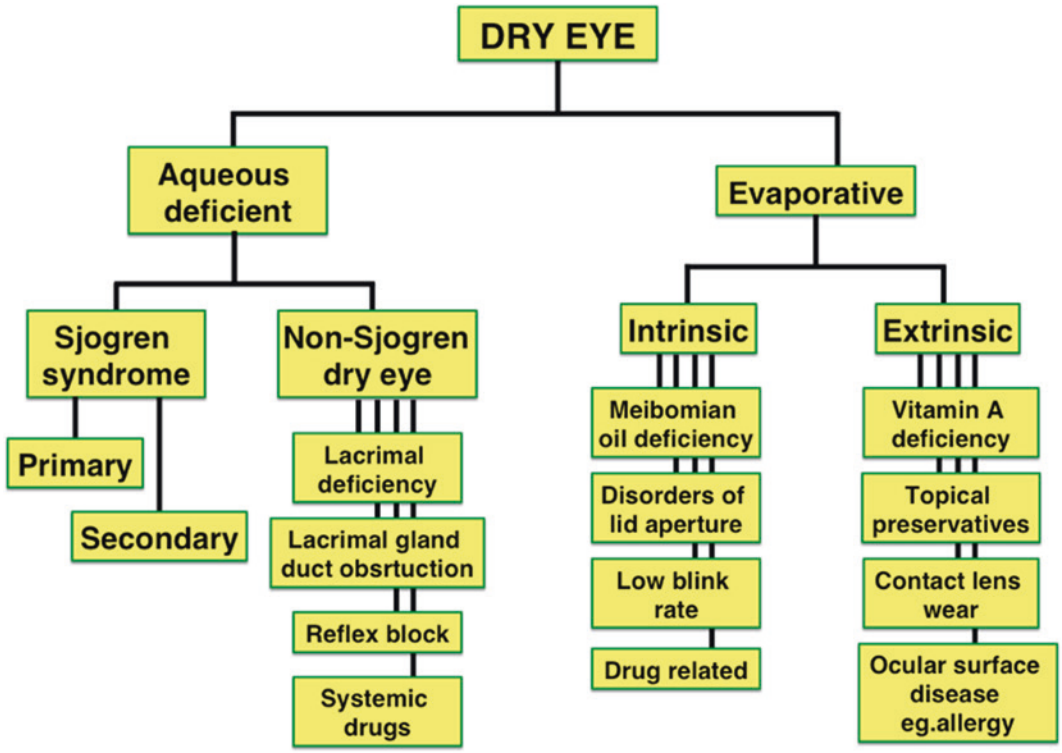

Aqueous Deficiency Dry Eye Disease

(a) Sjogren Syndrome: It is an auto-immune exocrinopathy affecting lacrimal and salivary glands.

(b) Non-Sjogren Dry Eye: It is a lacrimal dysfunction where the systemic autoimmune features have been excluded.

(i) **Sjogren Syndrome**:

Sjogren syndrome (SS) is the second most common autoimmune rheumatologic disease. It is characterised by lymphocytic infiltration of the lacrimal and salivary glands resulting in the "classic sicca complex" of dry eye (keratoconjunctivitis sicca) and dry mouth (xerostomia).

Types of Sjogren syndrome:

(a) Primary Sjogren Syndrome: Features of SS without any associated systemic connective tissue disease.

(b) Secondary Sjogren Syndrome: Features of primary SS along with features of systemic autoimmune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), PAN etc.

(ii) **Non-Sjogren Dry Eye Disease**:

There are various causes for Non-Sjogren Dry Eye Disease.

(A) Lacrimal gland deficiency:

It is characterised by a lacrimal glad dysfunction. It can be divided into:

(a) *Primary Lacrimal Gland Dysfunction*: Caused by age related dry eye resulting from periductal fibrosis, acinar cell loss; use of hormone replacement therapy, congenital alacrimia (Riley-Day syndrome).

(b) *Secondary Lacrimal Gland Dysfunction*: Caused by lacrimal gland infiltration secondary to sarcoidosis, lymphoma, amyloidosis, hemochromatosis.

(B) Lacrimal gland obstruction: This is characterized by obstruction of lacrimal gland ducts such as in cases of cicatrizing conjunctivitis caused by trachoma, mucus membrane pemphigoid, chemical and thermal burns.

(C) Reflex Block: A reflex sensory block is seen in cases with impaired neurosensory pathways such as diabetes mellitus, neurotrophic keratitis. This contributes to dry eye in two ways. A reduced reflex-induced lacrimal secretion, and an increased evaporative loss caused by reduced blink rate.

(D) Drug-induced: Long term use of certain drugs has been shown to cause dry eye disease. These include beta-blockers, selective serotonin reuptake inhibitors (SSRIs) and anti-histamines.

Evaporative Dry Eye Disease

Evaporative dry eye disease is characterised by a normal tear film production and secretion, but an increased tear film evaporation from the surface. This could be caused by intrinsic and extrinsic factors.

(A) Intrinsic factors

(a) Meibomian gland dysfunction (MGD): It is defined as a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion.

Types of MGD:

1. *Low-delivery type or Obstructive type*: Keratinized plugs at the gland orifices secondary to squamous metaplasia of the epithelium causes inspissation of lipids and cell debris within dilated ducts. Consequently, there is absence/hyposecretion of meibum and gland atrophy.
2. *High-delivery type or Seborrheic type*: In this type of MGD, hypersecretion of meibum causes inflammation of the ocular surface. There are no morphological changes seen in the meibomian glands.

(b) Disorders of the lid aperture: Increased tear film evaporation is seen in cases of lagophthalmos, proptosis and craniosynostosis where there is increased lid aperture or incomplete closure of the lids.

(c) Low Blink rate: A low blink rate is a physiological phenomenon that occurs during performing certain tasks like working on a computer (computer vision syndrome). Neurological diseases like Parkinson's disease also cause blink rate to reduce.

(B) Extrinsic factors

Extrinsic factors causing ocular surface damage and subsequent dryness and keratinization are known:

(a) Chronic ocular surface disease like allergic conjunctivitis, vernal catarrh, contact lens wear etc.

(b) Nutritional deficiencies: Nutritional imbalance has been shown to increase the oxidative stress affecting the ocular surface, and supplementation of these nutrients has promising results in the treatment of DES.

1. **Vitamin A deficiency**: Vitamin A deficiency is a leading cause of childhood blindness all over the world. It is most prevalent in developing countries where most children suffer from malnourishment and infectious disorders. Among adults, it is known to occur as a result of intestinal malabsorption, liver diseases and poor dietary intake. The spectrum of ocular disease arising from vitamin A deficiency is known as *xerophthalmia.* Ocular changes include conjunctival and corneal drying (xerosis), corneal ulceration and melting (kerotomalacia), night blindness (nyctalopia) and retinopathy. Vitamin A deficiency is associated with a high degree of morbidity and mortality, mainly because affected children are more susceptible to respiratory and intestinal infections.

Pathophysiology

Vitamin A is a fat-soluble vitamin that is ingested as carotene from plant sources (green leafy vegetables, red palm oil, yellow fruits) and as retinol from animal sources (fish, eggs, milk, meat, liver). It is absorbed from the small intestine. Within the intestinal mucosal cells,

carotene is converted to retinol. Along with already absorbed retinol, it is esterified to palmitic acid. Retinyl palmitate is then transported via lymphatics to the liver, where it is stored. When metabolic requirement of vitamin A arises, retinyl palmitate is hydrolysed and reconstituted to retinol. This retinol is attached to retinol-binding protein (RBP) and transported via bloodstream to the target tissue.

Vitamin A has two roles in ocular metabolism. First, in the retina, vitamin A serves as a precursor to the photosensitive visual pigments that participate in the initiation of neural impulses from the photoreceptors. Second, it is necessary for conjunctival epithelial cell RNA and glycoprotein synthesis, which help to maintain the conjunctival mucosa and corneal stroma.

Vitamin A is essential for maintaining the visual pigments in both rods and cones. In rod cells, retinal combines with the protein opsin to form the photosensitive pigment called rhodopsin. When light hits the rod cells, there is isomerization of the retinal to initiate the visual signal. The pigment is broken down to opsin and all-trans retinal. The correct geometrical form of retinal has to be reconstituted to combine with opsin to reform the pigment. However, in this process, some of the retinal always is lost, so a constant source of vitamin A must be available for adequate levels of rhodopsin and optimal rod function.

Vitamin A is also needed to maintain mucosal and epithelial surfaces. Lack of vitamin A causes loss of goblet cells and inappropriate keratinization of epithelium. Also, the colliquative necrosis of the substantia propria of the cornea results in keratomalacia.

Ocular Manifestations

Table.
World Health Organization Reclassification of Xerophthalmia Signs

Classification	Ocular Signs
XN Night blindness	
X1 Conjunctival xerosis	• X1A Conjunctival xerosis • X1B Bitot's spots
X2 Corneal xerosis	
X3 Corneal ulceration-keratomalacia	• X3A Corneal ulceration-keratomalacia involving one-third or less of the cornea • X3B Corneal ulceration-keratomalacia involving one-half or more of the cornea
XS Corneal scar	
XF Xerophthalmic fundus	

Night Blindness

Night blindness is the earliest sign of Vitamin A deficiency. Subclinical deficiency can be diagnosed by using electroretinography and dark adaptation study, which shows impaired retinal function. Night blindness usually responds within 24–48 hours of Vitamin A administration.

Conjunctival manifestations

Vitamin A deficiency leads to loss of mucosal goblet cells and keratinization of the conjunctival epithelium. The term "xerosis" is used to describe this dryness. Conjunctival xerosis (X1A) is found typically in the temporal, interpalpebral, bulbar conjunctiva. It appears as a dry, granular patch with loss of transparency, thickening and wrinkling. It stains with Rose Bengal.

Bitot's spots (X1B) are triangular, gray plaques of keratinized conjunctival debris overlying areas of conjunctival xerosis. They are occasionally found in individuals with normal vitamin A levels too. When these are associated with vitamin A deficiency, they tend to disappear with treatment.

Corneal Manifestations

The earliest corneal manifestation is a loss of the corneal sheen and a resultant dull appearance of the cornea with superficial punctate keratopathy.

This occurs due to an unstable tear film and if left untreated, the keratopathy progresses to epithelial defects, stromal edema, and keratinization in the interpalpebral fissure. Corneal epithelial defects can progress to ulcers. These ulcers are characteristically small, with sharp borders and located nasally in the peripheral cornea. They may progress to involve the visual axis and may get secondarily infected. A full-thickness liquefactive necrosis may occur and is termed as "keratomalacia". Clinically, it appears as a grayish-yellow, opaque, sharply demarcated lesion. Vitamin A supplementation speeds healing and often, it is associated with a preceding systemic stressor, such as measles, diarrhea, or respiratory infection, or with concurrent severe protein-energy malnutrition.

Xerophthalmic Fundus

Appearance of yellow and white dots in the periphery indicating structural damage to the retina, although rare, is known to occur in xerophthalmia. These dots indicate retinal pigment epithelium defects. Rarely, patients can present with scotomas corresponding to the area of retinal involvement. These changes can respond to vitamin A therapy, with scotomata disappearing in 1–2 weeks and retinal lesions fading in 1–4 months.

Vitamin D

Vitamin D and its role in the etiopathogenesis of dry eye disease has been the subject of a many recent reseach publications. Studies have demonstrated the association of vitamin D deficiency with DED. Vitamin D exhibits anti-inflammatory and immunoregulatory properties and its deficiency results in inflammatory or immune mediated dryness of the eyes. It can influence the severity of symptoms by modulating nociception by regulating nerve homeostatis and inflammatory responses. The exact mechanism linking Vitamin D to pain remains elusive however several theories have been put forward. Serotonin which can perpetuate chroin pain response was found to be high in patients with DED and vitamin D is known to affect serotonin synthesis indicating a role of vitamin D in nociception. Studies have shown that Vitamin D decreases nitric oxide, a nociceptive neurotransmitter production and resulting hyperinnervation there by modulating pain. Vitamin D and its agonists have been found to inhibit maturation and induce tolerance in dendritic cells resulting in the arrest of inflammatory processes. Lower vitamin D levels were associated with an increase in DCs with dendritic processes (mature phenotype) in our cohort which supports the current understanding regarding the immunomodulatory role of vitamin D on DCs. Vitamin D also modulates the expression of various inflammatory cytokines in various cells, including corneal epithelial cells substantiating the anti-inflammatory/immunomodulatory functions of vitamin D.

Essential Fatty Acids

The Dry Eye Workshop demonstrated that the pathophysiology of DES was associated with an inflammatory mechanism. MGD is associated with altered lipid composition, dietary supplementation with antioxidants like omega-3 fatty acids has been recommended in both the International Dry Eye Workshop and International Workshop on Meibomian Gland Dysfunction as primary therapy.

Essential fatty acids, including the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), perform numerous roles in the human body and are considered essential nutrients.

Clinical studies have shown the beneficial role of omega-3 FAs in tear function parameters, such as the Schirmer test, tear film break-up time, and fluorophotometry, indicating that omega-3 FAs increase tear secretion and decrease the rate of tear evaporation.

O3FA and O6FA are the precursors of eicosanoids that function as lipid-based inflammation regulators.

Eicosanoids derived from O3FA are anti-inflammatory, decreasing inflammation and apoptosis of the acini and secretory epithelial cells of the lacrimal glands, resulting in increased secretory function of the lacrimal glands and tear production. They also retard evaporation of the tear film through restoration of the lipid layer, by clearing meibomitis, and resulting in secretion of a better quality, more fluid lipid.

Eicosanoids derived from O6FA are pro-inflammatory.

Combined use of O3FA and O6FA could achieve better protective effects against DES. Also the balance between O3FA and O6FA in the supplement is important because they function synergistically

O3FAs in a dose of 2,400 mg/day for 45 days does improve dry eye symptoms and tear film stability.

However, the role of Omega 3 fatty acids has been challenged currently and is becoming controversial with a large number of studies indicating that it does not have a beneficial effect in evaporative dry eye.

Other nutrients

Vitamin C helps to regenerate other anti-oxidants like vitamin E. These help in maintaining the blood vessels and connective tissues and helps in free-radical scavenging. Free radicals are responsible for damage of conjunctival and corneal epithelium and tear-secreting tissues.

(c) Chronic Anterior Blepharitis

It affects the area surrounding the base of eyelashes. It could be staphylococcal or seborrheic. Staphylococcal blepharitis is known to be caused by coagulase negative staph or *S. aureus*. It is characterised by scaling, crusting, erythema of the eyelid margin with collaret formation at the base of the cilia. Seborrhoeic variety is marked by greasy scaling of eyelid and is associated with seborrheic dermatitis of eyebrows and scalp.

Diagnosis

History and symptoms:

(a) Abnormalities in tear film cause symptoms like dryness, grittiness, soreness, redness, photophobia and ocular fatigue. These symptoms may or may not correlate with the severity of the disease with regard to tear film metrics. Increasing age and long-term contact lens wear decreases corneal sensations and may result in symptoms that are disproportionate to the severity of the disease.

(b) Examination of the lids is mandatory in all cases. Abnormalities in the eyelid position and blink rate, punctal ectropion or stenosis, the presence of any blepharitis with scaling or lash inflammation should be noted. meibomian glands should be expressed by gentle pressure and its secretions should be clear or slightly yellow and express easily. In a patient with gross epiphora, it is mandatory to irrigate the lacrimal passages

Subjective tests:

Validated questionnaires allow quantification and scoring of symptoms and consist of a series of questions with numerical values attributed to the answers. This ensures consistency in recording systematic information. Furthermore, the scores can be correlated with various imaging and tear film metrics to determine changes that are strongly associated with ocular symptomatology. Few of these validated questionnaires are:

1. Ocular surface disease index (OSDI)
2. Impact of Dry Eye on Everyday Life questionnaire (IDEEL)
3. Standard Patient Evaluation of Eye Dryness (SPEED)
4. Dry Eye Questionnaire
5. McMonnies Questionnaire.

OSDI and SPEED are two questionnaires which are frequently used.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?.	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?.	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?.	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?. . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Fig. 1 Ocular surface disease index questionnaire

The OSDI is a 12-item questionnaire that assesses both dry eye symptoms and their effects on vision (Fig. 1).

It has a Likert design and assesses frequency of ocular symptoms (soreness, blurred vision), difficulty with vision-related function (television, visual display unit, driving, reading) and discomfort due to environmental triggers (low humidity, high wind). Patients are asked about the frequency of occurrence of various symptoms and difficulty encountered with vision-related activities and for their response on a 0–4 scale that ranges from "none of the time" to "all of the time." The final score is calculated by multiplying the sum of all the scores by 25 and then dividing the total by the number of questions answered. Scores range from 0 to 100 with 0 to 12 representing normal, 13–22 mild dry eye

disease (DED), 23–32 moderate DED, and more than 33 severe DED.

Limitations of the OSDI include variation of difficulty between categories of questions, no linear relationship of the results to symptom severity, and analysis issues from the use of ordinal ranking. The final percentage score may also be artificially high when difficult questions are not answered or deemed not applicable by the patient.

The SPEED (Standard patient evaluation of eye dryness) questionnaire is a frequently used questionnaire. It is quick and easy to perform and detects severity of disease as well.

- **Objective tests**

I. **Quantitative tests**:

a. **Schirmer's test**: It is done to assess the aqueous tear production. It is an invasive test in which a strip of filter paper (5 × 35 mm Whatman filter paper) is placed in lower conjunctival cul-de-sac and measurement of wetting length is done over a certain period of time, usually 5 min. There are two commonly used variants of Schirmer's test.

Schirmer's I: measures the total tear production including both basal and reflex tears. Jones modification of this test can measure only basal secretion with the aid of an anaesthetic agent.

Schirmer's II: Schirmer II test is performed by irritating the nasal mucosa with a cotton-tipped applicator prior to measuring tear production, which is mainly used for measuring the reflex tear secretion of main lacrimal gland.

A value of less than 5 mm wetting in 5 minutes is considered abnormal for both tests. A 1-minute (with anesthesia) and 2-minute Schirmer test has been suggested, with cut-offs of 6 mm and 10 mm respectively (99% confidence interval). It has been found to lack accuracy and reproducibility.

b. **Phenol Red test**: The phenol red thread is less invasive than the Schirmer's test (although more difficult to perform) and has been described as an index of tear volume. A cotton thread impregnated with phenol red dye is used. The thread is inserted for 15 seconds and the dye, which is pH sensitive, turns color from yellow to red when wetted by tears. The crimped end of a 70 mm thread is placed in the lower fornix. After 15 seconds wetting length is measured which normally is between 9 and 20 mm. A value of less than 9 mm indicates dry eye. Several studies have found the phenol red test to be more repeatable than the Schirmer test (with and without anesthestic) as well as more reliable in diagnosing dry eye (Fig. 2).

c. **Meniscometry**: Tear meniscus height and radius are amongst the best indicators of dry eye. This can be measured using slit-lamp, micrometer, keratograph or Fourier domain ocular coherence tomography (FD-OCT). The average tear meniscus height measured with the keratograph and FD-OCT is 0.232 ± 0.074 mm and 0.308 ± 0.129 mm, respectively. Heights of less than 0.2 mm indicate reduced tear fluid quantity.

d. **Tear turn over**: It is defined as the rate at which newly secreted tears reside within the tear film before they are lost either to evaporation or drainage through the lacrimal puncta and the nasolacrimal ducts. Tear volume and turnover are most accurately measured by dye dilution studies.

In this method, a small amount of fluorescein dye is instilled into the tear film and the

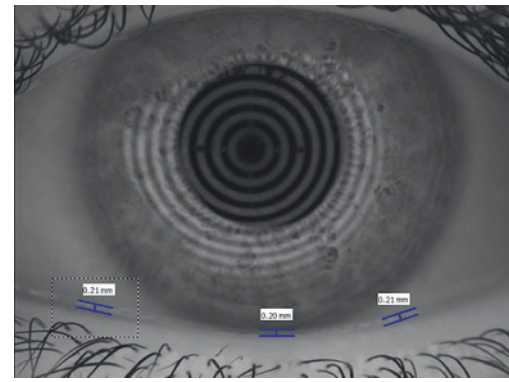

Fig. 2 Tear meniscus height on Oculus Keratograph

concentration of the dye is measured over time. Gamma scintigraphy and fluorophotometry use the electromagnetic spectrum to monitor a tracer molecule in the tear film.

An alternative, inexpensive method of semi-quantitatively grading fluorescein dilution can be done by instilling 5 μL of 1% fluorescein dye into the tear film. The patient is asked to blink to distribute the dye and serial 1-minute Schirmer's tests are performed every 10 min. Initially, the staining of the paper strip with the dye will be intense. Persistent staining (beyond 10 minutes) indicates delayed tear clearance (DTC).

II. **Qualitative tests**:

a. **Tear break-up time**: The tear break-up time (TBUT) is defined as the time interval between a complete blink and the first appearance of a dry spot in the tear film after preservative free fluorescein administration. A TBUT of less than 10 seconds suggests tear film instability, and less than 5 seconds suggests definite dry eye.

Factors, which reduce the reliability/reproducibility of this test, include:

- Volume of fluorescein administered
- Preservatives, such as benzalkonium chloride, shorten the BUT.
- Superficial punctate keratopathy.

There are nonfluorescein (noninvasive) measurements of BUT that employ reflective devices with a grid projected onto the corneal surface. These values are slightly higher that the invasive technique. Instruments such as a Keratometer, hand-held Keratoscope or Tearscope are required to measure NIBUT. A pre-rupture phase that precedes actual break up of the tear film can also be observed with some techniques. This pre-rupture phase is termed Tear Thinning Time (TTT). Measurement is achieved by observing the distortion (TTT) and/or break up (NIBUT) of a keratometer mire (the reflected image of keratometer grid). The clinician focuses and views the crisp mires, and then records the time taken for the mire image to distort (TTT) and/or break up (NIBUT). NIBUT measurements are longer than fluorescein break up time. NIBUT values of less than 15 seconds are consistent with dry eyes (Fig. 3).

b. **Tear film interferometry**:

When white light is projected over the cornea, a color interference pattern is produced due to specular reflection at the lipid-aqueous interface. An appropriately thick lipid layer spans the tear surface in a continuous manner whereas a thin lipid layer degenerates into discontinuous patchy regions denoting an unstable tear film.

The technology of interferometry has also been applied in a kinetic fashion in evaluating

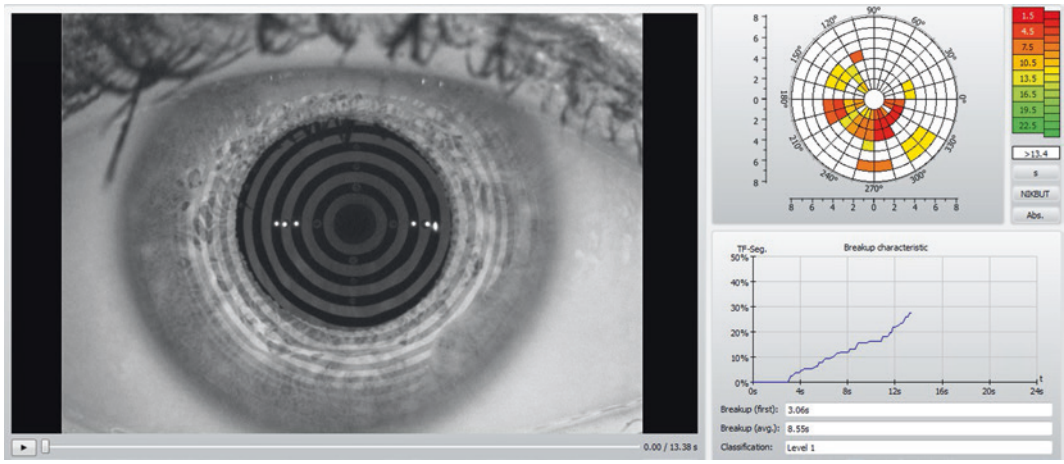

Fig. 3 Non-invasive keratograph break-up time (NIKBUT) measured on Oculus Keratograph

the spread of lipids through the tear film with blinking. LipiView (TearScience Inc., Morrisville, NC) is a commercially available interferometer that provides quantitative values of the tear-film lipid layer thickness (LLT), and this automated assessment of the LLT might be a suitable screening test for detecting meibomian gland dysfunction (MGD). LipiView uses interferometry to measure the lipid layer's thickness between blinks, and gives a quantitative assessment in interferometric color units, which are close to, nanometers. Studies of lipid layer thickness have found a connection between a patient's lipid layer thickness and his dry-eye symptoms. Patients with severe dry-eye symptoms have a LLT of 60 nm or less. On the other end of the spectrum, patients with no symptoms have a LLT of 75 nm or thicker. Several other commercial devices have been available as well.

Blink rate and number of partial blinks can also be studied using the LipiView device. This can be used to counsel patients with evaporative dry eye to maintain better blink patterns to prevent rapid evaporation of the tear film (Fig. 4).

c. **Tear Osmolarity**: An increase in tear osmolarity is seen in patients with dry eyes. Osmolarity values greater than 308 mOsm/L are a sensitive indicator of mild dry eye and values greater than 312 mOsm/L are indicative of moderate to severe dry eye (sensitivity 73%; specificity 92%). Tear film osmolarity can be measured in three ways: freezing point depression (FPD), (considered to be the gold standard); vapor pressure and electrical conductivity or impedance. Since the electrical impedance of tear samples requires a small sample size (0.05 μl) and short test duration (30 seconds), it is considered more suitable for clinical use.

The TearLab osmolarity system, based on electrical impedance, collects a 50-nL tear sample and provides instant assessment of tear osmolarity using a test card. The test card serves two purposes. First, it can be used to collect tears through a microfluidic channel so that evaporation of fluid is eliminated. Second, it presents tear osmolarities as numerical values. The TearLab osmolarity system has proven to be an accurate and reliable laboratory tool for the detection of dry eye syndrome (Fig. 5).

d. **Meibography**: Meibography is the only clinically in vivo technique to visualize the morphology of the meibomian glands (Fig. 6).

Tapie used a diaphanoscope with a red-light filter to transilluminate the lids and a slit lamp microscope to observe the Meibomian glands. Mathers et al. were the first to refer to Infra-red

Fig. 4 Interferometric pattern showing a healthy and poor lipid layer in the tear film

Fig. 5 Tear lab osmometer (courtesy of Tearlab Inc., Escondido, California)

photography of meibomian glands as ''meibography''. Noncontact meibography with infra-red transmitting device was first used by Arita et al. in 2008. Various type of Meibography techniques currently available are:

1. ***Infra-red meibography***
   Infrared meibography is the technology most commonly utilized in contact and noncontact techniques. Phoenix (Version 2.5) by Costruzione Strumenti Oftalmici (CSO, Florence, Italy)), Oculus Optikgeräte GmbH (Wetzlar, Germany), Bosch infrared camera, Topcon SLM system mounted on slit lamp are some of the most widely used devices for meibography. Even an autorefractometer can be used to evaluate the Meibomian glands.
2. ***Laser Confocal Meibography***
   It has the ability to resolve and characterize the microenvironment and microscopic structures of the meibomian glands. However, it is more invasive than infrared meibography. Periglandular inflammatory cell infiltrates and periglandular fibrosis were observed in obstructive type of MGD
3. ***OCT based meibography***
   OCT based meibography (OCTM) is a noninvasive method capable of obtaining 2-D and 3-D tomograms of the meibomian glands in vivo. The distinguishing feature of OCTM from other forms of meibography is the capability to quantify meibomian gland morphology volumetrically.

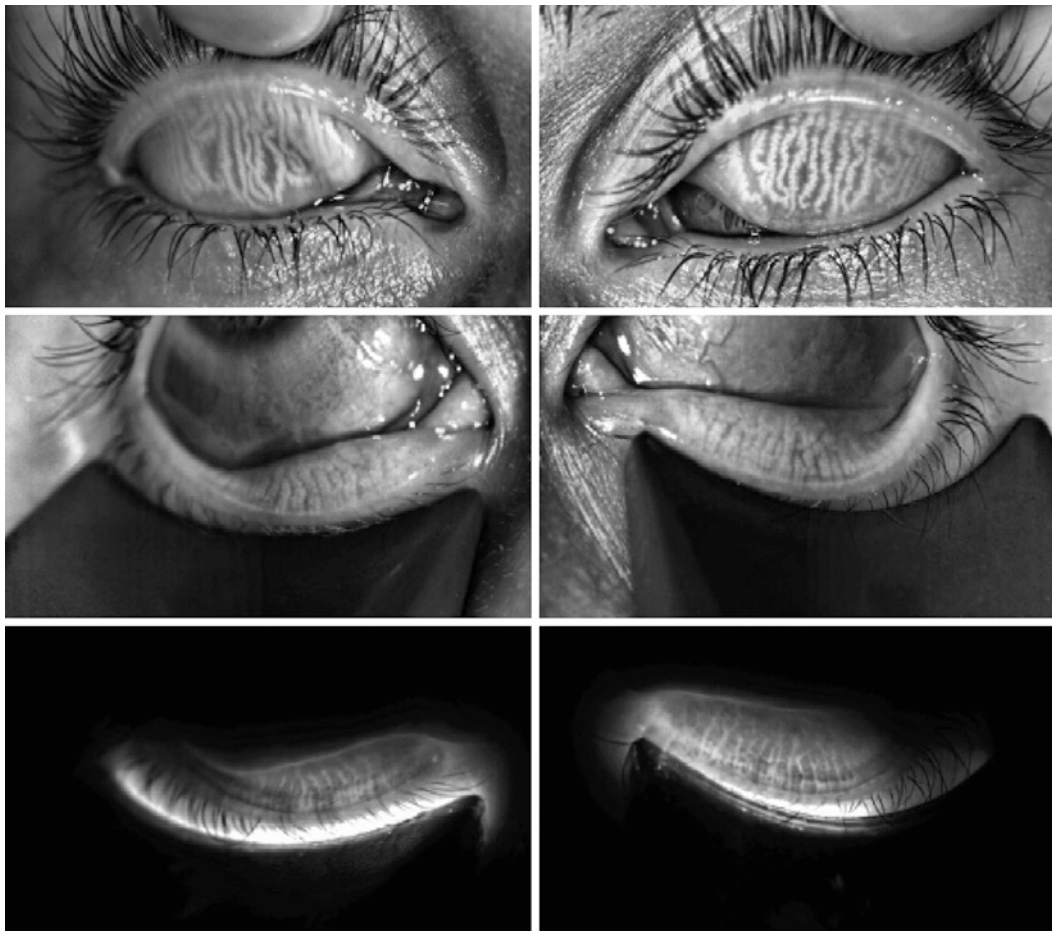

Fig. 6 Image of Meibomian Glands Meibomian gland on Lipiview II

Meiboscore

It was first proposed by Arita et al. in 2008. Graded based on the presence of gland drop outs.

(0): lid has no partial or missing glands
(1): involved lid area is <33%
(2): involved lid area is 33–66%
(3): involved lid area is >66%.

Meiboscores for the upper and lower lid are summed to derive a total meiboscore from 0 to 6 for each eye.

Meiboscore has been shown to correlate with lid margin abnormality score and meibum scores indicating that it validates the other scores. However, it does not take into account the morphologic changes that precede gland drop out.

Meibograde

Considers gland distortion, gland shortening, gland dropout. A score of 0 through 3 is given to each of the three categories and then sums the categories to obtain a meibograde from 0 through 9 for each eyelid.

It helps us identify subtle pathologic changes in the Meibomian glands before irreversible changes like gland drop-outs occur (Figs. 7 and 8).

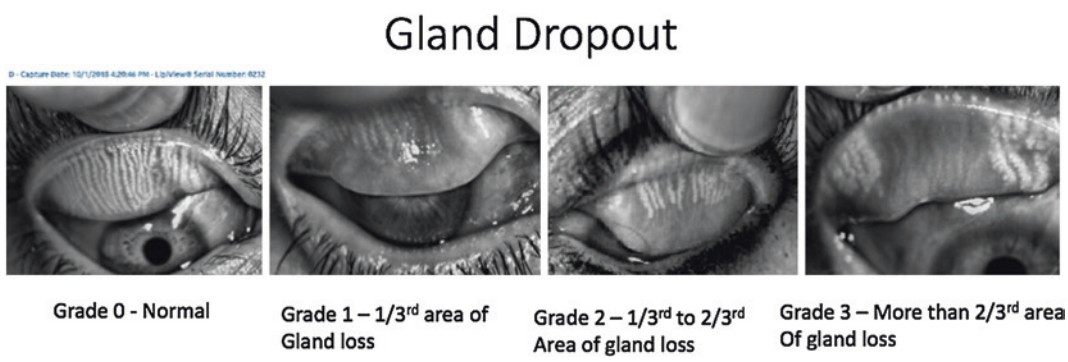

Fig. 7 Images denoting different grades of gland dropout

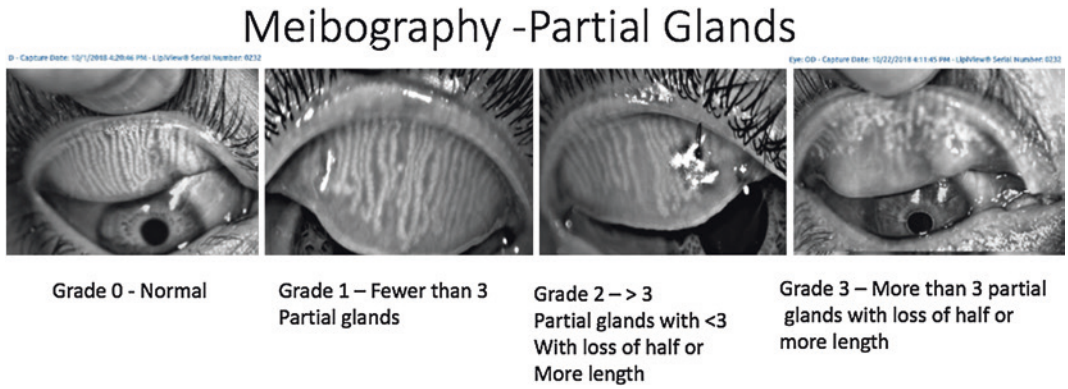

Fig. 8 Images denoting different grades of partial gland loss

III. **Tests for ocular surface**

a. **Corneal and conjunctival staining**: The following dyes have been used to evaluate epitheliopathy:

1. **Fluorescein**: Penetrates poorly into the lipid layer of the corneal epithelium, and therefore, it does not stain normal cornea. Instead, the surface is stained whenever there is disruption of the cell-to-cell junctions. Fluorescein pools in epithelial erosions and stains exposed basement membrane; generally, it stains the cornea more than the conjunctiva. The conjunctival staining by the fluorescein is not clearly seen due to the poor contrast because of the sclera. However, this staining can be more readily viewed if a yellow (blue-free) filter is used.
2. **Rose Bengal**: It was originally thought to stain dead or devitalized cells. However rose bengal is currently believed to stain any part of the ocular surface that is not adequately protected by the tear film. It is an excellent diagnostic tool. It has been shown to be toxic to epithelial cells and causes stinging. It has been shown to have anti-viral activity.
3. **Van Bijsterveld** developed a scoring system for rose bengal that evaluates the intensity of staining on a scale of 0–3 in 3 areas: (1) nasal conjunctiva, (2) temporal conjunctiva, and (3) cornea. With this system, the maximum possible score is 9, and a score of 3.5 or higher is considered positive for dry eye syndrome.

4. **Lissamine green**: It is a synthetic organic acid dye that stains in a similar fashion to rose bengal, but without causing stinging and without affecting the viability of the cells. It stains healthy epithelial cells that are not protected by a mucin layer like rose bengal and stains degenerating or dead cells like fluorescein. However, staining with lissamine green is dose-dependent and an inadequate volume results in weak staining that is transient and thus can be overlooked on slit-lamp examination. A minimal dosage of 10–20 μL is recommended for accurate diagnosis.

A linear pattern of inferior conjunctiva and corneal staining by rose bengal or lissamine is characteristic of meibomian gland dysfunction.

b. **Fluorophotometry**: Fluorophotometry has also been used as "a sensitive measure of epithelial integrity". To detect changes in fluorescence emitted from the ocular surface following the instillation of fluorescein, measurements are taken 10 minutes after washing out the dye with saline, then again every 10 minutes up to an hour. The fluorescein uptake at the center of the cornea is assessed, and patients with dry eye demonstrate an increased corneal permeability and a slower rate of fluorescein elimination compared to patients with normal eyes. Residual fluorescein in the tear film can give a false reading with this technique.

c. **Lid Wiper Epitheliopathy Evaluation (LWE)**: The diagnosis of LWE involves sequential staining with a mixture of 2% fluorescein and 1% lissamine green. The lid is then everted and the fluorescein is graded from 0 to 3 depending on the linear area and severity of the staining, followed by the same grading system for lissamine green. The highest final score is taken to be the LWE severity grade. The classification is no LWE, grade 1 LWE (mild, 0.25–1.0), grade 2 LWE (moderate, 1.25–2.0), or grade 3 LWE (severe, 2.25–3.0).

d. **Lid Parallel Conjunctival Folds (LIPCOF)**: Lid parallel conjunctival folds (LIPCOF) may be observed in the temporal and nasal areas bordering the posterior lid margin in primary gaze. Pult et al. suggested an optimized grading scale where 0 indicated no conjunctival folds; 1 indicated one permanent and clear parallel fold; 2 indicated two permanent and clear parallel folds (normally <0.2 mm); 3 indicated more than two permanent folds (normally >0.2 mm).

IV. **Laboratory tests**:

1. **Tear ferning**: Tear samples dried on a slide and examined under a microscope display a crystalline pattern of tear mucin. In aqueous tear deficiency, this pattern resembles ferns. This test has been reported to have greater specificity and sensitivity than the Schirmer's test, particularly for more severe forms of dry eye disease.
2. **Tear protein analysis**: Lactoferrin, lysozyme, lipocalin, cytokines and MMP-9 are the few proteins analysed in tear films.

A commercially available point-of-care test, RPS InflammaDry Detector (RPS, Inc, Sarasota, FL, USA) offers an easy-to-administer and rapid turn-around test (10 minutes) for measuring MMP-9 levels in the tear film. MMP-9 is considered to be a reliable marker for the presence of inflammation, commonly associated with dry eye. It utilizes Direct Sampling Micro-Filtration technology. MMP-9, if present in the tear sample, is captured between MMP-9 specific monoclonal and polyclonal antibodies at concentration greater than 40 ng/ml (Fig. 9).

V. **Histological tests**:

1. **Impression cytology**: This minimally invasive procedure involves applying nitrocellulose filter paper to the area of interest on the ocular surface to remove the superficial 2–3 layers of cells. Cells are air dried and stained with periodic acid—Schiff and hematoxylin. The cells are then subjected to histological, immunohistochemical, and molecular testing.

Fig. 9 RPS InflammaDry Detector (Manufactured by Quidel Corporation, San Diego, California, USA.)

2. **Conjunctival brush cytology**: Under topical anaesthesia, a soft brush is used to obtain both superficial and basal cells. The sample can then be assessed for the presence of squamous metaplasia, inflammatory cells, and the expression of surface markers on the ocular surface epithelium. This is often combined with flow cytology, which gives a highly sensitive and specific analysis of epithelial cell markers, inflammatory cells and goblet cells.

VI. **Systemic Evaluation**:

Serum Vitamin A levels

The biochemical definition of vitamin A deficiency is plasma level of 35 μmol/dl or less. High-pressure liquid chromatography is the most reliable method. Vitamin A levels may be decreased despite adequate intake in cases of protein deficiency.

Total and holo-RBP test

Total and holo-RBP (complex of Vitamin A and RBP) for serum RBP tend to correlate with measures of serum vitamin A. These, too, can be depressed in the presence of protein deficiency.

Conjunctival Impression Cytology

It can help in detecting preclinical xerophthalmia. Squamous metaplasia is evident by the presence of enlarged, irregular, and keratinized epithelial cells and loss of goblet cells.

Antibodies for Sjogren's

Sjögren syndrome (SS) is characterized by the combination of aqueous tear deficiency (ATD) and dry mouth (xerostomia).

At this time, the most comprehensive criteria for a diagnosis of SS include the following:

- Abnormally low Schirmer test result
- Objective evidence of low salivary flow
- Biopsy-proven lymphocytic infiltration of the labial salivary glands
- Dysfunction of the immune system, as manifested by the presence of serum autoantibodies (e.g., antinuclear antibody [ANA], rheumatoid factor [RF], and anti-Ro [SS-A] and anti-La [SS-B] antibodies)

A novel test called Sjo is available from IMMCO Laboratories. It is used to evaluate for proprietary early markers of SS. These early antibodies may enable the clinician to identify SS up to 4 years earlier than the traditional antibody panel.

Treatment

(A) **Tear Supplementation**: Traditionally, tear substitutes usually form the first line of treatment for any type of dry eye. Commonly used lubricants include Hydroxypropyl Methylcellulose (HPMC), Carboxymethyl cellulose (CMC), sodium hyaluroate,

polyethylene glycol (PEG). They are available in a liquid form and a gel and semi-gel forms.

Artificial tears or lubricants have several beneficial effects:

(i) Act as lubricants to the dry ocular surface
(ii) Replace deficient tear constituents
(iii) Dilute pro-inflammatory substances
(iv) Reduce tear osmolarity

It should be noted however that tear substitutes have several disadvantages including:

- The health of the lacrimal gland is not restored
- The underlying inflammation is not fully addressed
- The effect is temporary as rate of drainage through the puncti is always higher
- They do not improve patient's life, and raise the issue of patients' compliance with lifelong treatment

Constituents of Artificial Tears

(i) Hydrogels: Hydrogels have the property of swelling up in water and retaining moisture. They enhance the viscosity and prolong tear retention owing to their mucous adhesive property.
(ii) Preservatives: These are used to increase the shelf life of artificial tears and facilitate the use of multi-dose bottles. Commonly used preservatives include Benzalkonium Chloride (BAK) and Chlorobutanol. BAK is known to be epitheliotoxic. Newer preservatives like purite (sodium chlorite) and sodium perborate are less damaging to the ocular surface. Purite degrades to chloride ions and water and sodium perborate is converted to water and oxygen on contact with the tear film. If tears substitutes are required frequently, non-preserved ones are recommended.
(iii) Inactive ingredients: HP guar promotes the retention on surface, bicarbonate containing artificial tears promote healing in severe dry eyes. Oil containing eyedrops are beneficial in meibomian gland dysfunction. These eyedrops replenish the lipid layer of the tear film and prevent tear evaporation.

(B) **Autologous Serum**: Autologous serum produced from the patient's serum is particularly useful in severe DED. Tears contain Epithelial Growth Factors (EGF), Transforming Growth Factor beta (TGF-b), and vitamin A to maintain a healthy ocular surface. Serum contains EGF, Nerve Growth Factor (NGF), substance P that helps in epithelial healing

In Keratoconjunctivitis sicca, pro-apoptotic cytokines TNF-a and -b and IL-1 are increased. Autologous serum particularly helps in these cases. The blood is first drawn from the recipient and allowed to clot. The supernatant is then centrifuged to separate the serum from other blood components. The serum is then diluted to up to 20% concentration for use as eyedrops. It can be stored at 4 degree Celsius for up to 1 month.

(C) **Treatment of chronic anterior blepharitis**: Apart from maintaining lid hygiene and warm compresses, topical antibiotics must be given to decrease bacterial load from the eyelid margins. Tetracyclines are particularly useful for cases of acne rosacea. A short course of topical steroids is recommended especially if there is associated marginal keratitis or phlyctenules.

Demodecosis should be considered in patients who did not improve with treatments. Weekly 50% tea-tree-oil eyelid scrubs & daily tea-tree-oil shampoo scrubs for at least 6 weeks are given. Oral ivermectin must be given in cases of recalcitrant Demodex blepharitis.

(D) **Anti-inflammatory therapy**: Inflammation as evidenced by the tear hyperosmolarity is caused by several factors like chronic irritative stress (e.g., contact lenses) or systemic inflammatory/autoimmune disease (e.g., rheumatoid arthritis). Topical and oral steroids and cyclosporine are used for anti-inflammatory effects. Cyclosporine 0.05% eye drops and the more specific lifitegrast (Xiidra; Shire US Inc, MA) are used for 3–6 months to reduce lymphocytic infiltration and inflammation of the lacrimal glands. This can result in increased tear production in a large number of patients, particularly when used early in the disease process before atrophy of the acini.

(E) **Tear Secretagogues**: Oral cholinergic agonists are given to patients with severe aqueous deficient DED. Oral pilocarpine is given in a dose of 5 mg BD. Side effects include sweating, flushing, hypersalivation, increased urinary frequency. Cevimeline, which has a high affinity to muscarinic receptors M1 and M3, is given in a dose of 15–30 mg TDS. Adverse effects of Cevimeline include nausea, vomiting and increased sweating. They are rarely used nowadays. Plasma Injection (PRP) in the area of the lacrimal gland is postulated to increase tear production.

(F) **Meibomian glands heat therapy**: A very effective technique in cases of MGD and is regarded by many as the single most important treatment method. It includes application of localized heat and pressure therapy to the meibomian glands and tarsus to facilitate release of lipid from the cystic partially occluded meibomian glands and ducts. This allows removal of old tenacious secretions and reconstituting with new more effective meibom.

Several machines are now available that provide controlled heat and intermittent pressure therapy to eyelids. They deliver heat at a temperature of 42.5 °C to the eyelid, and pressure to the outer eyelid surface simultaneously, that continually pressurize and depressurize, squeezing the meibomian glands against the lid warmer. The duration of each treatment is 12 min. If the ducts are blocked, debridement of the lid margin can be done first with a cotton tip or a burr. Meibomian duct dilatation with specially designed probes has been advocated to ensure duct patency and proper lipid flow before the heat therapy

(G) **Lacrimal Occlusive Devices**: Occluding the nasolacrimal system to conserve the tear film is one of the most common nonpharmacological therapies used in aqueous deficient patients. Types of lacrimal occlusive devices:

a. *Punctal occluders*:
(i) Total punctal occluders
(ii) Partial punctal occluders
b. Canalicular occluders:
I. Horizontal canalicular occluders
II. Vertical canalicualr occluders

Both horizontal and vertical occluders could be temporary or permanent. (32) They are inserted under topical anesthesia in the office and have the following advantages:

- They maintain normal, diurnal and environmental adjustment of tear composition
- Their maximum effect occurs in early cases with decreased but not absent tear secretion
- Being non-patient dependent, they improve life style
- They allow prolonged effect of artificial tears and reduce the amount needed

(H) **Neurostimulation**: Stimulation of the anterior nasal mucosa by micro electric pulses results in increased natural tear production by the lacrimal gland. A portable hand held device;True Tears device (Allergan Inc, USA) was approved in 2017 to be used by patients to stimulate the lacrimal functional unit with increased secretion of aqueous glands, goblet cells and meibomian glands. This returns the ocular surface to a more normal physiologic state without prescribing drops or surgery.

(I) **Tarsorrhaphy**: Partial tarsorrhaphy is reserved for severe or refractory DED. Indications include paralytic lagophthalmos from 7th cranial nerve damage, cicatricial lagophthalmos, poor blink reflexes, and neurotrophic keratopathy. It reduces area of exposed ocular surface thereby benefitting cases of severe epitheliopathy, persistent epithelial defects, or frank stromal ulceration.

(J) **Salivary gland transplant**: This surgical procedure involves transplantation of salivary submandibular gland to replace the deficient mucin and aqueous tear film phase. It is indicated only in end stage disease when there is Schirmer-test wetting of 1 mm or less and persistent severe pain despite punctal occlusion and at least hourly application of unpreserved tear substitutes.

Suggested Readings

1. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007;5(2):75–92.
2. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–83.
3. Asbell PA, Stapleton FJ, Wickström K, Akpek EK, Aragona P, Dana R, et al. The international workshop on meibomian gland dysfunction: report of the clinical trials subcommittee. Invest Ophthalmol Vis Sci. 2011;52(4):2065–85.
4. Mathers WD, Shields WJ, Sachdev MS, Petroll WM, Jester JV. Meibomian gland dysfunction in chronic blepharitis. Cornea. 1991;10(4):277–85.
5. Brown NA, Bron AJ, Harding JJ, Dewar HM. Nutrition supplements and the eye. Eye Lond Engl. 1998;12(Pt 1):127–33.
6. Rogers EL, Douglass W, Russell RM, Bushman L, Hubbard TB, Iber FL. Deficiency of fat soluble vitamins after jejunoileal bypass surgery for morbid obesity. Am J Clin Nutr. 1980;33(6):1208–14.
7. Sommer A, Tarwotjo I, Djunaedi E, West KP, Loeden AA, Tilden R, et al. Impact of vitamin A supplementation on childhood mortality. A randomised controlled community trial. Lancet Lond Engl. 198624;1(8491):1169–73.
8. Tupas A, Pecache LV, Melo A. Xerophthalmia and keratomalacia in children. J Philipp Med Assoc. 1947;23(4):137–43.
9. Kurtul BE, Özer PA, Aydinli MS. The association of vitamin D deficiency with tear break-up time and Schirmer testing in non-Sjögren dry eye. Eye Lond Engl. 2015;29(8):1081–4.
10. Barragan M, Good M, Kolls JK. Regulation of Dendritic Cell Function by Vitamin D. Nutrients. 2015;7(9):8127–51.
11. Shipton EE, Shipton EA. Vitamin D Deficiency and Pain: Clinical Evidence of Low Levels of Vitamin D and Supplementation in Chronic Pain States. Pain Ther. 2015;4(1):67–87.
12. Singman EL, Poon D, Jun AS. Putative corneal neuralgia responding to vitamin d supplementation. Case Rep Ophthalmol. 2013;4(3):105–8.
13. Saccà SC, Cutolo CA, Ferrari D, Corazza P, Traverso CE. The Eye, Oxidative Damage and Polyunsaturated Fatty Acids. Nutrients. 2018;10(6).
14. Hom MM, Asbell P, Barry B. Omegas and Dry Eye: More Knowledge, More Questions. Optom Vis Sci Off Publ Am Acad Optom. 2015;92(9):948–56.
15. Putnam CM. Diagnosis and management of blepharitis: an optometrist's perspective. Clin Optom. 2016;8:71–8.
16. Asiedu K, Kyei S, Mensah SN, Ocansey S, Abu LS, Kyere EA. Ocular surface disease index (OSDI) versus the standard patient evaluation of eye dryness (SPEED): a study of a nonclinical sample. Cornea. 2016;35(2):175–80.
17. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017;15(3):539–74.
18. Şimşek C, Doğru M, Kojima T, Tsubota K. Current management and treatment of dry eye disease. Turk J Ophthalmol. 2018;48(6):309–13.
19. Markoulli M, Duong TB, Lin M, Papas E. Imaging the tear film: a comparison between the subjective Keeler Tearscope-Plus™ and the objective Oculus® Keratograph 5 M and LipiView® Interferometer. Curr Eye Res. 2018;43(2):155–62.
20. Masmali A, Alrabiah S, Alharbi A, El-Hiti GA, Almubrad T. Investigation of tear osmolarity using the TearLab Osmolarity System in normal adults in Saudi Arabia. Eye Contact Lens. 2014;40(2):74–8.
21. Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology. 2008;115(5):911–5.
22. Jester JV, Nicolaides N, Smith RE. Meibomian gland studies: histologic and ultrastructural investigations. Invest Ophthalmol Vis Sci. 1981;20(4):537–47.
23. Robin JB, Jester JV, Nobe J, Nicolaides N, Smith RE. In vivo transillumination biomicroscopy and photography of meibomian gland dysfunction. A clinical study. Ophthalmology. 1985;92(10):1423–6.
24. Matsumoto Y, Shigeno Y, Sato EA, Ibrahim OMA, Saiki M, Negishi K, et al. The evaluation of the treatment response in obstructive meibomian gland disease by in vivo laser confocal microscopy. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol. 2009;247(6):821–9.
25. Bizheva K, Lee P, Sorbara L, Hutchings N, Simpson T. In vivo volumetric imaging of the human upper eyelid with ultrahigh-resolution optical coherence tomography. J Biomed Opt. 2010;15(4):040508.
26. Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci. 2011;52(4):1938.
27. Dogru M, Tsubota K. Pharmacotherapy of dry eye. Expert Opin Pharmacother. 2011;12(3):325–34.
28. Pan Q, Angelina A, Marrone M, Stark WJ, Akpek EK. Autologous serum eye drops for dry eye. Cochrane Database Syst Rev. 201728;2:CD009327.
29. da Rocha MC, Travassos AR, Uva L, Sequeira H, Filipe P. Demodicosis treatment with systemic ivermectin. Skinmed. 2017;15(4):293–5.
30. Tsifetaki N, Kitsos G, Paschides C, Alamanos Y, Eftaxias V, Voulgari P, et al. Oral pilocarpine for the treatment of ocular symptoms in patients with Sjögren's syndrome: a randomised 12 week controlled study. Ann Rheum Dis. 2003;62(12):1204–7.
31. Zhao Y, Veerappan A, Yeo S, Rooney DM, Acharya RU, Tan JH, et al. Clinical Trial of Thermal Pulsation

(LipiFlow) in Meibomian Gland Dysfunction With Preteatment Meibography. Eye Contact Lens. 2016;42(6):339–46.
32. Jehangir N, Bever G, Mahmood SMJ, Moshirfar M. Comprehensive review of the literature on existing punctal plugs for the management of dry eye disease. J Ophthalmol. 2016;2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4800096/
33. Zhang X, Yang N, Liu X, Su J, Cong X, Wu L, et al. Autonomic reinnervation and functional regeneration in autologous transplanted submandibular glands in patients with severe keratoconjunctivitis sicca. Int J Oral Sci. 2018;10(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5944256/