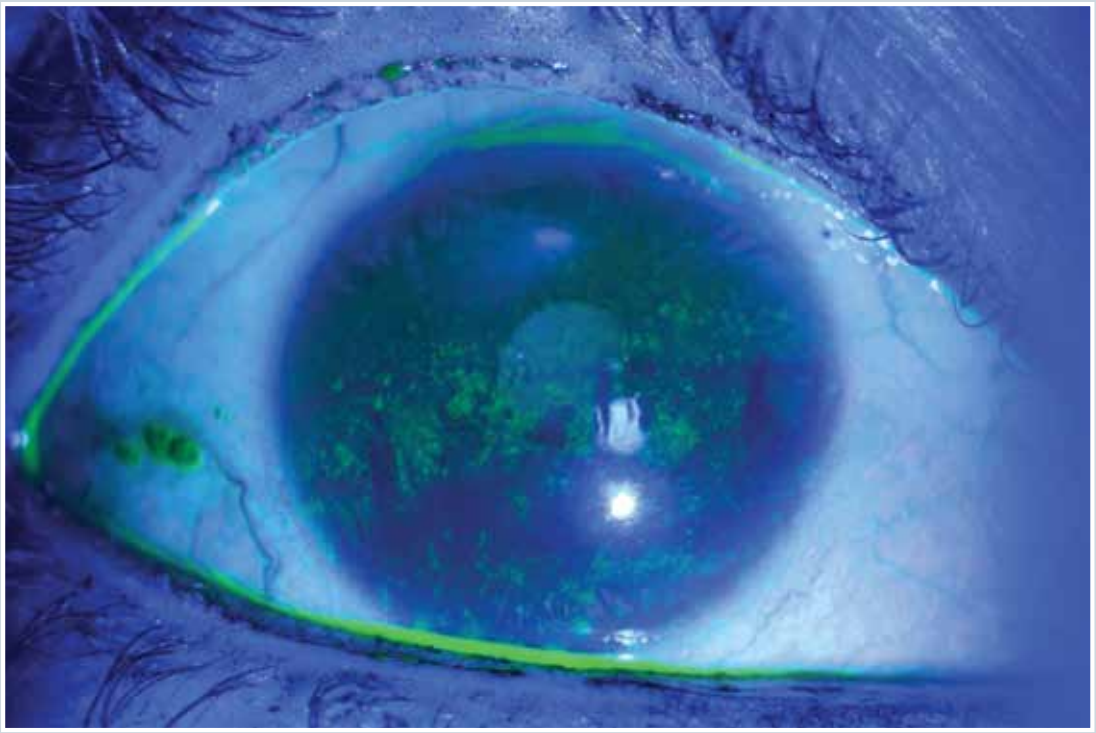
Nordic Guidelines 2016

Dry Eye Disease



Introductory Background

Diagnosis and monitoring

Management and therapy

Tear supplementation: Lubricants

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Conflict of interest: The authors have not received any compensation from any party for the production of this script and have no commercial interest in it's publication.

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Foreword

Dear colleagues !

Dry eye disease is a very common disease in the world and with the increase of the elder population all over the world there is a huge demand for treating the disease as optimal as possible.

Many different health care persons treat dry eye disease patients and many patients try different drops before seeking professional help.

We wished by writing the Nordic Guidelines 2016 to present an easy going pamphlet usable for health care persons dealing with this patient category.

Many different ocular conditions may lead to dryness, burning and a sandy/gritty sensation of the eye. Therefore, the correct diagnosis is essential and it is important to perform the tests described in the Guidelines 2016.

The field is developing fast and many new treatment strategies and ointments have been introduced to the market.

In order to help the reader we have put all the different lubricants in the Nordic market in one table and dependent on the cause of the dry eye disease in your patient, a treatment strategy should be made.

We all hope the reader find the Nordic Guidelines 2016 for Dry Eye Disease valuable.

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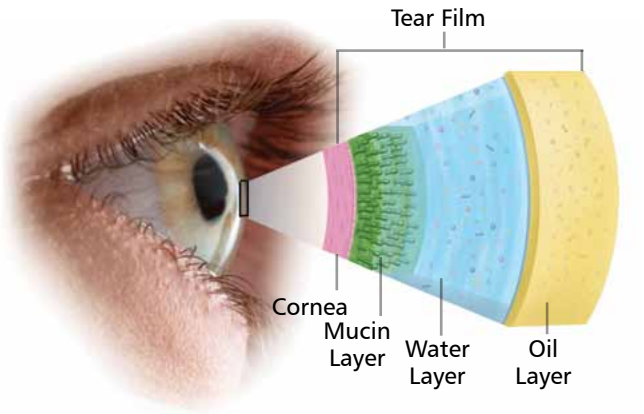

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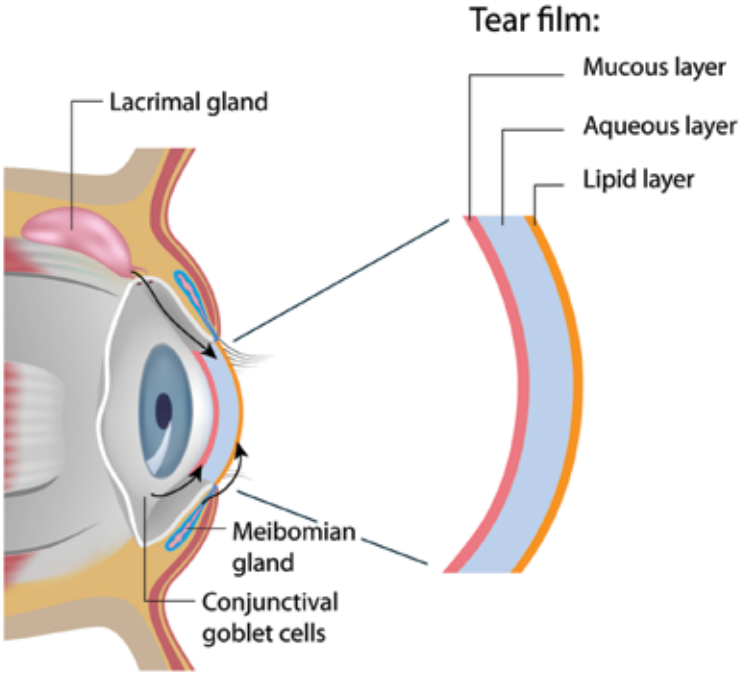


Introductory Background

Introduction

Millions of people suffer from dry eye. This condition can be caused by many different internal and external factors and it is therefore mandatory to find out what causes the dry eye in order to give the correct treatment.

Dry eye disease (DED) may lead to ocular surface discomfort, often described as feelings of dryness, burning, a sandy/gritty sensation, or itchiness and thus causes ocular discomfort for many, many people.

This may lead to decreased visual acuity, sensitivity to light, and blurred vision for patients suffering from dry eye disease.

Tear glands and glands important for maintaining the tear film

The tear volume is mainly produced in the lacrimal gland which is a tubuloacinar gland. It consists of two parts: The smaller *palpebral portion* that lies along the inner surface of the eyelid and the *orbital* portion.

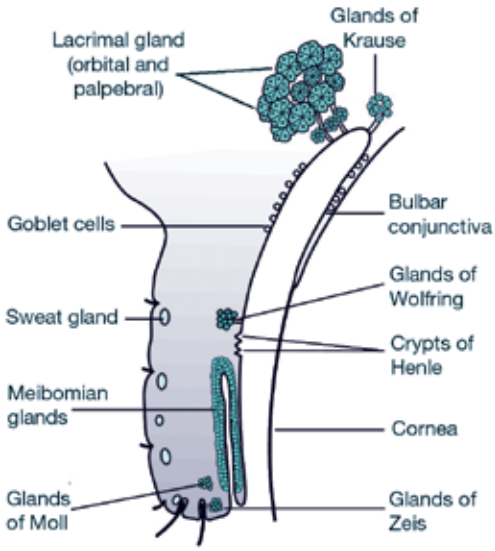
The lacrimal gland is innervated by the lacrimal nerve (sensory) afferent pathway, the facial nerve (parasympathetic) efferent pathway for reflex secretion, and the sympathetic nervous system.

The tear gland secretes the aqueous layer of the tear film.

The accessory lacrimal exocrine glands of *Wolfring* and *Krause* structurally resemble the main lacrimal gland.

The glands of *Krause* are located in the superior and inferior conjunctival fornices.

The glands of *Wolfring* can be found along the upper border of the superior tarsus, below the lower tarsus and an occasional gland in the



caruncle and in the plica semilunaris.

The *meibomian glands* are found closely packed within the tarsal plate and are arranged in a parallel fashion, extending the entire height of the tarsal plate. They are taller and more numerous in the larger superior tarsus than in the smaller inferior tarsus.

The *glands of Zeis* are found along the roots of the eyelashes, to which their contribution is less significant.

Conjunctival goblet cells are found in greatest concentration along the eyelid margins, conjunctival fornices, antimarginal tarsal borders (crypts of Henle), and corneal-scleral limbus (glands of Manz).

The accessory lacrimal glands have been called the ***basal secretors*** because they do not possess direct secretory motor fibres. The other basal secretors are the sebaceous glands (meibomian

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and Zeis) and the mucous glands in the conjunctiva (goblet cells).

The ***reflex secretor*** is the lacrimal gland. Reflex secretion provides additional secretion by peripheral sensory (fifth nerve efferent, seventh nerve afferent), retinal or psychogenic stimulation.

Tears

Each time we blink, a protective coating of tears is spread like a film on top of the cornea. The tear film serves four important purposes:

1. Protects and lubricates the eyes.
2. Provide nutrients and supports the health of cells in the cornea.
3. Protects the exposed surface of the eye from infections.
4. Washes away foreign particles.

Fig. 1. Normal healthy tears

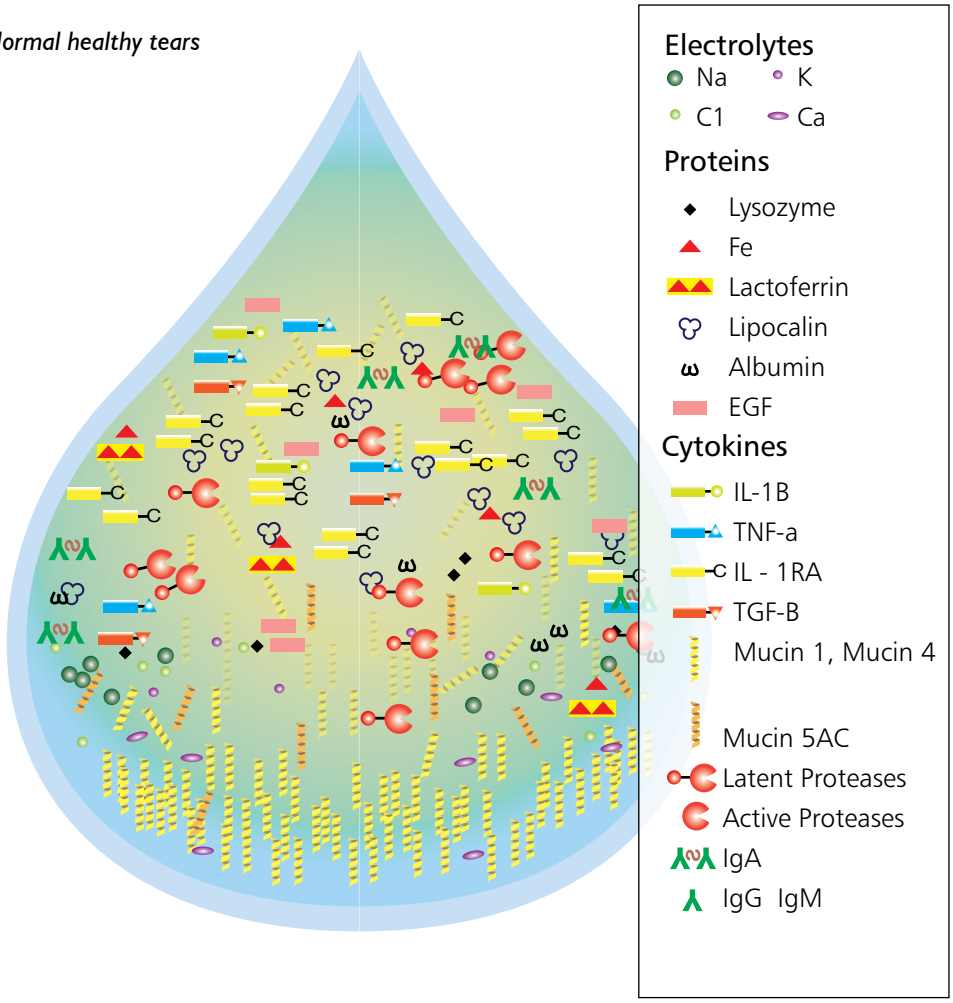

Fig. 1

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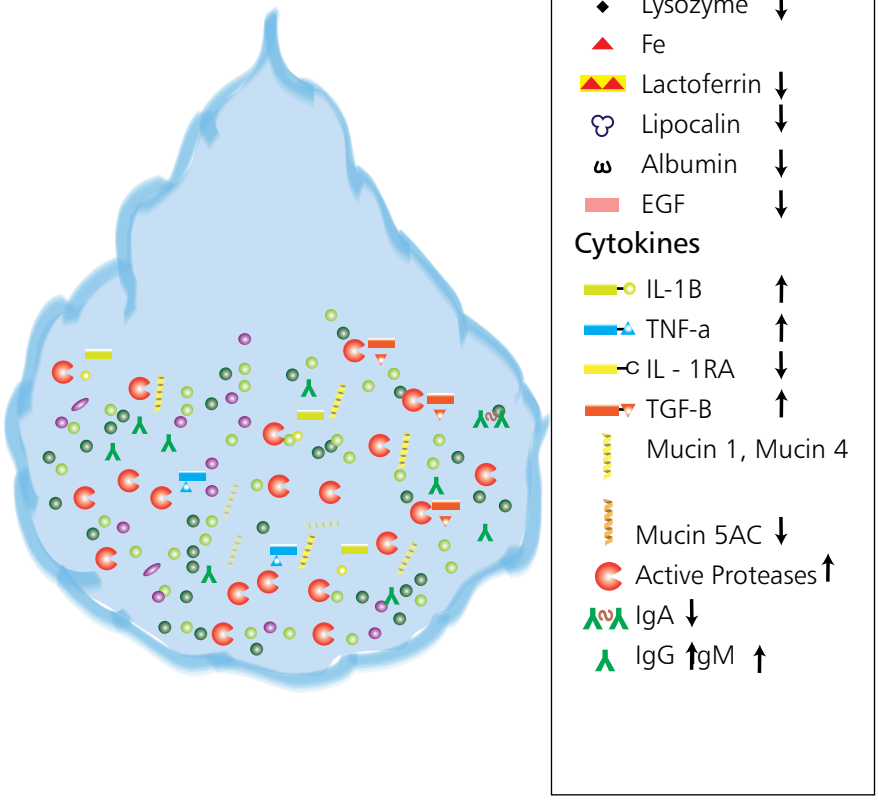
Normal healthy tears contain a complex mixture of proteins and other components that are essential for ocular health and comfort (Figure 1).

Clear vision depends on homogenous composition and even distribution of tears over the ocular surface.

For Sjögren's syndrome patients, inflammation of tear-secreting glands reduces tear production, resulting in chronic dry eye. In addition, changes in the composition of tears contribute to dry eye (Figure 2).

Fig. 2. Alteration in tear composition in dry eye



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The tear film consists of three layers

The tear film is made up of three layers – an oil (lipid) layer, a water (aqueous) layer and a mucin layer.

When any part of the tear film is not functioning properly, you may start to experience dry eye symptoms.

Oil / Lipid Layer:

The outer layer of the tear film is an oil or lipid-based layer. Its main purpose is to seal the tear film which reduces evaporation of the tears. The **lipid layer** is derived primarily from the meibomian glands in the lids as well as some secretion from the glands of Zeis.

The oily layer prevents escape of aqueous tears over the edge of the eyelid margin and retards evaporation of the watery layer. It also provides a lubrication effect between the lid and cornea.

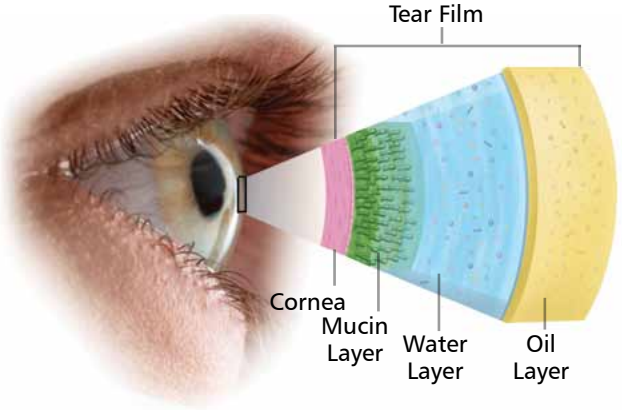
Water (Aqueous) Layer:

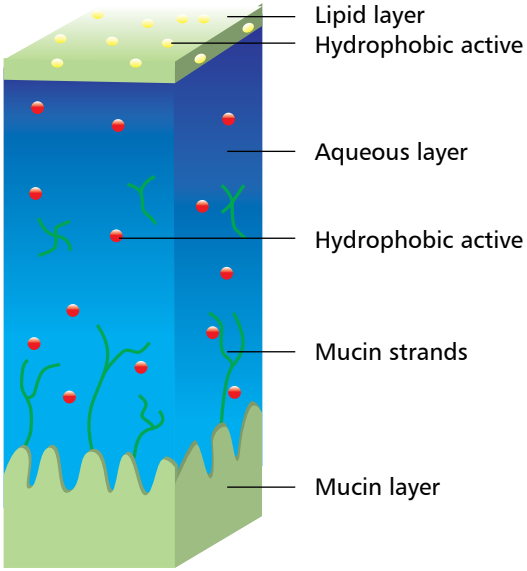
The middle layer is mostly comprised of water and is the thickest layer of the precorneal tear film. It is produced by the main lacrimal gland and the accessory lacrimal glands (Wolfring and Krause).

It lubricates the eye, washes away particles and prevents infection as it contains most of the bactericidal lysozymes and other proteins.

Mucin (Mucous) Layer:

The inner and densest layer is the mucin layer and is produced by the conjunctival goblet cells and the conjunctival epithelial cells. The mucin layer allows the watery layer to spread evenly over the surface of the eye and helps the eye remain moist and lubricated. It also provides the underlying cornea epithelium with nourishment. This layer helps the tears adhere to the surface of the eye, but also to clear debirs and pathogens.





Dry eye disease

Definition

"Dry eyes are a multifactor disease of the tears and the 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." [1]

Dry eye is recognised as a disturbance in the lacrimal functional unit, which is an integrated system comprising the lacrimal gland, the ocular surface, the lids and the sensory and motor nerves that connect them. The functional unit controls the major components of the tear film in a regulated fashion and responds to environmental, endocrinological, and cortical influences. Its overall function is to preserve the integrity of the tear film, the transparency of the cornea and the quality of the image projected to the retina.

Characterisation of Dry Eye Disease

Dry eye disease can be divided into (figure 3):

1. Quantitative Dry Eye Disease = Aqueous deficient
2. Qualitative Dry Eye Disease = Evaporative

Either the tear quantity or tear quality can be compromised.

If there is decreased secretion of tears by the lacrimal and the other tear producing glands the quantity of the tears are diminished.

If the condition is caused by excess evaporation due to a diseased lipid layer, the quality of the tears is compromised.

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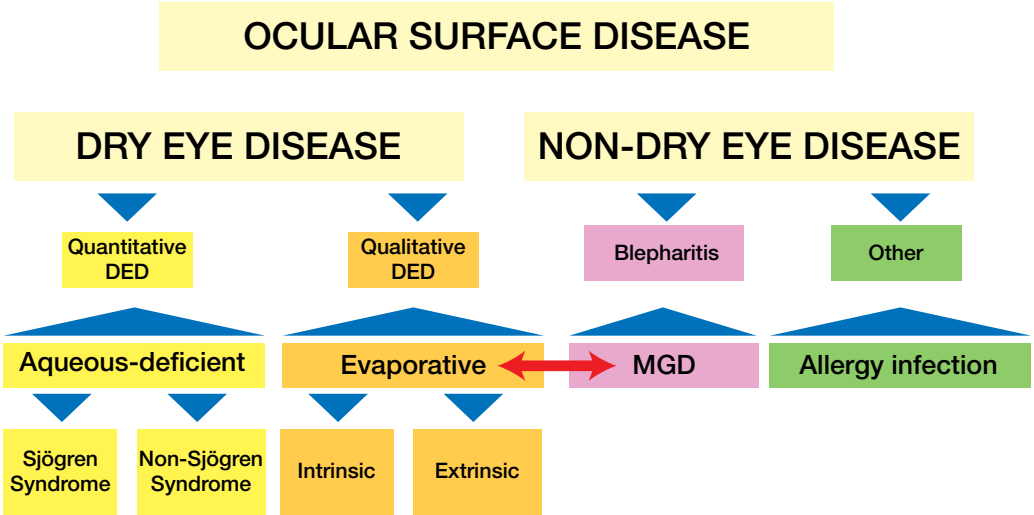
Fig. 3



Dry eye disease

1. Quantitative DED (Aqueous deficient) causes can be

i. Sjögren

1. Primary Sjögren
2. Secondary Sjögren

ii. Non Sjögren

1. Primary lacrimal gland deficiency
2. Secondary lacrimal gland deficiency
3. Obstructed lacrimal gland ducts
4. Reflex hyposecretion
5. Pharmacological agents

Aqueous Tear-defect

Aqueous tear-deficient dry eye implies dry eye as a result of a failure of the lacrimal tear secretion.

Sjögren Syndrome dry eye (SSDE) is an exocrinopathy in which the lacrimal and salivary glands are targeted by an autoimmune process. The ocular dryness in SSDE is due to lacrimal hyposecretion and the accompanying characteristic inflammatory changes in the lacrimal gland and the presence of inflammatory mediators in the tears and within the conjunctiva.

SSDE can be subdivided into primary form SSDE with the occurrence of aqueous tear defect dry eye in combination with symptoms of dry mouth, in the presence of auto antibodies, evidenced of reduced salivary secretion and a positive score on minor salivary gland biopsy. A secondary form of SSDE consists of the symptoms from primary SS together with the features of an overt autoimmune disease (rheumatoid arthritis, SLE, polyarteritis nodosa, Wegener's granulomatosis, systemic sclerosis, primary biliary sclerosis and mixed connective tissue disease).

Non-Sjögren syndrome dry eye is a form of aqueous defect dry eye due to lacrimal dysfunction, where the systemic autoimmune features characteristic of SSDE have been excluded. It can be the result of a number of various conditions and classified in accordance hereby.

a. Primary lacrimal gland deficiency can be the result of age related changes, congenital alacrima (rare) or familial dysautonomia. It represents primary changes in the lacrimal gland without underlying more generalised disease.

Dry eye disease

b. Secondary lacrimal gland deficiency is the result of changes in the lacrimal gland as lacrimal gland infiltration, sarcoidotic inflammation in the gland, gland lymphoma, T-cell infiltration in the gland in AIDS patients, lacrimal gland fibrosis following graft vs host disease, lacrimal gland ablation and lacrimal gland denervation.

c. Obstruction of the lacrimal ducts as the result of any form of conjunctival cicatrising as in trachoma, cicatricial pemphigoid and mucous membrane pemphigoid, erythema multiforma and following chemical and thermal burns.

d. Reflex hyposecretion can be the result of a sensory block. It can be initiated from an altered sensory drive from the ocular surface, by decreased reflex-induced lacrimal secretion and increased evaporation due to a lowered blinking rate. It can also represent a motor block from damage of the VII cranial nerve.

e. The use of various pharmacological agents can decrease the tear secretion. It includes antihistamines, beta blockers, antispasmodics, diuretics tricyclic antidepressants, selective serotonin uptake inhibitors, calcium channel blockers and cholesterol-lowering drugs.

Dry eye disease

2. Qualitative
Dry Eye Disease = Evaporative

Qualitative dry eye

iii. Intrinsic

1. Meibomian gland disorder
2. Lid disorders
3. Low blinking rate

iv. Extrinsic

1. Ocular surface disorders
2. Contact lens wearers
3. Ocular surface
4. Allergy

v. Environmental

1. Milieu interior
2. Milieu exterior

Evaporative dry eyes are the result of excessive water loss from the exposed ocular surface in the presence of normal lacrimal secretion. It is traditionally described as a result of intrinsic diseases affecting the lids or extrinsic resulting in ocular surface disease from extrinsic exposure. Environmental influence is also of importance [2].

Dry eye disease

a. **Intrinsic causes** include meibomian gland dysfunction, disorders in the lid aperture and a low blinking rate

   a. Meibomian gland dysfunction has multiple causes. It can represent a primary disorder or be associated to local diseases (anterior blepharitis), systemic diseases (acne rosacea, seborrhoeic dermatitis, atypia, ichtyosis and psoriasis), part of syndromes, reflect systemic toxicity or be the result of cicatricial changes in the lids.

   b. Disorders of the lid aperture can influence the evaporation from the ocular surface. It includes endocrine and other forms of proptosis and also some cases of craniostenosis.

   c. Low blinking rate increases drying of the ocular surfaces as a result of increased time of water drying between each blink. It often represents a physiological phenomenon and is frequently seen among heavy video, PC and microscopy users. However, it is frequently seen in patients with Parkinson disease.

b. Extrinsic causes

   a. Ocular surface disorders may lead to insufficient surface wetting, early break up time, tear hyperosmolarity and dry eye. It may represent vitamin A deficiency leading to a reduced number of goblet cells, and hereby decreased mucous production. But it might also result in lacrimal gland damage. Topical drugs and preservatives such as benzalkonium chloride and topical anaesthesia may induce a toxic response to the ocular surface.

   b. Contact lens wearers have an increased risk of developing dry eye and ocular discomfort. It has been reported increased 5-12 times in various studies. The background therefore is still debated.

   c. Chronic ocular surface disease may induce dry eye through tear film destabilisation and loss of goblet cells.

   d. Allergic conjunctivitis can damage the ocular surface and a release of inflammatory mediators may lead to allergic symptoms and reflex stimulation to the lacrimal gland. Surface irregularities on the cornea and conjunctiva can lead to tear film instability and subsequently local drying.

c. Environmental influence

   a. The milieu interior represents physiological variation between individuals that could influence the risk of dry eye development. Such factors could include the blinking rate, the height of the palpebral aperture in primary position, the age of the individual and the levels of sex hormones including both androgen and oestrogen levels. A number of systemic drugs might also affect lacrimal tear secretion.

   b. The milieu exterior represents occupational and environmental risk factors for dry eye development as relative low humidity (air travel, air conditioning,geographic variation), increased evaporation (wind) and slow blinking rate (PC terminal work).

Dry eye disease

The causative mechanisms of dry eye

Causative mechanisms

a. Tear hyperosmolarity

b. Tear film instability

The core mechanisms that initiate, amplify and potentially change the character of dry eye over time are tear hyperosmolarity and tear film instability.

a. Tear hyperosmolarity

Tear osmolarity is regarded the major factor causing ocular surface inflammation, damage and symptoms in dry eye as also the initiation of compensatory mechanisms in dry eye. Tear hyperosmolarity arises as a result of water evaporation from the exposed ocular surfaces. Hyperosmolarity stimulates a cascade of inflammatory events in the epithelial surface cells. There is evidence that these inflammatory events lead to apoptotic death of surface epithelial cells. This includes goblet cell death and decreased gel mucin production.

In the initial stage of dry eye it is considered to be ocular surface damage caused by osmotic, inflammatory and mechanical stress, which results in reflex stimulation of the lacrimal gland. Reflex trigeminal activity is thought to be responsible for the increased blink rate and a compensatory increased lacrimal secretion.

b. Tear film instability

In some forms of dry eye, tear film instability may be the initiating event, unrelated to prior tear hyperosmolarity.

Where the tear film break up time (BUT) is less than the blinking interval, it is easily understood that the tear film break up time in that individual is normal. When the value is less than one, then tear film break up occurs in the waking open eye condition. However, if the BUT is greater that the blinking rate but less than ten seconds, then the BUT value is still regarded as an index of tear film instability.

Classification based on severity

The basis for dry eye symptoms is not fully understood. It includes activation of sensory nerves at the ocular surface, and includes hyperosmolarity, break up, shear stress between lid and globe, reduced tear volume and reduced mucin at the surface, inflammatory mediators and hypersensitivity of sensory nerves.

The severity of dry eye symptoms has been summarised into a number of complaints and clinical signs graded from one to four. These parameters include discomfort and severity, visual symptoms, conjunctival injection, conjunctival staining, corneal staining, corneal/tear signs, lid/meibomian gland status, tear fluid break up time and Schirmer score. These parameters and their status at various severity levels are summarised in Table 1.

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Table 1: Dry eye severity grading scheme [Ref 1].

Dry Eye Severity Level	1	2	3	4*
Discomfort, severity & frequency	Mild and/or episodic; occurs under environmental stress	Moderate, episodic or chronic, stress or no stress	Severe, frequent or constant without stress	Severe and/or disabling and constant
Visual symptoms	None or episodic mild fatigue	Annoying and/or activity-limiting episodic	Annoying, chronic and/or constant, limiting activity	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+/–	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining (severity/location)	None to mild	Variable	Marked central	Severe punctate erosions
Corneal/tear signs	None to mild	Mild debris, ↓ meniscus	Filamentary keratitis, mucus clumping, ↑ tear debris	Filamentary keratitis, mucus clumping, ↑ tear debris, ulceration
Lid/meibomian glands	MGD variably present	MGD variably present	Frequent	Trichiasis, keratinization, symblepharon
BUT (sec)	Variable	≤ 10	≤ 5	Immediate
Schirmer score (mm/5 min.)	Variable	≤ 10	≤ 5	≤ 2

* Must have signs AND symptoms. BUT: fluorescein tear break-up time. MGD: meibomian gland disease.

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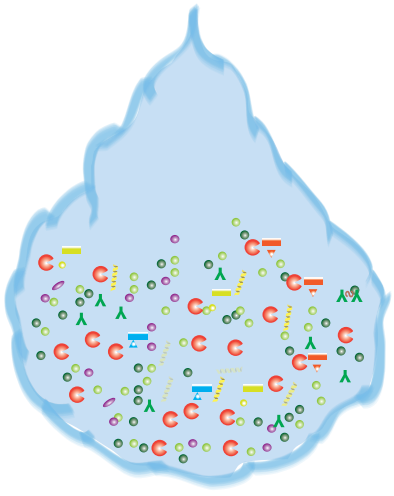
References:

1) DEWS 2007. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007; 5:73-92.

2) Dysfunctional tear syndrome. A Delphi approach to treatment recommendations. Cornea 2006:25:90-7.



Dry eye disease

The Epidemiology of Dry Eye Disease

Introduction

Epidemiology as a science studies the distribution, patterns, causes, effects and determinants of health and disease in defined human populations. Any epidemiological data on dry eye disease hence can, at its best only be an approximation. This is due to the fact that this clinical entity describes a multifactorial disease of the tears and ocular surface symptoms and clinical signs of the disease vary widely. The lack of specific definition results directly in the impossibility to totally agree on epidemiological data. This has been extensively illustrated in the work of the Epidemiology Subcommittee of the 2007 Dry Eye Work Shop[1].

Following its suggestion that dry eye is recognised as a disturbance of the Lacrimal Functional Unit (LFU), an integrated system comprising of the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that connect them, the large spectrum of symptoms and clinical signs become evident.

Hence, although there have been several attempts to help the ascertainment of the prevalence of the disease, standardised clinical diagnostic approach is still missing. The epidemiological insight about ocular surface disease and dry eye disease suffers from the insufficiency of diagnostics and terminology as well as definitions. This does concern especially the asymptomatic, milder and moderate forms of dry eye symptoms and signs.[2] A significant improvement in this situation that prevailed for decennials, was most recently the introduction of guidelines for an algorithm for diagnosis of severe forms of dry eye disease.[3] The turning point from a complaint to a disease is of major clinical and socio-economically importance. However, until today there is no common, global consensus on how to define different stages of DED. Only recently the challenges of combining signs and symptoms in dry eye diagnostics have been highlighted .[2] Any epidemiologic approach requires showing the indirect evidence, that dry eye disease is a disease and has an increasing prevalence in the Scandinavian population. In general, any reported official number of treated patients can only reflect prevalence of those patients in a popula-

Dry eye disease

tion that seek doctors' or ophthalmologists' attendance due to the severity of their complaints of dry eye. The rapid transition of an organized distribution of dry eye medication by professionals to treatments by pharmacy, internet and other health care providers as well as opticians does not allow anymore any clear statistics. The increased education via internet and the resulting self-medication does also decrease the objective knowledge about the epidemiology of dry eye disease. Any epidemiologic consideration on the prevalence of dry eye disease is hence based on indirect evidence such as on the age structure, environmental issues, poly-pharmacology and co-morbidity of diseases known to be associated this dry eye disease. In general, the Scandinavian countries have specific characteristics that do favour the occurrence of dry eye complaints and disease in the population.

In Scandinavia, dry eyes definition is simply that the precorneal tear film does not function sufficiently[4]. For Keratoconjunctivitis Sicca (KCS) and Sjögrens Syndrome the Copenhagen criteria[5] are used. According to these, two pathological values of the following three tests are needed: break-up time (BUT), Schirmers1 test (S1T) and rose-bengal score (RBS) .[6,7]

One of the hallmarks and clinical difficulty of the disease encompassed by the term "dry eye" is the dissociation between clinical signs and subjective symptoms.[8] Currently the symptoms are the first lead to the establishment of the diagnosis of dry eye. It is the incidence of symptoms associated with dry eye disease that most heavily impacts the current epidemiological picture of dry eye disease or ocular surface disease.

Prevalence and incidence

Individual research groups in various reports have used different operational definitions of dry eye. Furthermore, there is no consensus on which combination of tests should be used to define the disease. Apparently, various stages of the disease favour various investigations. There is a lack of correlation between patients' irritative ocular symptoms and the results of selected clinical tests for dry eye which can be explained by:

- lack of repeatability of many of the clinical tests
- natural variability of the disease process
- subjective nature of symptoms: variability in pain thresholds and in cognitive responses to questions
- development of relative corneal anesthesia with aging and with worsening disease
- possibility that symptoms are related to parameters not measured by the test

The DEWS subcommittee examined data from a number of large cohort studies and summarised the data in a table. Prevalence of DED varied between 5.5% and 33.7% .[1]

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Prevalence

Based on data from the largest studies of dry eye to date, it has been estimated that about 3.23 million (14.5%) women and 1.68 million (9.3%) men, of a total of 4.91 million (12.3%) Americans, 50 years and older, have dry eye. Data from the Women Health Study suggest that the prevalence of severe symptoms and/or clinical diagnosis of dry eye may be greater in Hispanic and Asian, as compared to Caucasian, women. Data from the two studies performed in Asia suggest the possibility of a higher prevalence of dry eye in those populations.[1]

Regarding Scandinavian studies, in 1995, for persons aged 30-60 in Copenhagen, the frequency of KCS was estimated to be 11% while the frequency of primary Sjogren's syndrome was to be between 0.2% and 0.8% according to the Copenhagen criteria.[9] In a recent (2012) Danish study[10] the prevalence of sicca symptoms and secondary Sjögren's syndrome among RA patients was at least 18% and 3.6% respectively.

A Swedish study 1989, in a 52-72 old population, showed a prevalence of KCS of 15.9% and of primary Sjogren's syndrome of 2.7% using the same criteria.[11]

In year 2000 in Iceland, among 40-50 and 70-75 years old population, 20.3% had subjective symptoms of dry eye, 26% had pathological Schirmer1 and 13% had abnormal BUT.[12] In the Norwegian Hordaland study (2008) the prevalence of primary Sjögren's syndrome among 40-44 and 71-74 years old Norwegians was 0.22% and 1.4% respectively, using from 1996 criteria.[13]

The studies indicate that female sex and older age increase the risk for dry eye.

Scandinavian countries are also known to have a shift of the population towards the aged. This is evident when comparing the mean age of for example Sweden and Finland to countries known to have the highest contingent of aged inhabitants such as Japan and Germany.

Country	Total	Male	Female	Year
Japan	44.6	42.9	46.5	2010 est.
Germany	43.7	42.3	45.3	2010 est.
Austria	42.6	41.5	43.6	2010 est.
Finland	41.6	40.2	43.0	2010 est.
Sweden	41.7	40.6	42.9	2010 est.

In this context, Japan has a special position as in 2012, about 24.1 percent of the population were over 65.[13] Although this high percentage is not reached by Scandinavian countries and they do have a significantly smaller population, the life expectancy is very high: 81.18 years (males: 78.86 years, females: 83.63 years).

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The past decades have shown a significant increase of the number of the aged. This may be nicely illustrated by an approximation for Finland comparing the distribution of age in 1917 and 2006:

Change of age distribution of the population in Finland 1917 to 2006 (%)

Age	0-25	26-50	51-75	76-100	
1917	45	35	17	3	100
2006	28	32	30	10	100

A similar structure, that is loss of the pyramidal shape of the age distribution, is evident when comparing the population of Japan and Finland in the first decade of the 20th century

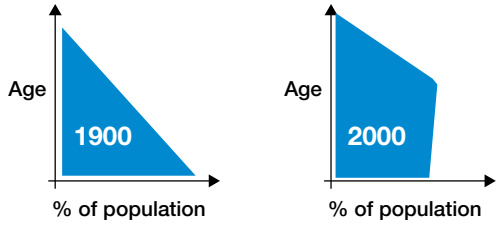
Age distribution of the population in Japan and Finland 1917 to 2006 (%)

Age	0-25	26-50	51-75	76-100	
Japan	29,4	33,2	28,5	8,9	100
Finland	28	32	30	10	100

In Norway the number of people aged above 65 years will increase from todays 13.7 %, that is 699 000 individuals (2014) to projected 22.2% by the year 2060.

This general trend of an increasingly older population seems to be detectable in the majority of the Scandinavian countries. This comes with an elevation of the average age in the population.

Change of Age distribution in Scandinavia 1900 to 2000



With aging follows an increasing polypharmacy which could further trigger the increase[15] observed or reported dry eye sensations. The specific side effects of drugs has been recently reviewed[16] and can also be found both on the national websites such as FASS in Sweden (www.fass.se) as well as at the website of the National Registry of Drug-Induced Ocular Side Effects.

Comorbidity as a reason to polypharmacy does in the dry eye disease group reflect especially to rheumatic diseases or in general connective tissue disease. Still today a large number of patients with mixed connective tissue diagnosis bypass the diagnosis of dry eye disease[17]. Within ophthalmology the biggest patient group that does constantly challenge their ocular surface balance by the application of topical drops is the patient group having glaucoma. It is not until recently that several substances such as preservatives have been pointed out as real toxic agents to the ocular surface such as benzalconium chloride (BAK). Although the Scandinavian outdoors climate is not extreme, weather conditions do lead to an increased exposure of the ocular surface to wind and sub-zero temperatures during winter time which do constitute environmentally

Dry eye disease

challenging conditions as outlined in DEWS. The geographical location of Scandinavia and the high percentage of its population working in the third sector do contribute to a significant exposure of the population to indoor environment. Draft, smoke, dust and low air humidity significantly contribute to the prevalence of dry eye disease. Another epidemiological factor that further contributes to the prevalence of dry eye disease in Scandinavian countries is the presence of depression, especially seasonal affective disorders (SAD)[18] and its associated side effects with the medications used.

Incidence

Epidemiologic data on DED extracted from data repositories and federal (USA) or public databases showed that dry eye case incidence per 100 fee-for-service Medicare beneficiaries increased from 1.22% in 1991 to 1.92% in 1998.[19]

The natural history of dry eye remains to be determined, including prognostic factors, the likelihood of disease progression, and the rates of treatment adherence and discontinuation and the long-term effect of the use of lubricants.

As stated above there is dissociation between signs and symptoms in dry eye and ocular surface disease. However, as initial signs usually are symptomatic complaints, symptom questionnaires are among the most commonly used diagnostic tools. It is well known that dry eye symptoms affect activities of daily living and are largely responsible for the care-seeking behaviour of dry eye patients.

Quality of life (QoL) in Dry Eye Disease (DED)

The high prevalence among the older age groups combined with the aging of the population increase the significance of dry eye in public healthcare. The pain and the irritative symptoms lower the quality of life (QoL) and decrease ocular and general health. Dry eye causes a substantial cost and also effect visual function and performance.

Patients with DED are significantly ($p < 0.001$), about three times more likely to report problems with reading, carrying out professional work, using a computer, watching television, driving during the day, and driving at night.

In a study on the effect on vision-targeted QoL of dry eye in patients with Sjögren´s Syndrome, the authors found[20] poor correlations between signs and symptoms of dry eye which may have been due to the capture of symptom intensity.

Sjögren's syndrome can affect many organ systems, and afflicted patients have a reduced quality of life also due to fatigue, anxiety, and depression.

Impact on Visual Function

Visual function is a measure of one's ability to perform vision-intensive tasks. Among these are reading, computer work, driving a car, or watching television. People with DED complain about disturbed vision which can clear temporarily with a blink. The result is diminished contrast sensitivity and visual acuity, thus affecting work performance and vision-related QoL[21].

Corneal epithelial desiccation, a consequence of dry eye, causes irregularity on the corneal surface. Corneal topography helps us visualise

Dry eye disease

and quantify this by different surface regularity indices. Surface irregularity has a negative impact on retinal image quality and visual acuity[21,22]. Punctal occlusion or/and artificial tears have been shown to have a beneficial effect.[23]

Ocular Morbidity in DED

Dry eye symptoms can cause contact lens intolerance and discontinuation of contact lens wear and has a negative impact on refractive surgery outcomes. The risk of infection and complications with ocular surgery could be elevated.

Risk Factors for DED

Risk factors were presented as a table in the DEWS report (2007). Female gender is one of the most common predisposing factors. As DED incidence increases with age, older women are the most DED affected subgroup with a prevalence of approximately 20%. Factors such as low air humidity, computer use with low blinking rates and wide ocular aperture are

Dry eye disease

known to cause ocular irritative complaints due to increased tear evaporation.

Contact lens wearers also experience ocular dryness symptoms and discomfort accounts for up to 50% of all contact lens wear discontinuation. Decreased corneal sensitivity, reduction in prelens lipid layer and rapid prelens tear film thinning have been proposed as contributing factors.

Dry eye is known to occur following refractive surgery such as PRK and LASIK, at least during the first postoperative year. Dry eye may negatively affect ocular wound healing and lead to refractive regression. The term Lasik-Induced Neurotrophic Epitheliopathy (LINE) has been coined, involving decreased corneal sensation due to disruption of trophic sensory support to the denervated region, which leads to reduction in blinking and lacrimal secretion. Reports of the prevalence of dry eye in LASIK patients without a prior history of dry eye vary up to 48%. Greater ablation depth due to higher preoperative myopia seems to be positively correlated with the risk of postoperative DED.

Autoimmune and immune-driven systemic diseases are associated with DED. Patients with Sjogren's syndrome, rheumatoid arthritis and Graves' disease report DED in significantly higher percentages. DED is also common in patients with chronic graft versus host disease after bone marrow stem cell transplantation.

Dry Eye Questionnaires

Questionnaires are employed in clinical research to screen individuals for the diagnosis of dry eye or in clinical practice to assess the effects of treatments or to grade disease severity. In epidemiologic research, questionnaires can be used for population-based studies or to study the natural history of disease. The purpose of a questionnaire affects the content and nature of the instrument. The Epidemiology Subcommittee evaluated dry eye symptom questionnaires. Fifteen were accepted but it was noted that information is limited for each of them. The questionnaires are summarised in a table and detailed information can be found at page 32[1].

The instruments varied in length, intended use, population in which they were tested, mode of administration and extent of validation. Instead, a set of several standardised, validated questionnaires suitable for a variety of purposes and available to investigators would be desirable.

From Malmö, Sweden a new core set of tests for primary Sjögren's syndrome was proposed including seropositivity for anti-SSA and complement levels.[24]

Advisable Features of Dry Eye Questionnaires:

A valuable dry eye questionnaire must be responsive, i.e. able to detect and measure a change in symptoms with effective treatment or disease progression. It should be sufficiently sensitive to detect therapeutic response by a drug. It must be reproducible; the changes detected must be real and not due to poor repeatability. The recall period should be speci-

fied. Other important points include the ability to set a threshold of severity of the disease as an inclusion criterion (ceiling and floor effects). One may use a different questionnaire to perform at baseline and at the primary outcome study visit. Dry eye examinations and the questionnaire should be administered at the same time of day in clinical trials. An item on visual function should be included in the definition of dry eye (fluctuating or transient blurred vision), distinct from "irritative" symptoms.

The members of Tear Film and Ocular Surface society are planning a new report, the DEWS II in short. Clinically meaningful changes in questionnaire scores need to be defined but detailed templates of current questionnaires can be accessed at: www.tearfilm.org.

Summary

DED seems to affect a large proportion of the population (>25%). It's more frequent in females and increases with age. Evaporative DED and especially MGD is the most common form. Extrinsic but also intrinsic factors contribute to the development of DED in different ways. Increased tear film osmolarity is a common marker, and it leads eventually to ocular surface damage.

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Diagnosis and monitoring dry eye disease

Introduction

Dry eye disease (DED) causes significant burden for the patient as well as health care professionals. It is therefore important that diagnosis and monitoring should be reliable and effective. With this in mind, we aim to present primary methods to diagnose and monitor DED for general ophthalmologists.

The primary methods include symptom questionnaires, tear film break-up time (BUT), vital staining, Schirmers test, and meibomian gland evaluation[1-13]. All methods are validated, low-cost, and are easy to adopt in a general ophthalmology practice. In case of difficult, refractory, or atypical DED, it may be advisable to refer these patients to dry eye specialists for more advanced methods to diagnose and monitor dry eye disease.

Primary methods to diagnose and monitor dry eye disease

Symptom questionnaires

Subjective evaluation should be performed by standardised questionnaires. Several symptom questionnaires have been developed to diagnose and monitor DED, such as the Ocular Surface Disease Index (OSDI), the National Eye Institute Vision Function Questionnaire-25 (NEIVFQ-25), McMonnies dry eye history questionnaire, Women's Health Study (WHS), International Sjögren's Classification, Schein classification, the Canadian Dry Eye Epidemiology Study (CANDEES), Dry Eye Questionnaire (DEQ), and Impact of Dry Eye on Everyday Life (IDEEL)[1]. In these questionnaires, patients are asked to describe their symptoms and assess the impact and duration of symptoms according to test questionnaires. Calculated scores have been related to the severity level of OSD from normal to mild, moderate or severe levels. These tests have a relatively good sensitivity for DED, correlate reasonably well with the quality of life, and most importantly are easily quantified. Yet, the questionnaires are unspecific and show only relatively good reproducibility. Therefore the questionnaires may carry a risk of overtreatment and these should always be used with objective measurements. The OSDI is a good choice for ophthalmologists unfamiliar with dry eye questionnaires. The OSDI is assessed on a scale of 0 to 100, with higher scores representing a greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with.
An OSDI score of $\geq$ 33 indicates a diagnosis of DED.

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Diagnosis and monitoring dry eye disease

Tear film break up time (BUT)

Tear film break-up time (BUT) measures the stability of the tear film in biomicroscopy examination[1,2]. The fluorescein dye is applied onto the outer surface of the eye either directly from a vial or fluorescein sodium-impregnated filter strip. After blinking the fluorescein mixes with the tear film, and then patient is then asked to keep their eyes open. A blue excitation filter from a hand ophthalmoscope or biomicroscopy is reflected on to the cornea. The time elapsing between the last blink and the formation of small dry areas on the corneal surface is called BUT (Figure 4). Stable fluorescein staining for >10 seconds have been considered to be normal. Although the assessment of BUT is very simple in theory, there is a large inter-observer variation and BUT seems not to be very reproducible.

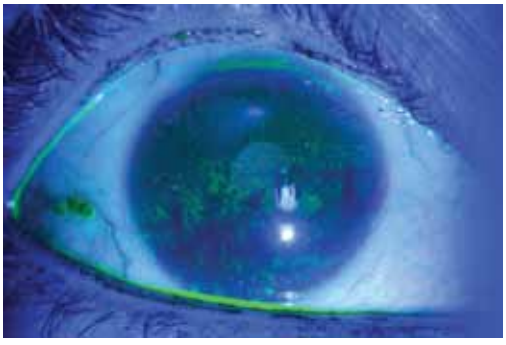

Fig. 4. Tear film break-up time (BUT) and vital staining using fluorescein dye

Vital staining

Fluorescein (Figure 4) or lissamine green (Figure 5) binds to damaged corneal epithelium and is seen as punctate staining pattern on the ocular surface.[1,3]

The Oxford Scheme is a commonly used test where surface damage to the exposed eye is graded against standard charts[5].

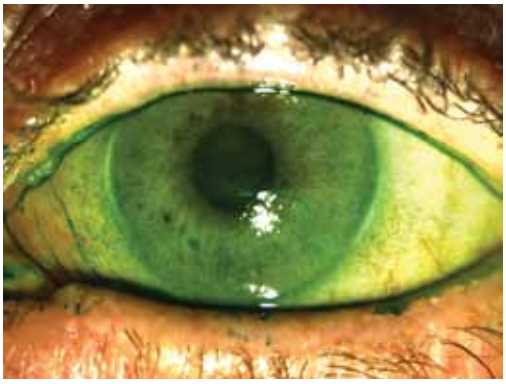

Fig. 5. Vital staining using lissamine green

Diagnosis and monitoring dry eye disease

Schirmer test

The Schirmer's test without anesthetic (Schirmer test I) is used to determine whether tear glands produce enough tears. Calibrated strips of a non-toxic filter paper are used. The free end of the strip is placed within the temporal part of the lower eyelid without anaesthesia (Figure 6) and both eyes are gently closed for 5 minutes.

At the end of test, the paper strips are removed from each lower eyelid and the amount of wetting of the paper strips is measured in millimetres. Schirmer scores for >10 millimeters are considered as normal.

The diagnostic cut-off for Ocular Surface Disease is ≤ 5.0 mm in 5 minutes[12].

Fig. 6. Schirmer test

Diagnosis and monitoring dry eye disease

Meibomian gland evaluation

Meibum quality is assessed in each of the eight glands of the central third of the lower lid on a scale of 0 to 3 for each gland:

0=clear, 1= cloudy, 2= cloudy with debris (granular) and 3= thick, like toothpaste (total score range, 0–24).[5, 7, 11, 14]

Expressibility is assessed on a scale of 0 to 3 in five glands in the lower or upper lid, according to the number of glands expressible:

0= all glands,

1=three to four glands,

2=one to two glands and

3= no glands.

It is best to use a cotton wool applicator to wipe off tear film from the the mucocutaneous junction and to apply gentle pressure for meibomian gland evaluation (Figure 7).

Fig. 7. Meibomian gland evaluation using a cotton wool applicator

Advanced methods to diagnose and monitor dry eye disease

Tear film osmolarity

Failure of homeostatic tear osmolarity is linked with DED and the osmolarity analysis is regarded by some as the "gold standard" in DED diagnosis and monitoring [2, 6, 9].

Tear film osmolarity is measured using a method to simultaneously collect and analyse the electrical impedance of a tear sample[2]. A tear sample (approx. 50 nL) is collected from the lower meniscus of the eye by passive capillary filtration (Figure 8).

Osmolarity readings are given in milliosmoles per liter (mOSMs/L). Osmolarity cut-off values changes in literature between 308 and 316 mOsms/L that reveal the mild or moderate DED [1, 9]. Cut-off osmolarity level for the severe DED has been estimated to be 325 mOSm/L[9]. The normal tear osmolarity levels changes within ±5 mOsms/L during one day, while higher variations are usually associated with DED.

Diagnosis and monitoring dry eye disease

Fig. 8. Tear film osmolarity analysis

Meibography in the diagnosis of MGD

Meibography is a non-invasive study that permits gross and microscopic examination of the structure of meibomian glands in minutes with minimal discomfort to the patient (Figure 9).

Infrared, laser confocal and optical coherent meibographies are various specialized imaging technologies to visualize the morphology of meibomian glands *in vivo*[14].

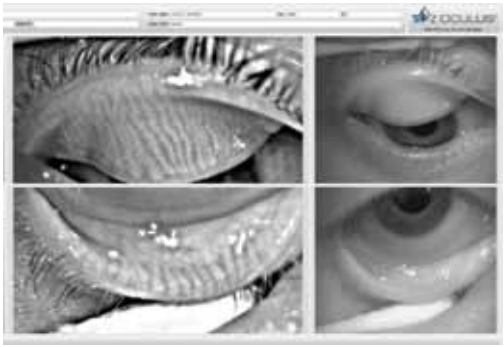

Fig. 9. Meibography showing normal meibomian glands without drop out.

Diagnosis and monitoring dry eye disease

Corneal imaging

Corneal imaging is non-invasive or minimally invasive. In vivo confocal microscopy can provide detailed information of the invasion of inflammatory cells to the cornea as well as detailed information of the corneal nerve architecture, but unfortunately it is very time-consuming and the instruments are expensive (Figure 10). Furthermore, most findings are non-specific and thus far no grading systems are available.

Aberrometry on the other hand provides a non-invasive procedure to see the optical quality of the cornea and can be used to assess the tear film instability. The instruments, however, are expensive, findings are non-specific, and the result is influenced by the quality of the blink and the wetting of the cornea.

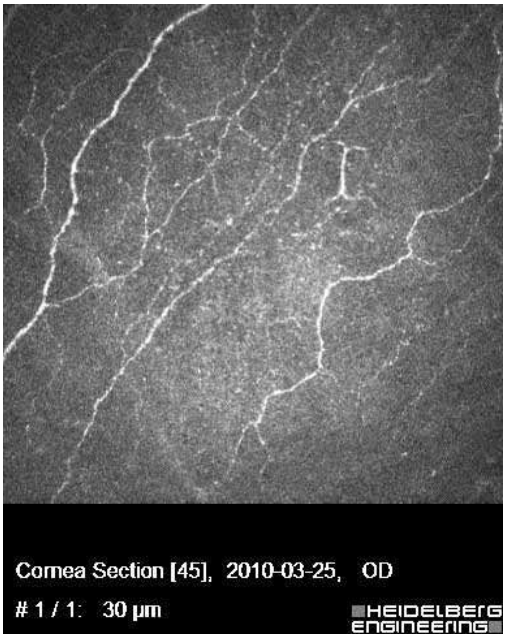

Fig. 10. In vivo confocal microscopy showing corneal nerves

Inflammatory markers

The advantage of measuring inflammatory markers, such as matrix metalloproteinases (MMP), interleukins and tumour necrosis factor, from the tears of DED patients is that they may provide insights into the pathogenesis of DED at the molecular level (Figure 11). Yet, increased expression of these inflammatory markers is being investigated in order to provide good evidence that the levels of these markers are correlated with the severity of the disease.

Fig. 11. RPS InflammaDry Test for detection of MMP9

Diagnosis and monitoring dry eye disease

Impression cytology

Impression cytology (Figure 12) is minimally invasive and provides a very good estimate of the goblet cell count. Yet, this method necessitates the use of a laboratory which is well established for cytological analysis.

Fig. 12. Impression cytology demonstrating the presence of goblet cells

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Table 2. Treatment algorithm for dry eye disease [Ref. 8]

Severity Level	Clinical description	Treatment
1	Discomfort, severity & frequency: Mild and/or episodic occurs under environmental stress Visual symptoms: None or episodic mild fatigue Conjunctival injection: None to mild Conjunctival staining: None to mild Corneal staining: None to mild Corneal/tear signs: None to mild Lid/meibomian glands: MGD variably present BUT (sec): Variable Schirmer score (mm/5min): Variable	Information about effect of environment and omega-3 fatty acid intake Elimination of offending systemic medications Artificial tear substitutes, gels/ointments
2	Discomfort, severity & frequency: Moderate episodic or chronic, stress or no stress Visual symptoms: Annoying and/or activity limiting episodic Conjunctival injection: None to mild Conjunctival staining: Variable Corneal staining: Variable Corneal/tear signs: Mild debris,↑ meniscus Lid/meibomian glands: MGD variably present BUT (sec): ≤ 10 Schirmer score (mm/5min): ≤ 10	*All the above, plus* Anti-inflammatory therapy Oral tetracycline (meibomian gland dysfunction) Punctal plugs Secretagogues Moisture chamber spectacles
3	Discomfort, severity & frequency: Severe frequent or constant without stress Visual symptoms: Annoying, chronic and/or constant limiting activity Conjunctival injection: +/- Conjunctival staining: Moderate to marked Corneal staining: Marked central Corneal/tear signs: Filamentary keratitis, mucous clumping, ↑ tear debris Lid/meibomian glands: Frequent BUT (sec): ≤ 5 Schirmer score (mm/5min): ≤ 5	*All the above, plus* Serum Contact lenses Permanent punctal occlusion
4 Must have signs AND symptoms.	Discomfort, severity & frequency: Severe and/or disabling and constant Visual symptoms: Constant and/or possibly disabling Conjunctival injection: +/++ Conjunctival staining: Marked Corneal staining: Severe punctate erosions Corneal/tear signs: Filamentary keratitis, mucous clumping, ↑ tear debris, ulceration Lid/meibomian glands: Trichiasis, keratinization, symblepharon BUT (sec): Immediate Schirmer score (mm/5min): ≤ 2	*All the above, plus* Systemic anti-inflammatory therapy Surgery (lid surgery, tarsorraphy, mucus membrane, salivary gland, amniotic membrane transplantation)

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BUT: Tear film break-up time. MGD: meibomian gland disease

Management and therapy of dry eye disease

Introduction

The International Dry Eye Workshop (2007) presented a novel evidence-based approach to the management of Dry Eye Disease (DED) graded by the level of disease as demonstrated in Table 2. The Dry Eye severity level is based on symptoms (ocular discomfort and visual symptoms) and signs (e.g. conjunctival injection, ocular surface staining, meibomian gland dysfunction, Tear Film Break-Up Time (BUT), and Schirmer score) with four levels of disease severity. If the symptoms and findings of a patient fit best with e.g. severity level 2, the management should include treatment at severity level 1 plus the various treatments at severity level 2. The recommendations may be modified by practitioners based on individual patient profiles and clinical experience. Likewise, the International Workshop on Meibomian Gland Dysfunction (MGD, 2011), presented a similar evidence-based treatment algorithm for MGD with four stages of disease[5] as shown at page 43, Table 3.

Tear supplementation: Lubricants

General considerations

Artificial tear substitutes are considered the base of treatment in DED[6]. The general properties of the lubricants currently available in the Nordic countries are presented at page 46-47, Tear supplementation: Lubricants.

It is very important to find out what is causing the dry eye disease. Is it a quantitative (aqueous deficient) dry eye disease or a qualitative (evaporative) dry eye disease. If the DED disease is caused by a quantitative dry eye disease the main substitute should be an aqueous layer substitute and if the DED is caused by a qualitative dry eye disease, the main substitute should be a lipid layer substitute.

Artificial tear substitutes primarily lubricate the ocular surface, but they are also believed to reduce elevated tear film osmolarity, dilute or wash out inflammatory or inflammation-inducing agents, and replace missing tear constituents. None of these agents have proven to be superior to others. Treatment should be individualised, and the patients should be allowed to try different products in order to find out which substitute suits their needs best.

Patients with minor symptoms will often manage well using artificial tear substitutes with low viscosity a few times daily. Patients with more severe symptoms need more viscous tear substitutes and tear supplementation needs to be more frequent. Yet, the choice of treatment is individualised. Some of these patients will also need to use an ointment before going to bed.

Viscosity agents

Macromolecules are added to the artificial lubricants to stabilise the lubricants and make them viscous. Carboxymethyl cellulose is commonly used as a viscous agent in traditional lubricating tears. Other viscous agents as polyvinyl alcohol, glycerine, propylene glycol, polyethylene glycol 400, hydroxymethylcellulose, and trehalose, vary in viscosity, and so give different corneal surface retention time. Hydroxypropyl-guar (HP-guar) is a gelling agent, which is believed to preferentially bind to and protect the more hydrophobic areas of the surface epithelial cells. Hyaluronic acid has a long ocular surface retention time, and is used in several tear substitutes.

Management and therapy of dry eye disease

Electrolyte composition

Some formulations mimic the electrolyte composition of human tears. Potassium is important to maintain corneal thickness, whereas bicarbonate-containing solutions promote the recovery of epithelial barrier function following damage to the corneal epithelium.

Osmolarity

As the core mechanisms of dry eye disease are driven by tear hyperosmolarity and tear film instability, hypo-osmotic artificial tears have been developed. Furthermore, recent formulations also provide protection against the adverse effects of increased osmolarity (osmoprotection). Osmoprotectants such as erythritol, taurine, trehalose, and L-carnitine may directly protect cells against hyperosmolarity and thereby break the vicious circle of DED[2].

Preservatives

Benzalkonium chloride (BAK) should not be used in patients with DED due to epithelial toxic effects. As an alternative to BAK, other preservatives such as polyquad, sodium purite and sodium perborate are used. It is recommended to use tear substitutes without preservatives. Preservatives make the tear film unstable and decreases BUT. Tear substitutes, either as drops, gels or ointments do not support bacterial growth, and many of the medical companies now produce tear substitutes without preservatives. This is achieved using bottles with special filters which protect against contamination or single dose units.

Tear Retention

Punctal occlusion

Fig. 13. Punctal occlusion

Punctal occlusion (Figure 13) is indicated in aqueous deficient DED[13]. Punctum plugs block the tear ducts and thus reduce tear drainage, retain moisture in the eye, and enables the patient to reduce the use of lubricants. Diagnostic/temporary punctal plugs are made of collagen or polymers and last for variable periods of time (3 days to 6 months). Permanent plugs comprise of silicone plugs that rest on the punctal opening or cylindrical plugs which expand and increase in diameter. It is recommended to treat the ocular surface inflammation prior to plug insertion. Toxic tear syndrome is a potential threat to the ocular surface after punctal occlusion due to increased tear retention time.

Moisture chamber spectacles

Despite limited evidence, the use of moisture chamber spectacles is recommended to alleviate ocular discomfort associated with dry eye[11].

Contact lenses

Contact lenses may be indicated in severe DED[1]. Contact lenses may protect and hydrate the corneal surface and include soft silicon lenses and gas permeable scleral-bearing hard contact lenses.

Management and therapy of dry eye disease

Tear stimulation: Secretagogues

Secretagogues are agents that may potentially stimulate aqueous secretion, mucous secretion, or both.

Biological tear substitutes

Serum

Autologous serum eye drops have advantages compared to tear substitutes (Noble et al. 2004). Serum lacks antigenicity, and contain lots of important epithelial protecting factors such as growth factors, vitamins, immunoglobulins, extracellular matrix proteins, and neutrophins. These are factors that protect and stimulate the epithelium to regenerate, which to date has been impossible to incorporate in artificial tears.

Salivary gland autotransplantation

Salivary gland autotransplantation may be indicated in severe DED[4], and refers to the transplantation of a salivary gland graft under the upper eyelid.

Management and therapy of dry eye disease

Anti-inflammatory therapy

Cyclosporine

Cyclosporine (at a concentration of 0.02-0.05%) is a pivotal agent in the treatment of the ocular surface inflammation underlying DED[10, 3]. Cyclosporine is found to significantly decrease ocular irritation symptoms, conjunctival rose bengal staining, superficial punctate keratitis, and the expression of immune and inflammation activation markers. Furthermore, cyclosporine has been demonstrated to significantly increase Schirmer test scores.

Corticosteroids

Corticosteroids are effective anti-inflammatory agents in DED[10]. Corticosteroids are found to significantly decrease ocular irritation symptoms, fluorescein and rose bengal staining.

Tetracyclines

Tetracyclines are indicated in evaporative DED secondary to MGD[3]. Tetracyclines have anti-bacterial, anti-inflammatory and anti-angiogenic properties.

Essential fatty acids

Essential fatty acids (EFA) administered orally are found to significantly decrease ocular irritation symptoms and ocular surface staining.

Management and therapy of dry eye disease

Environmental strategies

External factors that increase tear evaporation

Several external factors are known to increase evaporation from the eyes. These include the use of air- conditioning in buildings (dry air, draught from fans), air blowing towards the face (cycling, driving car with the windows open, or with the heating fan in the car pointing directly at the face), cigarette smoke, and evaporating strong liquids (hairdressers, painters). These problems may be reduced by changing the direction of fans, improving the environment in buildings and protecting the eyes with shields and glasses etc. Lowering the computer screen to below eye level decreases the eye aperture and may decrease evaporation from the cornea. Increased eye blink rate and regular breaks may also be helpful to avoid computer screen-related DED.

Medication that may decrease tear production

Systemic anticholinergic drugs, like older antihistamines[12] are known to induce dry eye symptoms. The newer drugs in these groups have less anticholinergic effects and are better tolerated.

Diuretics may induce dry eye symptoms by decreasing lacrimation. Oestrogen therapy may also increase the risk of developing DED. Other medications like oral beta-blockers, antipsychotic medication and chemotherapeutics may also increase dry eye symptoms. The medications mentioned above should, if possible, be stopped or reduced in patients with DED.

Meibomian Gland Dysfunction

Meibomian gland dysfunction

The International Workshop on Meibomian Gland Dysfunction (2011)[5] presents a evidence-based treatment algorithm for MGD with four stages of disease as shown in Table 3 on page 43. The stage is based on symptoms (ocular discomfort, itching, and photophobia) and signs (lid margin features, meibum quality, expressibility, and ocular surface staining). In addition, "plus" diseases which may be causal of, or secondary to MGD, require treatment.

Eyelid treatment

Eyelid treatment consists of mechanical lid hygiene, eyelid warming, and mechanical massage of the eyelids on a regular basis, and is performed to improve the quality and quantity of tear film lipids[5]. Eyelid warming is applied to melt pathologically altered meibomian lipids. Heat may be delivered using a warm towel compresses, eye warmer masks, or eyelid warming devices (Blephasteam, Thea Nordic). Lid massage is performed to express obstructed glands.

Lipid-containing artificial tears

Lipid-containing artificial drops or eyelid sprays are supposed to help in restoring or increasing the lipid layer of the tear film.

Tetracyclines and azithromycine

The antibacterial and anti-inflammatory properties of tetracyclines[3] and azithromycine[7] are found to be beneficial in the treatment of MGD.

A three month course of 40-100 mg of tetracycline is recommended to bring MGD under control. Furthermore, topical treatment with azithromycine twice daily for the first two days followed by once daily for the next twelve days has shown significant improvements in meibomian gland plugging, quality of meibomian gland secretions, and eyelid redness.

Meibum quality is assessed in each of eight glands of the central third of the lower lid on a scale of 0 to 3 for each gland:

0, clear;

1, cloudy;

2, cloudy with debris (granular);

3, thick, like toothpaste (total score range, 0–24).

Expressibility is assessed on a scale of 0 to 3 in five glands in the lower or upper lid, according to the number of glands expressible:

0, all glands;

1, three to four glands;

2, one to two glands; and 3, no glands.

Oxford staining is obtained by summing the scores of the exposed cornea and conjunctiva with score range: 1–15.

Table 3. Treatment algorithm for MGD

Stage	Clinical description	Treatment
1 subclinical MGD	Symptoms: none Lid margin features: none Meibum quality ≥ 2-4 Expressibility 1 Oxford staining score 0	Information about MGD, Omega-3 fatty acid intake, Effect of work/home environment, and drying effects of systemic medications Eyelid hygiene with warming and massage (±)
2 minimal to mild MGD	Symptoms: minimal to mild ocular discomfort, itching, or photophobia. Lid margin features: scattered Meibum quality ≥ 4 to <8 Expressibility 1 Oxford staining score 0-3	*All the above, plus* Eyelid hygiene with warming and massage (+) Artificial lubricants Topical azithromycin Topical emollient lubricant or liposomal spray Oral tetracycline
3 moderate MGD	Symptoms: moderate ocular discomfort, itching, or photophobia with limitations of activities. Lid margin features: plugging, vascularity Meibum quality ≥ 8 to <13 Expressibility 2 Oxford staining score 4-10	*All the above, plus* Lubricant ointment at bedtime (±) Anti-inflammatory therapy (±)
4 severe MGD	Symptoms: severe ocular discomfort, itching, or photophobia with definite limitations of activities. Lid margin features: dropout, displacement Meibum quality ≥13 Expressibility 3 Oxford staining score 11-15 Conjunctival hyperemia, phlyctenules	*All the above, plus* Anti-inflammatory therapy (+)
"Plus" disease	1. Exacerbated inflammation 2. Mucosal keratinization 3. Phlyctenular keratitis 4. Trichiasis 5. Chalazion 6. Anterior blepharitis 7. Demodex-related anterior blepharitis	1. Pulsed soft steroid 2. Contact lenses 3. Steroid therapy 4. Epilation, cryotherapy 5. Intralesional steroid or excision 6. Topical antibiotic or antibiotic/steroid 7. Tea tree oil scrubs

The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. Geerling G, Tauber J, Baudouin C, Goto E, Matsumoto Y, O'Brien T, Rolando M, Tsubota K, Nichols KK. Invest Ophthalmol Vis Sci. 2011 Mar 30;52(4):2050-64.

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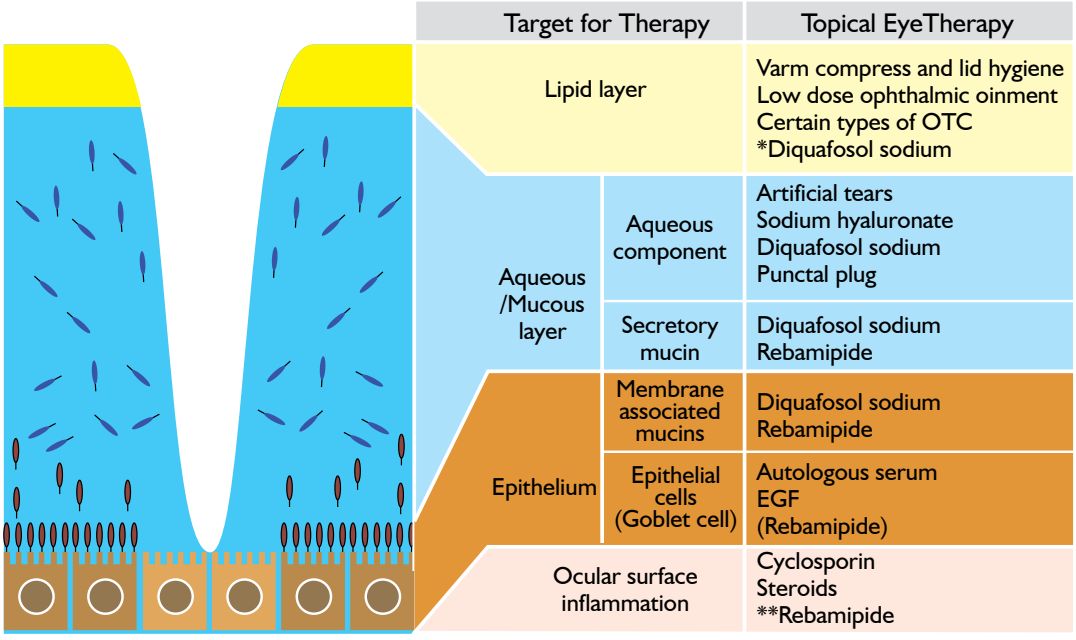
Future perspectives

The Japanese Dry Eye Society has introduced a novel perspective termed Tear Film Oriented Therapy (TFOT). This therapeutic approach has been increasing in importance due to the introduction of ophthalmic solutions which stimulate the secretion of mucin and water. By selecting topical therapy, each layer of the ocular surface can be targeted for therapy, thus further stabilising the tear film. In Japan, this approach has ushered in a new era of increasingly effective dry eye treatments. Figure 14 illustrates the current topical dry eye therapy options which contribute to the treatment of each layer of the ocular surface.

Fig. 14. Tear Film Oriented Therapy (TFOT). Supervision: Dry Eye Society



* *Diquafosol sodium may increase the function of the tear film lipid layer by promoting spreading of the lipid layer through lipid and tear fluid secretion*

** *Rebamipide may suppress the inflamation of the ocular surface in dry eye by its anti-inflammatory action*

Management and therapy of dry eye disease

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Tear supplementation: Lubricants

DROPS								
		Supplement of:						
Product	Viscosity	Water	Lipid	Mucin	Contact lens Yes or No	Expire Month	Preser-vatives	Pack-age
CLASS: Carboxymethylcellulose (CMC)								
Cellufluid	Low	Yes	No	Yes	Yes	Unidosis	-	Pipette
Celluvisc	Low	Yes	No	Yes	Yes	1	-	Pipette
Optive	Low	Yes	No	Yes	Yes	6	Purite	Bottle
Optive Plus	Low	Yes	Yes	Yes	No	6	Purite	Bottle
Optive Fusion	Low	Yes	No	Yes	Yes	6	Purite	Bottle
Refresh Tears	Low	Yes	No	Yes	Yes	6	Purite	Bottle
Thera Tears	Low	Yes	No	Yes	Yes	Unidosis	-	Pipette
Thera Tears Liquid Gel	Middle	Yes	No	Yes	Yes	Unidosis	-	Pipette
CLASS: Hydroxypropyltrimethylammonium (HPMA) + Povidone								
Tears Naturale II	Low	Yes	No	Yes	Yes	1	Polyquad	Bottle
						Unidosis	-	Pipette
CLASS: Hydroxymethylcellulose (HPMC)								
Artelac	Middle	No	No	Yes	Yes		CTRM*	Bottle
						Unidosis	-	Pipette
Bion Tears	Low	Yes	No	Yes	Yes	Unidosis	-	Pipette
Isopto Plain	Low	Yes	No	Yes	No	1	BAC	Bottle
						Unidosis	-	Pipette
Dacriosol	Low	Yes	No	Yes	Yes	1	BAC	Bottle
Hyprosan	Low/middle	Yes	No	Yes	Yes	1	-	Bottle
Viscous eye drops	Low	Yes	No	No	Yes	1	BAC	Bottle
CLASS: Polyethylene								
Blink Contacts	Low	Yes	No	Yes	Yes	1.5	OcuPure	Bottle
Blink intensive tears	Low/middle	Yes	No	Yes	Yes	1.5	OcuPure	Bottle
Blink intensive tears plus	Middle/high	Yes	No	Yes	Yes	1.5	OcuPure	Bottle
CLASS: HP Guar + PE/PEG								
Systane Ultra	Low/middle	Yes	No	Yes	Yes	6	Polyquad	Bottle
						Unidosis	-	Pipette
CLASS: Polyvinyl alcohol (PVA)								
Refresh Classic	Low	Yes	No	Yes	No	1	BAC	Bottle
Sincon	Low	Yes	No	Yes	No	Unidosis	-	Pipette
CLASS: Povidone								
Oculac	Low	Yes	No	Yes	No	1	BAC	Bottle
					Yes	Unidosis	-	Pipette

* CTRM: Cetrimide

Tear supplementation: Lubricants

DROPS (continued)								
		Supplement of:						
Product	Viscosity	Water	Lipid	Mucin	Contact lens Yes or No	Expire Month	Preser-vatives	Pack-age
CLASS: Sodium Hyaluronate								
Hyabak	Low	Yes	No	Yes	Yes	3	-	Bottle
Hylo-Comod	Low/middle	Yes	No	Yes	Yes	6	-	Bottle
OsmoTears CI	Low	Yes	No	Yes	Yes	3	-	Bottle
Oxyal	Low/middle	Yes	No	Yes	No	2	Oxyd	Bottle
Tearsagain Eye drops	N/A	Yes	No	N/A	Yes	3	-	Bottle
CLASS: HP Guar + PE/PEG + Sodium Hyaluronate								
Systane Hydration	Middle	Yes	No	Yes	Yes	6	Polyquad	Bottle
						Unidosis	-	Pipette
CLASS: Trehalose								
Thealoz	Low	Yes	No	Yes	Yes	3	-	Bottle
CLASS: Trehalose + Sodium Hyaluronate								
Thealoz Duo	Low	Yes	No	Yes	Yes	3	-	Bottle
GELS								
CLASS: Carbomer								
Oftagel	High	Yes	No	Yes	Yes	1	BAC	Bottle
						Unidosis	-	Pipette
Viscotears	High	Yes	No	Yes	No	1	Cetrimid	Bottle
							-	Pipette
CLASS: HP Guar + PE/PEG								
Systane Gel drops	Middle/high	Yes	No	Yes	Yes	3	Polyquad	Bottle
CLASS: Tammarind seed and polysaccharide								
Visine trætte øjne gel	Low	Yes	No	Yes	No	1	BAC	Bottle
CLASS: Povidon								
Visine tørre øjne gel	Middle/high	Yes	No	Yes	No	1	BAC	Bottle
CLASS: Liquid paraffin and vaseline								
Øjensalve neutral	High	No	Yes	No	Yes	1	-	Bottle
OIL EMULSION								
Class: Mineral oil and glycerol								
Cationorm	Low	Yes	Yes	Yes	Yes	3	--	Bottle
Class: HP Guar + PE/PEG + Lipitech								
Systane Balance	Low	Yes	Yes	Yes	Yes	6	Polyquad	Bottle
LIPOSOMAL SPRAY								
CLASS: Phospholipid Liposomes								
Tearsagain	-	No	Yes	No	Yes	6	PNE**	Bottle
Tearsagain Sensitive	-	No	Yes	No	Yes	6	-	Bottle

** PNE: Phenoxyethanol