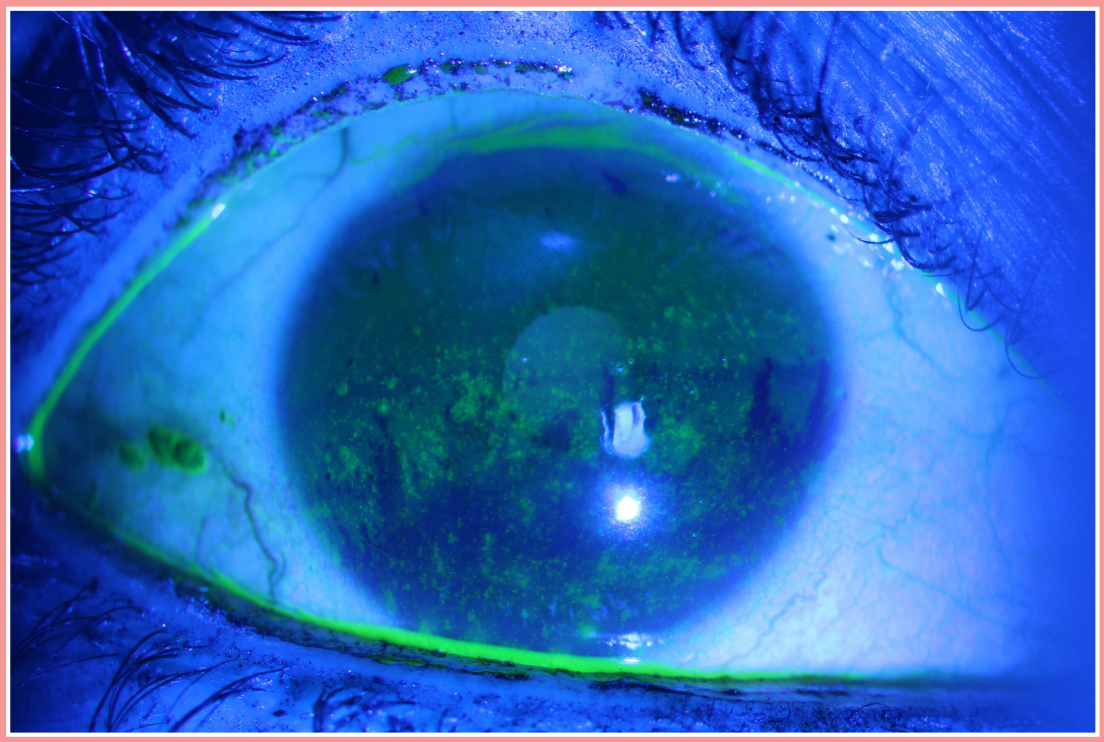
Nordic Guidelines
Second Edition 2022

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 !

Dear Colleagues! Dry eye disease (DED) is a very common condition world-wide. The increase in the world's elder population has created a huge demand for optimised treatments.

There is a range of healthcare providers treating DED and patients will try a range of treatments before seeking professional help.

A new edition of the TFOS International Dry Eye WorkShop (DEWS 2) was released in 2017 and we therefore wanted to update our former Dry Eye Disease, Nordic Guidelines from 2016.

Our aim is to present an 'easy-going' pamphlet that is easily used by health care professionals dealing with DED.

The increasing incidence of dry eye means that more and more new treatments, strategies and ointments are being introduced in 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 2022 for Dry Eye Disease valuable.

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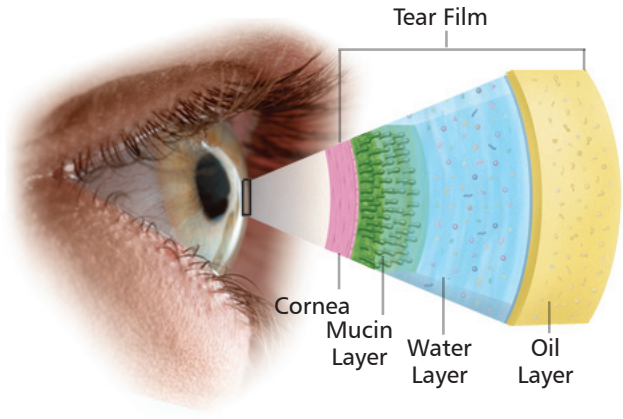


New Definition of dry eye disease:

"Dry eye is a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".

What is new in the TFOS DEWS II report?

There is a new Definition of dry eye disease:

"Dry eye is a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film and accompanied by ocular symptoms, in which tear instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles".

This means that symptoms must be present before a diagnosis of DED can be made. The loss of homeostasis leading to inflammation and ocular surface disease plays a key role in dry eye pathogenesis, along with induced neurosensory abnormalities.

Considering neuropathic pain in dry eye disease, DEWS II reports that it has been found that cold thermoreceptors continuously discharge nerve impulses at the normal ocular surface temperature, responding to warming or cooling and to osmolarity increases. In dry eye disease in general the osmolarity increases. This likely contributes to reflex control of basal tear production and blinking. Studies to date suggest potential merit in exploring treatment strategies involving cold receptors to manage dry eye disease symptoms.

The role of increased friction in dry eye disease and its subsequent sequelae deserves further investigation. Inflammation of the ocular surface can cause inhibition of lacrimal secretion and loss of epithelial barrier function at the ocular surface.

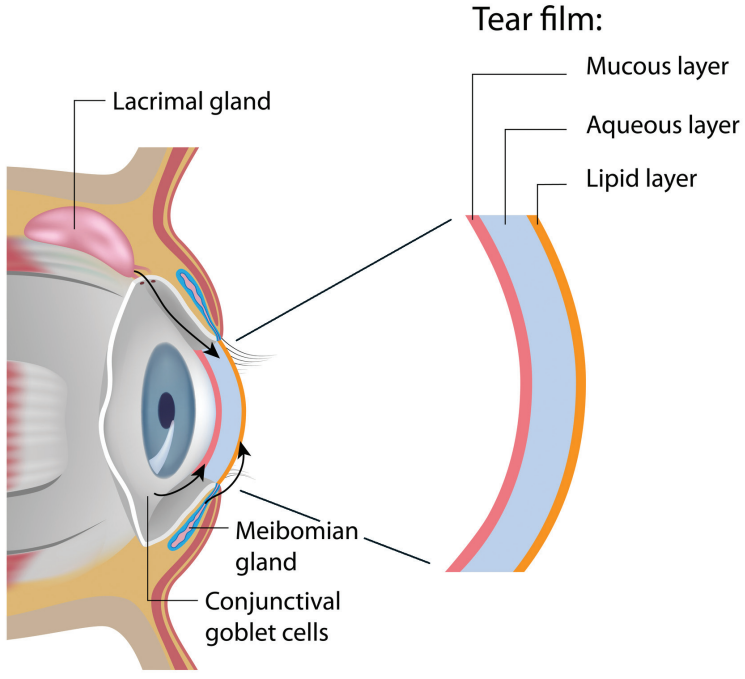
Restoration of tear film homeostasis is the ultimate goal in dry eye disease management. This involves breaking the vicious circle of the disease.

We still need to make new discoveries in dry eye disease, find novel approaches and better-validated instrumentation and techniques. These are ccrucial due to the ever rising incidence of dry eye disease. The importance of linking underlying causes in an individual and then advising the most suitable therapies to manage their dry eye disease. Although staged management and treatment recommendations in dry eye disease have been suggested, the heterogeneity of the dry eye disease patient population mandates that practitioners manage and treat patients based on individual profiles, characteristics, and responses.

Ref: TFOS International Dry Eye WorkShop (DEWS II). Ocular Surf. 2017;15:269-650.

Steffen Heegaard

Introductory Background



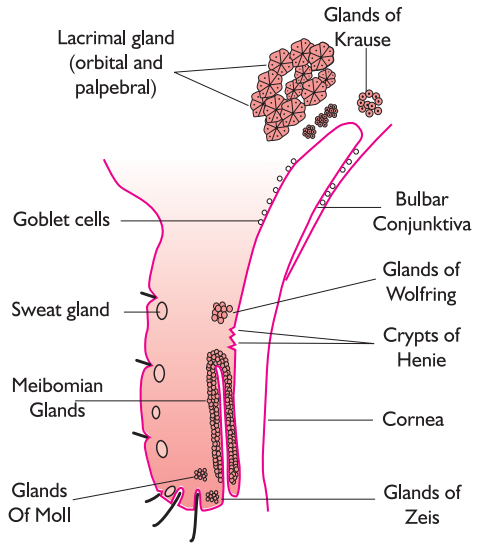
Introductory Background

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 people.

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



The function of the glands and their importance in 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 Lacrimal 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 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

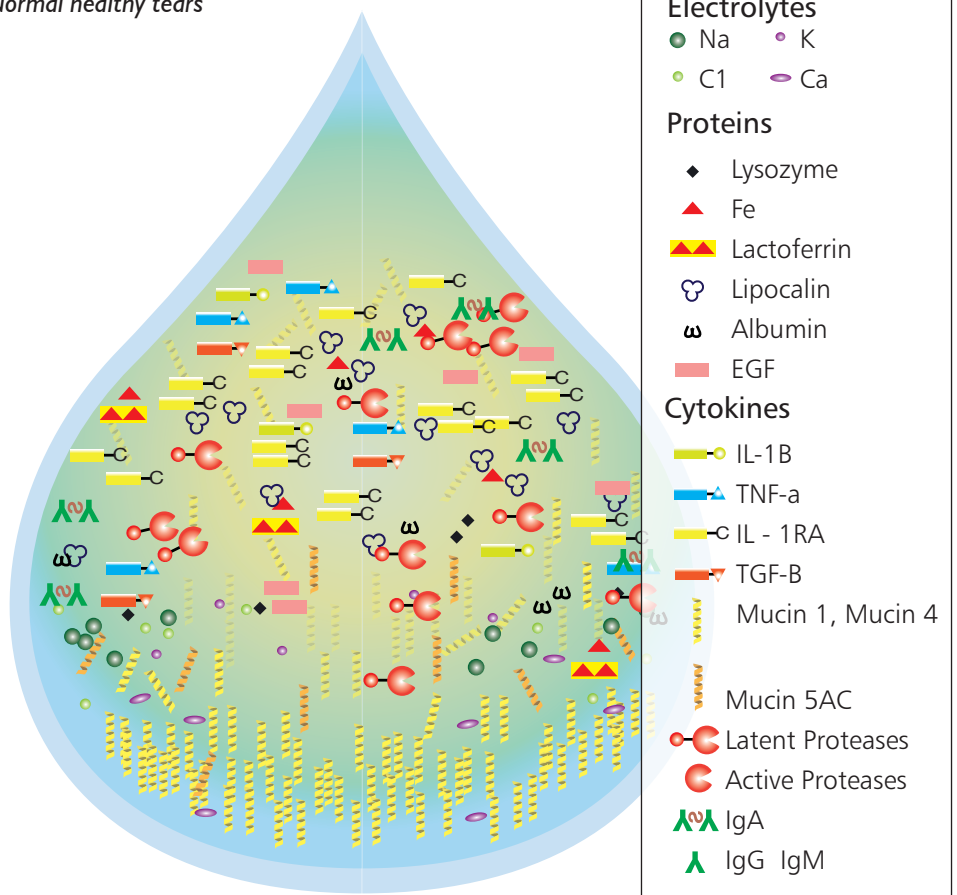


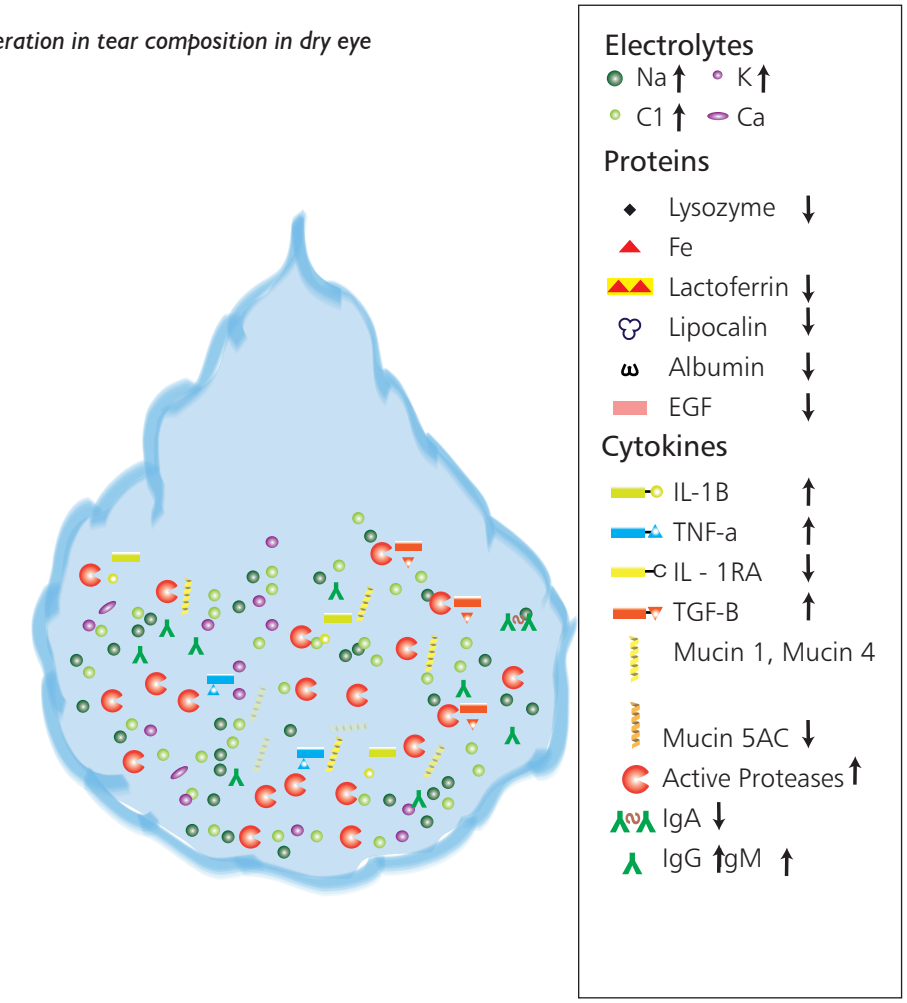
Fig. 1

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 DED (Figure 2).

Fig. 2. Alteration in tear composition in dry eye



Introductory Background

The tear film

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

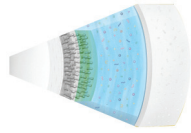
When any part of the tear film is not functioning properly, you may start to experience dry eye symptoms.

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:

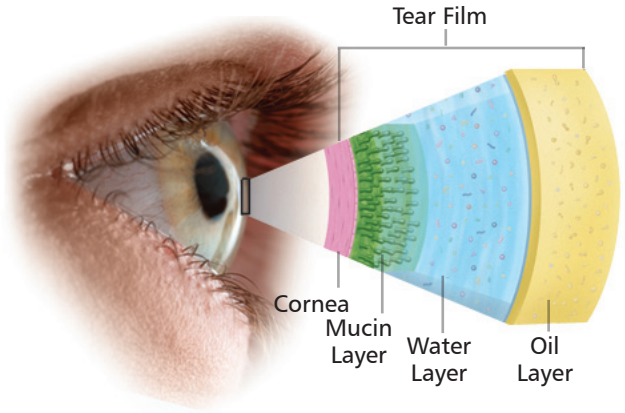


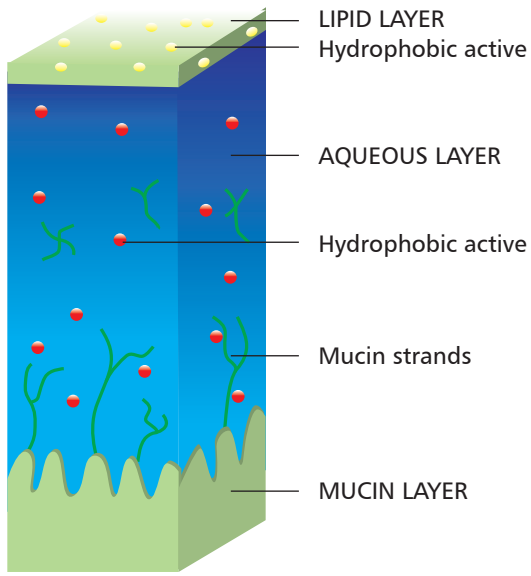
The middle layer is mostly comprised of water and is the thickest layer of the precorneal tear film. It is produced by the main lacrimal gland and the accessory lacrimal glands (Wolfring and Krause).

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 debris and pathogens.





Dry eye disease

New definition (TFOS DEWS II)

"Dry eye is 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 inflammation and damage, and neurosensory abnormalities play etiological roles" (Craig et al., 2017).

A clinical guideline for DED improves the understanding of this disorder and gives a rational base for an appropriate treatment. The first international guideline was introduced more than 30 years ago and has been revised since then. The previous DEWS I guideline classified dry eye disease into two main categories, i.e. tear deficit and evaporative disorder. Secondly patients were sub-divided into intrinsic and extrinsic factors. However, the classification was challenged in clinical practice.

Firstly, deficiencies in both tear quality and quantity was in some cases observed simultanously. Secondly, the DEWS I sub-classification could be misleading, since some patients were classified into more than one subgroup, i.e. Sjøgren syndrome. Thirdly, the various etiologies of DED are not taken into account.

The new evidence based DEWS II classification present aqueous deficient and evaporative dry eye as a continuum rather than two separate entities. It recognizes the multifactorial nature of dry eye, where loss of tear film homeostasis is central in the pathophysiology. It emphasises that it can arise from a multitude of factors and acknowledges the significant role of inflammation and hyperosmolarity in the disease. There has been an increased focus on nuronal effects in DED in the new classification. Abnormal activity of corneal cold nerve thermoreceptors underlying the unpleasant sensation of dry eye disease has been observed. The underlying mechanism remains unknown but it is likely to be the result of dry eye tissue damage.

The classification of dry eye disease represent a clinical decision algorithm assessing symptoms (triaging questions) followed by a review of the ocular surface (clinical examination). The new DEWS II classification therefore includes the present understanding of dry eye disease and represents the clinician a better tool for a staged management approach (Craig et al., 2017).

New classification of dry eye disease

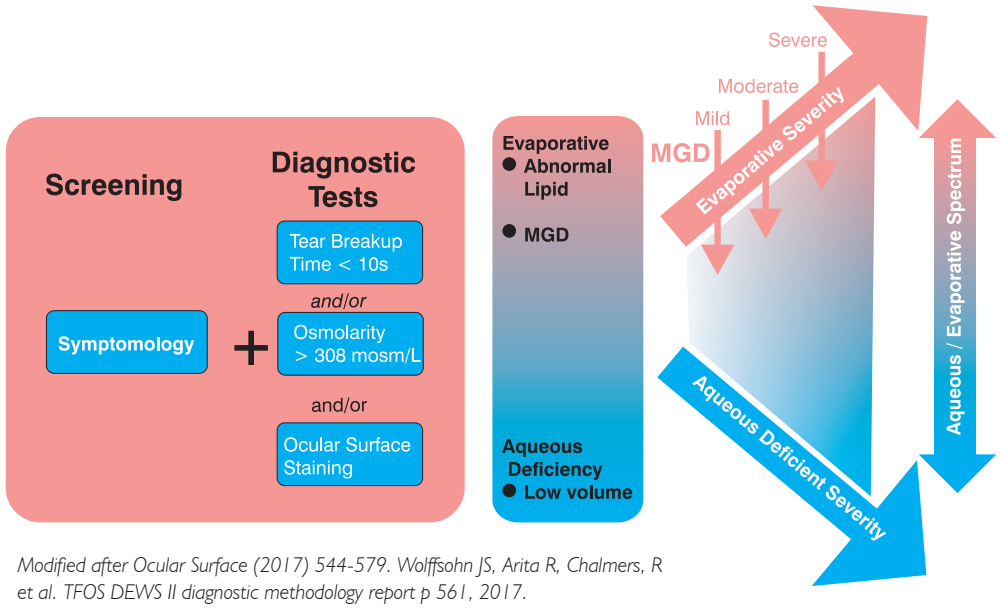
1. Asymptomatic with signs of ocular surface disease
- Corneal nerve damage secondary to long-standing DED
- Preclinical state of dry eye

2. Asymptomatic without signs of ocular surface disease
- Normal, no required treatment.

3. Symptomatic without signs of ocular surface disease
- Could indicate a preclinical state of dry eye, especially when the symptoms are intermittent.
- Could be the result of corneal nerve damage, due to long standing DED. Could also be the result of other corneal diseases?.

4. Symptomatic with signs of ocular surface disease.
- Dry eye disease (triaging questions)
- Other ocular surface disease (triaging questions)

Diagnostic Algorithm of Dry Eye Disease



Modified after Ocular Surface (2017) 544-579. Wolffsohn JS, Arita R, Chalmers, R et al. TFOS DEWS II diagnostic methodology report p 561, 2017.

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 deficiency

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 deficiency 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 tear deficiency 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.

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.

2. Qualitative
Dry Eye Disease = Evaporative

Qualitative dry eye

iii. Intrinsic

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

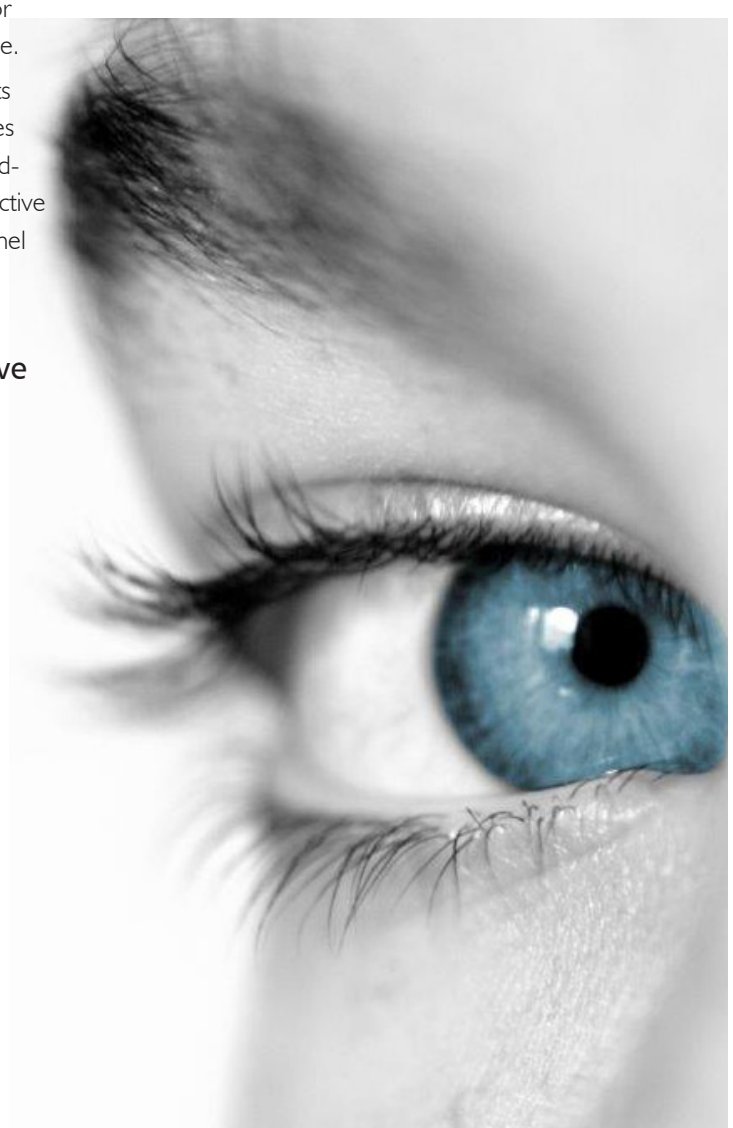
iv. Extrinsic

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

v. Environmental

1. Interior environment
2. Exterior environment

Evaporative DED is the result of excessive water loss from the exposed ocular surface in the presence of normal lacrimal secretion. It is traditionally described as the effect of intrinsic diseases affecting the eye lids or extrinsic disease. Environmental factors are also important (Behrens et al., 2006)



III. Intrinsic causes include Meibomian gland dysfunction, disorders of the lid aperture and a low blink rate

1. Meibomian gland dysfunction has multiple causes. It can represent a primary disorder or be associated to local diseases (anterior blepharitis), systemic diseases (acne rosacea, seborrheic dermatitis, atypia, ichthyosis and psoriasis), part of syndromes, reflect systemic toxicity or be the result of cicatricial changes in the lids.
2. 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.
3. Low blink rate increases evaporative ocular surface drying as a result of the increased lid opening time. It can occur physiologically in heavy video screen and microscope users. It occurs in disorders such as Parkinson disease.

IIII. Extrinsic causes

1. Ocular surface disorders may lead to insufficient surface wetting, reduced' tear break up time, tear hyperosmolarity and dry eye. Vitamin A deficiency causes goblet cell loss with a reduction in mucin production, as well as lacrimal gland damage. Topical drugs such as local anaesthetics and drug preservatives like Benzalkonium Chloride frequently induce a toxic response of the ocular surface.
2. 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.
3. Chronic ocular surface disease may induce dry eye through tear film destabilisation and loss of goblet cells.
4. 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.

V. Environmental influence

a. The internal environment is affected by physiological variation such as the blink rate, the shape of the eyes, the age of the individual and androgen / oestrogen levels. Systemic medications and drugs also affect lacrimal tear secretion.

b. The external environment is affected by occupational and environmental factors that cause dry eye. These include low humidity environments (air travel, air conditioning and geographic variation), increased evaporation from wind and a low blink rate (e.g. PC terminal work).

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 as 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

Tear film instability may initiate DED independently to 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 causes of dry eye symptoms are not fully understood. They include activation of sensory nerves at the ocular surface that induce hyperosmolarity, increased break up time , shear stress between lid and the ocular surface, reduced tear volume and reduced mucin at the ocular surface, increased inflammatory mediators and hypersensitivity of sensory nerves. The severity of dry eye symptoms has been categorised into a number of complaints and clinical signs graded from one to four. These parameters include discomfort, 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 1References:

1) Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, Liu Z, Nelson D, Nichols JJ, OD, Tsubota K, MD, Stapleton F. TFOS DEWS II Definition and Classification Report. The Ocular Surface 15:276-283; 2017.

2) Behrens A, Doyle JJ, Stern L, Chuck RS, McDonnell PJ, Azar DT, Dua HS, Hom M, Karpecki PM, Laibson PR, Lemp MA, Meisler DM, Del Castillo JM, O'Brien TP, Pflugfelder SC, Rolando M, Schein OD, Seitz B, Tseng SC, van Setten G, Wilson SE, Yiu SC. Dysfunctional tear syndrome. A Delphi approach to treatment recommendations.

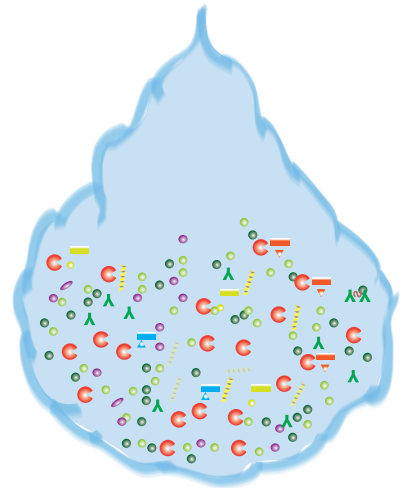
Dry eye disease

Table 1: Dry eye severity grading scheme

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	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.

Reprinted with permission from Behrens A, Doyle JJ, Stern L et al. Dysfunctional tear syndrome; A Delphi approach to treatment recommendations. Cornea 2006;25:900-7.



The Epidemiology of Dry Eye Disease

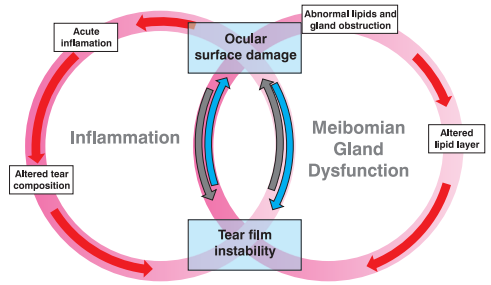
Introduction

Epidemiology is the science that studies the distribution, patterns, causes, effects and determinants of health and disease in defined human populations . Epidemiology evolves with the changes taking place in society and the emergence of new diseases (Frérot et al., 2018). With this in mind, the current pandemic with Covid-19 might significantly alter the epidemiology of various diseases, including DED. All general currently available data for population statistics is based on established population stability. This stability, regretfully, belongs to the pre-pandemic time. As DED is mainly a disease of the elderly, the disproportional impact on this age group on the population as target for the corona-viruses may , at least temporarily, affect current statics and epidemiological models, especially DED. Recognized as a multifactorial disease of the tears and ocular surface symptoms, the clinical signs of the disease vary widely. This has been extensively illustrated in the work of the Epidemiology Subcommittee of the TFOS DEWS II, Dry Eye Work Shop (DEWS) recognizing dry eye disease (DED) as a disturbance of the Lacrimal Functional Unit (LFU), comprising the lacrimal glands, ocular surface, lids, as well as nerves that connect them (DEWS I).

After this, DEWS II (2017) identified the loss of tear film homeostasis as key to the development of DED. After this the TFOS DEWS II report (2017) updated the definition of dry eye to: "Dry eye is 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."

DEWS II states a prevalence on symptoms alone in the age group of 20 – 40 years to be between 10 and 20% whereas using clinical signs as criterion the prevalence showed a wide variation between 14.5 % and 52.4% reflecting the impossibility to give a number for global prevalence. The correlation of increased prevalence of DED with age is greater when using clinical signs such as TBUT, Schirmer test and corneal fluorescein staining than when compared to symptom reports. Notably there is a peak increase in the 40 - 50 year old group considering the prevalence of DED in which immune-mediated disease and ocular surgery have been shown to be as important risk factors in women pointing out gender as another decisive parameter (DEWS II). Other factors contributing to a higher prevalence seem to be race, continuous contact lens wear, hematopoietic stem cell transplantation, Sjögren syndrome, use of visual

displays, environmental exposures, as well as nutritional issues such as Vitamin A deficiency. Others included refractive surgery, diabetes as well as psychological disorders



The description of a vicious cycle illustrated connection between the key elements of multicausality (Baudouin 2007). As DED is a rapidly changging field increasing insights future studies will reveal further insights and possible changes in the definition. The nature of the disease and it's perception reflects on the detectability and diagnostic possibilities. Consistency of complaints and redundancy reflects on the reported or detectable incidence, thus influences significantly the epidemiological data. The epidemiological insight about ocular surface disease and dry eye disease suffers from the insufficiency and heterogeneity of it's diagnostics and terminology as well as definitions. The introduction of guidelines for an algorithm for diagnostics of severe DED has significantly facilitated this issue (Baudouin et al., 2014). Minor and occasional complaints are often not considered significant enough to be added to the known incidence, emphasizing the enigma of dissociation between signs and symptoms (Sullivan 2012). The seasonal characteristics of less severe dry eye disease (van Setten et al., 2017) do not make dry eye epidemiology or demographics any easier.

New models of DED such as the anatomical dry eye (van Setten 2017) or surgically induced dry eye, further complicate the estimation of the numbers as to incidence and distribution of DED in a population. Even if we restrict to the clinical significant and treatment requiring conditions of tear film deficiencies, recently suggested measurable values as decision aids such as osmolarity >308 mOsmol /L (Craig et al 2017) have been questioned by the introduction of osmokinetics, i.e. the significance of daily variation of osmolarity (van Setten 2019, van Setten 2020). This approach offers a new option to define DED and facilitate the epidemiological need for clear diagnostics. Although interpretation and thresholds may vary, DED diagnostics are still dependent on the tear breakup time (TBUT) , Schirmer test score and fluorescein score and which remain the main clinical observation tools (Stapleton et al. 2017). The basis for epidemiology based on the diagnostic of an specialized eye care provider, has been weakened by the common accessibility of various tear fluid substitutes and lubrication agents, internet education and social networking. The current pandemic will further decrease the visit of patients with simple DED complaints at their eye specialist as a result of recommended social distancing. More than ever before indirect evidence and known causal relationship for DED and other comorbidity, age or gender will serve as basis of updated epidemiological data reflecting epidemiology. Still, in Scandinavia, the definition of dry eye is simply that the tear film does not function properly (Hedqvist 2020). For keratoconjunctivitis sicca (KCS) and Sjögren syndrome (SS) the Copenhagen criteria have become less useful as the

use of Rose Bengal has decreased significantly (Prause et al., 1987) and DEWS II offers an updated approach.

One of the hallmarks of DED is still the topical irriation, leading to the establishment of the diagnosis. The effects of friction (Bron et al.. 2017) and attrition (van Setten 2020) may to a large extent occur before any detectable ocular surface signs characteristic of DED. Any epidemiological study also needs to cover the seasonal aspects of dry eye disease (van Setten et al., 2016). It is the symptoms that most heavily impact the current epidemiological picture of dry eye and ocular surface disease. However, there is still no consensus on which combination of tests should be used to define the disease. (Willcox et al., 2017) .

Evaluating the epidemiology of DED has the difficulty that individual research groups in various reports have used different operational definitions of dry eye. Apparently, various stages of the disease favor various investigations. The lack of correlation between patients' irritative ocular symptoms and the results of selected clinical tests for dry eye (Nichols et al. 2004, Sullivan et al., 2012) can be explained by, amongst others

- 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.

Prevalence

Prevalence of DED describes the presence of this condition within a population at a given point in time. Identification of existing cases is dependent on the diagnostics. Any estimates for the prevalence of DED hence vary depending on the operational definition used and the characteristics of the population studied. Acknowledging the inherent diagnostic difficulties (Willcox et al., 2017) the DEWS Subcommittee examined data from a number of large cohort studies and concluded that the prevalence of DED in a population varies between 5% and 50% (Stapleton et al., 2017) . The quality of life is affected in 10–30% of the human population worldwide (Gayton 2009). Data from the largest study so far including nearly 37 000 patients revealed that in Americans aged 50 or older 14.5 % of all women and 9.3 % of all men have dry eye, i.e. a total of 4.91 Million (12.3% of the population) (Schaumberg et al., 2003) Naturally there is an increased incidence of DED with age. One study found that more than 54% of patients over age 65 and 43% of the female patients had their dry eye underestimated by their clinician (Asbell et al. 2010). This is an important aspect for the prevalence of DED in Nordic Countries as the population is older compared to other countries. Age is the foremost risk factor for developing DED (Stapleton et al., 2017). A Danish Study revealed the prevalence of Sicca Symptoms and secondary Sjögrens Syndrome amongst RA patients to be at least 18 % and 3.6% respectively (Haga et al., 2012) . The frequency of KCS for persons aged 30-60 years in Copenhagen was estimated to be 11% while the frequency of primary Sjögren's syndrome is between 0.2%

and 0.8% according to the Copenhagen criteria (Bjerrum 1997) . A Swedish study investigating a 52-72 year old population, showed a prevalence of KCS of 15.9% and of primary Sjogren's syndrome of 2.7% . (Jacobsson et al., 1989). In 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 an abnormal TBUT (Atladóttir et al., 2000). In the Norwegian Hordaland study (2008) the prevalence of primary Sjogren's syndrome among 40-44 and 71-74 years old Norwegians was 0.22% and 1.4% respectively, using 1996 criteria (Haugen et al., 2008). The TFOS DEWS II report confirmed that the prevalence of dry eye increased linearly with age, and Similarly, female sex is consistently associated with DED. (Sullivan et al. 2017). Scandinavian countries are known to have a shift of the population, increasing the incidence of DED. This is evident when comparing the mean age of for example Sweden and Finland to other countries. As the median age is lower in the Nordic countries, this means that the future will also lead to a higher prevalence of DED.

Median of age in years

Country	Total	Male	Female	Rank of 186
Japan	47.3	46.0	48.7	2
Germany	47.1	46.0	48.2	3
Finland	42.5	40.9	44.3	26
Denmark	42.2	41.2	43.2	30
Sweden	41.2	40.2	42.2	41
Norway	39.2	35.9	40.0	57
Iceland	36.5	35.9	37.1	71

Human Development Report 2019 age (median)

Life expectancy in years

Country	Male	Female	Both	Rank of 186
Monaco	85.6	93.5	89.4	1
Japan	81.9	88.8	85.3	2
Iceland	80.9	85.4	83.1	6
Sweden	80.2	84.2	82.1	16
Norway	79.8	84.0	81.9	21
Finland	78.0	84.1	81.0	31
Denmark	77.1	82.1	79.5	47

Data from CIA The World Factbook/ Median Age 2018. Retrieved 03/12/2017

Additionally another study found that clinician assessment underestimated dry eye severity in 41% of patients by at least one grade compared with the patients' self-assessment. (Chalmers et al., 2005). Notably there is a link between prevalence of DED to psychological issues such as depression. Patients with diagnosed DED The TFOS DEWS II report confirmed that the prevalence of dry eye increased linearly with age, and Similarly, female sex is consistently associated with DED. (Na et al., 2015). This association between depression and DED was shown to be statistically significant (van der Vaart et al., 2015). This, however, may also be season related and hence has importance for the estimation of prevalence of DED in Scandinavian countries, such as in seasonal affective disorders (SAD) (Kurlansik et al., 2012) and its associated side effects with the medications used.

Dry eye disease

Incidence

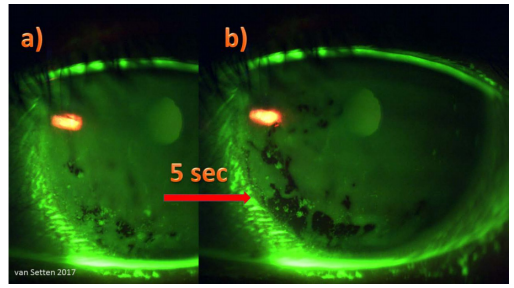
The rate of new or incident cases of a DED over time, has been estimated to be higher in women (25%) than men (17.3%) confirming age as a risk factor for increased incidence. However, there is considerable variability between the currently available studies. Describing new cases of DED encompasses the seasonal increase of DED during winter and dry air conditions; an increase in incidence that could also be linked to Seasonal Affective Depression (SAD). As this psychological condition increases with latitude (Kegel et al 2009) it might play an important role for the Northern Countries and the incidence of DED. The incidence of DED in this patient group could in turn be enhanced by the occurrence of undesired side-effects of the drugs used for the treatment of depression (Koer et al., 2015). Pharmacology may play an important role in the epidemiology of DED as aging comes with increasing polypharmacy which could further trigger the increase of observed or reported dry eye sensation (Gu et al., 2010). The specific side effects of drugs can also be found updated both on the national websites such as FASS as well as at the National Registry of Drug-Induced Ocular Side Effects website http://www.eyedrugregistry.com. Often conditions like rheumatic disease and other connective tissue diseases bypass the diagnosis of dry eye.

Within ophthalmology the biggest patient group who constantly challenge their ocular surface balance by the application of topical drops are those with glaucoma. It is not until recently that several excipients preservatives like Benzalkonium choride (BAK)(Baudouin et al., 2008). Even with unpreserved eye drops does the increased friction after external filtration surgery causes attrition and epitheliopathy requiring treatment. (van Setten 2018). Additionally, although the Scandinavian outdoors climate is not extreme, weather conditions do lead to an increased exposure of the ocular surface to wind and subzero temperatures during winter time which constitute environmentally challenging conditions outlined in the TFOS DEWS II report. The geographical location of Scandinavia and the high percentage of its population working within areas of finance, administration, governance, management and communications, contribute to a significant exposure of the population to an adverse indoor environments. Drafts, smoke, dust and low air humidity significantly contribute to the prevalence of dry eye disease.

The increasing number of operations affecting the ocular surface such as cataract and glaucoma surgeries paired with its availability in the Northern Countries favours an increased incidence of DED, that at least in part may be attributed to the anatomical dry eye (van Setten 2017). However, in this subgroup of DED is often temporary or when persistent, potentially treatable. Therefore, the anatomical or post surgical dry eye needs to be identified with its two hallmarks: presence of a **constant location** of tear film break up and, 2. its **constant appearance** (spreading pattern).

Typical appearance of the anatomical dry eye: Localized premature (early) break up of the fluorescein layer in tear film over a region with

Dry eye disease



minimal topographical abnormalities. (Van Setten, G. (2017) The Anatomical Dry Eye—A Different Form of Ocular Surface Disease Deserves Focus. Open Journal of Ophthalmology, 7, 184-190.).

The severe impact of DED on public health is emphasized by the results of investigation on the Quality of Life (QoL) in patients with DED such as recently reviewed (Stapleton et al. 2017) Identifying the Issue, Dry Eye Questionnaires Although there is a plethora of tests available, they all show that the impact of dry eye on quality of life (QoL) is mediated through pain and irritative symptoms, decreased ocular and gen[1]eral health, and also effect on visual function and performance (Schiffman et al. 2000, Rajagopalan et al. 2005). The need for frequent instillation of lubricant eye drops and the cost of treatment add to the impact. With direct treatment costs of > 750 US$ per patient & year this amount with work productivity loss and societal impact to > 55 billion US$ annually only for DED for the US population alone. Correct identification of the disease seems of major importance worldwide.

Questionnaires are employed in clinical practice to screen individuals for the diagnosis of dry eye and identifying the intensity of the disease. In both clinical practice and reaearch they are used 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 the disease. The purpose of a questionnaire affects the content and nature of the investigation. The Epidemiology Subcommittee evaluated the published dry eye symptom questionnaires in DEWS II in detail (Stapleton et al., 2017).

These tests vary in length, intended use, population in which they were tested, mode of administration and extent of validation. Instead, a set of several standardized, validated questionnaires suitable for a variety of purposes and available to investigators would be desirable. One of the most common and frequently used test is the OSDI (Ocular Surface Dry Eye Index) test (http://www.supereyecare.com/resources/OSDI.pdf; even available as a free App: https://apps.apple.com/us/app/dry-eye-osdi-questionnaire/id849849034)

Facilitating the Diagnosis of Dry Eye: Questionnaires

Dry eye diagnostics should be easy and time efficient. 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 specified.

Other important points include the ability to set a threshold of of disease severity 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 the 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. For detailed information please see DEWS I and The TFOS DEWS II report.

Impact on Visual Function

This impact on Visual function has been reviewed recently (Kaido 2018) . To assess the effect of dry eye on visual function and QoL, the Ocular Surface Disease Index (OSDI) and the Impact of Dry Eye on Everyday Life (IDEEL) questionnaire have been developed and validated specifically for research on the impact of dry eye (Gulati et al., 2006) . Patients with DED are significantly ($p < 0.001$), and 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. Corneal topography helps us visualise and quantify this by different surface regularity indices. In non-SS keratoconjunctivitis sicca patients, daily roles consistently limited, bodily pain or discomfort caused, decreased vitality or energy, perceptions of health, physical functioning, social functioning, and role-emotional limitation were all linked to increased severity of dry eye symptoms. (Rajagopalan et al., 2005).

Impact of Surgery

Dry eye is known to occur following refractive surgery as LASIK (Hammond et al., 2005) sometimes involving decreased corneal sensation due to disruption of trophic sensory support to the denervated region leading to Lasik-Induced Neurotrophic Epitheliopathy (LINE) with reduced blinking and lacrimal secretion (Ambrosio et al. 2008, Wilson 2001. Toda et al., 2001). The extent of preoperative myopia and hence the ablation depth seems to be correlated with the risk of DED (de Paiva et al., 2006). Even photorefractive keratectomy (PRK) may cause milder DED complaints (Rajan et al., 2004) just as LASIK, at least during the first postoperative year. Dry eye may negatively affect ocular wound healing and lead to refractive regression.

Only in recent years cataract surgery (Naderi et al., 2020) as well as glaucoma surgery been identified as potential risk factor for (temporary) DED. Here postoperative treatment with lubricants may play an essential role as surface desiccation may negatively affect ocular wound healing.

DED ocular premorbidity

DED can cause contact lens intolerance with discontinuation of contact lens wear and have a negative impact on refractive surgery outcomes, especially in glaucoma patients. Its presence influence the choice of surgery.

Low air humidity, computer use with low blinking rates and wide ocular aperture are known to cause ocular irritative complaints due to increased tear evaporation, disclosing tear film insufficiencies.

DED Comorbitity

DED needs to be considered with increased number of transplantation surgeries, graft versus-host disease (GVHD) , immunosuppressive therapy in autoimmune diseases (Sjögren's syndrome) as well as cancer therapy with cytotoxic medications and radiation. Here rapid diagnosis and therapy may be decisive to preserve vision in the presence of potentially rapidly developing progressive dry eye disease

Summary

DED is more frequent in the aged and in females. With increasing age and life expectancy of the population in the Nordic Countries an increased prevalence is to be expected. This may be triggered by surgery engaging the ocular surface such as refractive laser but also cataract and glaucoma surgery. Aspects of seasonality play a role in the incidence as well as comorbidity and polypharmacology and psychological aspects such as SAD. Additionally, to these intrinsic factors several external and environmental factors play a role in the enhanced prevalence of DED in Nordic Countries. DED is not necessarily a continuous disease but it can be episodic and seasonal, too

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Diagnosis and monitoring dry eye disease

Introduction

Dry eye disease (DED) is one of the most common ophthalmological reasons for an eye examination. Therefore, it is important that the diagnosis and monitoring of DED are reliable and effective. Primary methods to diagnose and monitor DED are shown below. The primary methods include symptomology questionnaires. fluorescein tear break-up time (FBUT), Ocular surface staining, Schirmer's test,

meniscometry, lid parallel conjunctival folds and Meibomian gland evaluation (Wolffsohn et al., 2017). 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 DED.

Primary methods to diagnose and monitor dry eye disease

Symptomology questionnaires

Subjective diagnosis should be performed by standardized questionnaires. Several symptom questionnaires have been developed to diagnose and monitor DED, such as Dry Eye Questionnaire (DEQ), 5-Item Dry Eye Questionnaire (DEQ-5), Dry Eye-Related Quality-of-Life Score (DEQS), Impact of Dry Eye on Everyday Life (IDEEL), McMonnies dry eye history questionnaire (MQ), Ocular Comfort Index (OCI and OCI-C), Ocular Surface Disease Index (OSDI), National Eye Institute´s Visual Function Questionnaire (NEI VFQ-25), Symptom Assessment in Dry Eye (SANDE) and Standard Patient Evaluation of Eye Dryness (SPEED) (Amparo et al., 2015; Stapleton et al., 2017). In these questionnaires, patients are asked to describe their symptoms and assess the impact and duration of symptoms according to the 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. The questionnaires are an important tool to incorporate in routine eye examinations.. Questionnaires are also important in the monitoring of DED progression. The OSDI is a good choice for clinicians unfamiliar with dry eye questionnaires. The most used OSDI includes twelve questions and it is assessed on a scale from 0 to 100, with higher scores representing a greater disability. An OSDI score of ≥20 indicates a diagnosis of DED. So far, patient symptoms are the most sensitive indicator for DED (Wolffsohn et al., 2017).

Fluorescein tear break up time (FTBUT) and vital ocular surface staining

Fluorescein tear break-up time (FTBUT), also called tear film break-up time (TBUT), measures the stability of the tear film in biomicroscopy or hand ophthalmoscope examination. The fluorescein dye is applied onto the outer surface of the eye either directly from a vial or fluorescein sodium-impregnated filter strip. A patient is asked to blink three times and then keep the eyes open. A blue excitation filter from a hand ophthalmoscope or biomicroscopy is reflected onto the cornea. The time between the last blink and the formation of small dry areas on the corneal surface is called FBUT (Fig. 1). Stable fluorescein staining for >10 seconds have been considered to be normal (Lemp and Hamil

Diagnosis and monitoring dry eye disease

1973). Although the assessment of FBUT is very simple in theory, there is large inter-observer variations. FBUT also changes easily according to the fluorescein volume.

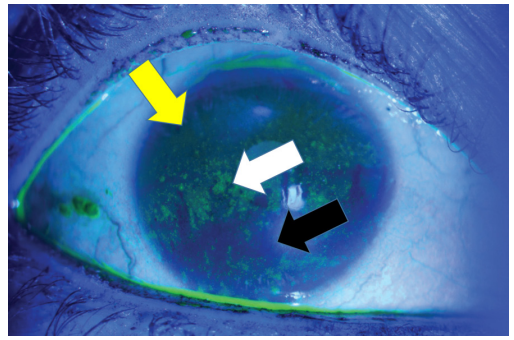

Fig. 1. *Tear film break-up time (TBUT) and vital staining using fluorescein dye. Yellow arrow indicates a stable staining, black arrow dry area and white arrow punctates.*

Biomicroscopic evaluation and ocular surface staining

In biomicroscopic examination an injured epithelium can often be seen even without a dye as punctate epitheliopathy and cloudy cornea. Dyes enable visualization of the more superficial and minute epithelial changes. Fluorescein and Lissamine green dye bind to the damaged corneal epithelium and is seen as a punctate staining pattern on the cornea and conjunctiva (Fig. 1). Dyes are left on the ocular surface for 30 seconds prior to analysis. The staining grading scales are demonstrated in van Bijsterveld system (van Bijstervald 1969), National Eye Institute/Industry Workshop guidelines (Lemp 1995), Collaborative Longitudinal Evaluation of Keratoconus (CLEK) schema (Barr et al., 1999), A-density combination index (Miyata et al., 2003), Oxford staining score (Bron et al., 2003), and in Ocular staining score (Whitcher et al., 2010). Clinical staining signs should be compared against standard charts. The Oxford grading scheme is one of the standard methods to analyze severity level of DED (Fig. 2).

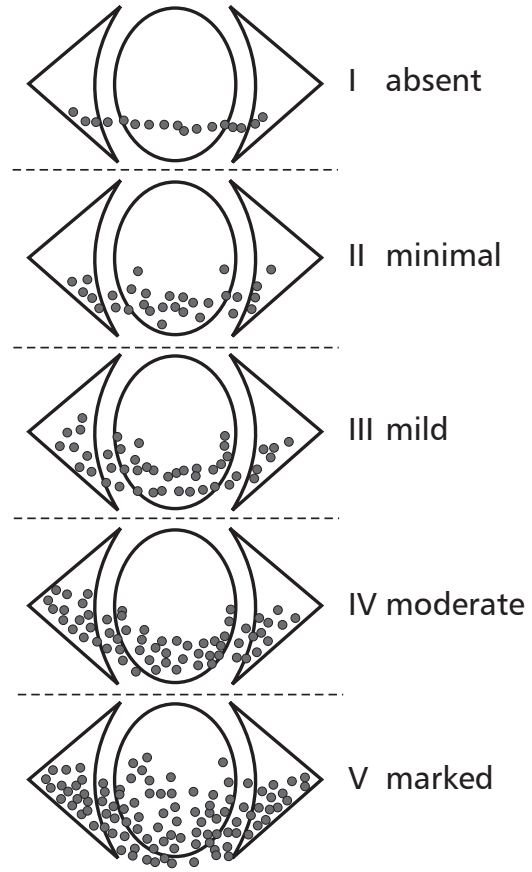

Fig. 2 *Schematic Oxford grading scale indicating punctate staining on conjunctiva and cornea*

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Schirmer's test

The Schirmer's test is used to determine whether an individual produces enough tears. Calibrated strips of a non-toxic filter paper (5x35 mm) are used. The free end of the strip is placed at the temporal third part of the lower eyelid without anaesthesia (Fig. 3) and both eyes are gently closed for 5 minutes.

Fig. 3. *Schirmers test*

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 millimeters. Note that measurement starts at the notch of the paper. (Fig. 3). Schirmer scores >10 millimeters are considered normal. The diagnostic cut-off for OSD is documented to be from ≤ 5 mm to ≤ 10 mm in 5 minutes (deMonchy et al., 2011; Wolffshon et al., 2017). The test can also be performed with topical anaesthetic eye drops to prevent the lacrimation due to irritation of the conjunctiva from the paper strips (basal tear production). It is nimportant that the anaesthetic eye drop is dried from the conjunctiva before placing the paper strips.

Meniscometry

Tear meniscus radius of curvature (TMC), height (TMH), width (TMW) and cross-sectional area (XSA) are advised to be measured using images due to observational analysis.
An image (fig 4.) is focused on the centre of the lower lid after a blink (Johnson et al., 2007). TMC, TMH and XSA were all reduced in magnitude in the dry eye group compared to the control group (mean ± SD; TMC: 0.314 ± 0.160 mm vs. 0.545 ± 0.259 mm, TMH: 0.244 ± 0.089 mm vs. 0.461 ± 0.173 mm, XSA: 0.0082 ± 0.0048 mm2 vs. 0.0176 ± 0.0103 mm2 (Mainstone et al., 1996).

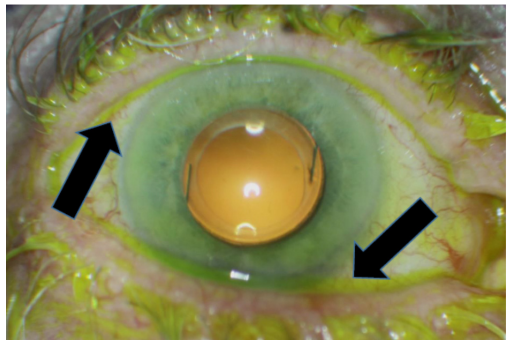

Fig. 4. *Arrows indicate tear meniscus in photographs.*

Lid parallel conjunctival folds

Lid parallel conjunctival folds (LIPCOF) are folds in the nasal or temporal part of the bulbar conjunctiva parallel to the lower lid margin. LIPCOF can be differentiated from conjunctivochalasis by its location outside the central part. LIPCOF is graded to 0=no folds, 1 = one permanent and one parallel fold, 2 = two permanent and other folds and 3= more than two permanent folds (Pult et al., 2011). LIPCOF can be observed

Diagnosis and monitoring dry eye disease

without fluorescein staining by using a slit-lamp microscope 16-25x magnification

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). 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 (Korb et al., 2008). It is best to remove the biofilm which may seal the gland orifices. This is known as lid debridement and can be performed with certain instruments. After successful debridement, gentle pressure can be applied for Meibomian gland evaluation. (Fig. 5B) (Wise et al., 2012).

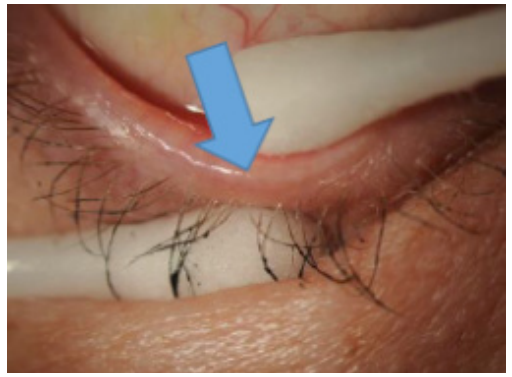

Fig. 5A. *Meibomian gland evaluation using a cotton wool applicator. An arrow indicates Meibomian glands on photographs.*

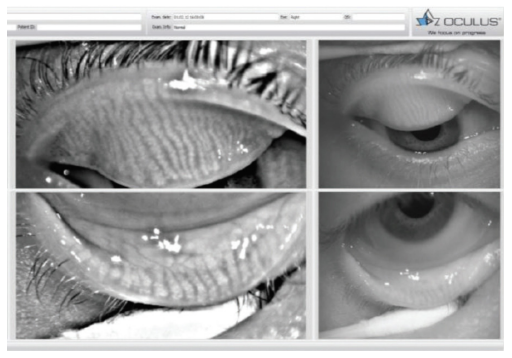

Fig. 5B. *Meibography showing normal Meibomian glands without drop out*

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Tear film osmolarity

Tear osmolarity is one of the most important tests to demonstrate the severity level of DED (Potvin et al., 2015). Tear film osmolarity is measured using a method to simultaneously collect and analyze the electrical impedance of a tear sample. A tear sample (approx. 50 nL) is collected from the lower meniscus of the eye by passive capillary filtration (Fig. 6). Osmolarity readings are given in milliosmoles per liter (mOSMs/L). Normal osmolarity values are 302 +/-8.3 mOsm/L. In mild to moderate cases of DED osmolarity values changes between 315.0 +/-11.4 mOsm/L and in severe cases the osmolarity is 336.4 +/-22.3 mOsm/L (Willcox et al., 2017). Osmolarity cut-off values to mild DED is 308 mOsms/L and 316 to severe DED.

Fig. 6. *Tear film osmolarity analysis*

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 (Fig. 7). Unfortunately, it is very time-consuming and the instruments are expensive (Smedowski et al., 2017). Furthermore, most findings are non-specific and common grading systems are not available. Aberrometry, on the other hand provides a non-invasive procedure to see the optical quality of the cornea and it can be used to assess the tear film instability. The instruments, however, are expensive, findings are non-specific, and the quality of the blink and the wetting of the cornea influence the results.

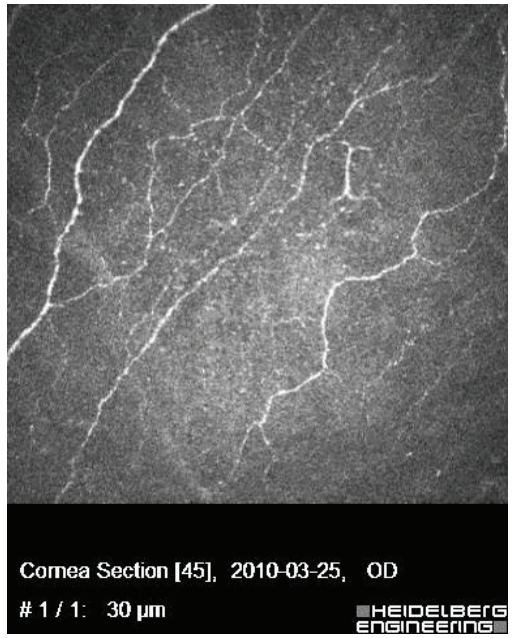

Fig. 7. *In vivo confocal microscopy showing corneal nerves*

Diagnosis and monitoring dry eye disease

Inflammatory markers

The molecular level analysis of DED covers inflammatory markers, such as matrix metalloproteinases (MMP), interleukins, and chemokines (Fig. 8). However, the increased expression of inflammatory markers is quite/rather non-specific and thus far there is not much clinical evidence that one inflammatory biomarker correlates well with the severity of the disease. Currently, these methods are mostly for scientific use.

Fig. 8. QUIDEL InflammaDry Test for detection of MMP9

Impression cytology

Impression cytology provides a very good estimate of the amount of goblet cells, limbal cell deficiency, ocular surface neoplasia and specific viral infections (Tole et al., 2001). This method requires an experienced laboratory and an expert to analyze the samples (Fig. 9).

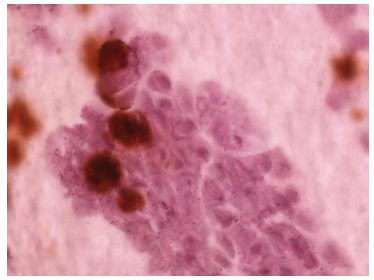

Fig. 9. Impression cytology demonstrating the presence of goblet cells

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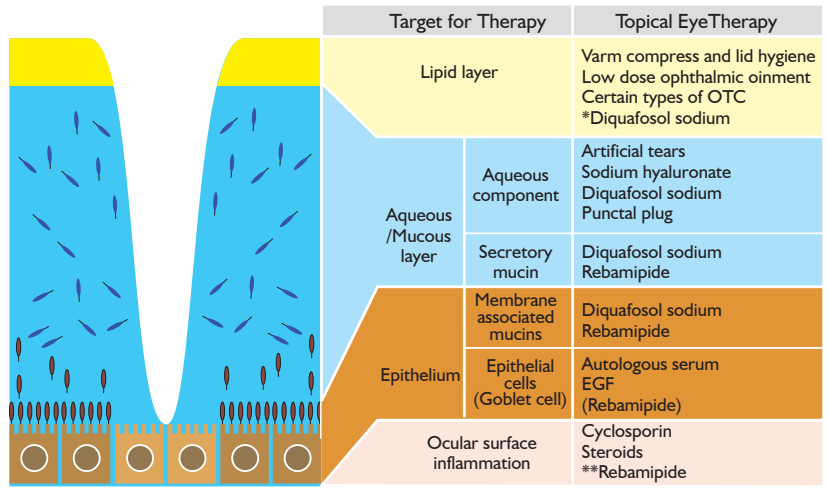
Management and therapy of dry eye disease

Treatment recommendations

The International Dry Eye Workshop I (DEWS I) presented a novel evidence-based approach to the management of Dry Eye Disease (DED) graded by the level of disease as demonstrated in Table 1. 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 (TBUT), 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. Likewise, the International Workshop on Meibomian Gland Dysfunction (Geerling et al., 2011), presented a similar evidence-based treatment algorithm for MGD with four stages of disease as demonstrated in Table 2. The International Dry Eye Workshop II (Jones et al., 2017) introduced a revised classification scheme that incorporates triaging elements to provide clarity in diagnosing DED from which the various etiologies can be considered, and an appropriate management plan can be instituted. The DEWS II report attempts to remove any perception of exclusivity in the classification of dry eye by indicating in the scheme that aqueous deficient and evaporative dry eye diagnoses exist on a continuum rather than as separate entities. The management algorithm presented in the DEWS II report does not represent a rigid stepwise approach, but should rather be viewed as an organizational tool to use when initiating treatment of DED, to select interventions likely to provide most benefit.

The following recommendations are based on The International Dry Eye Workshop I and II, and the International Workshop on Meibomian Gland Dysfunction.

Fig. 1. 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

I. TREATMENT FOR TEAR INSUFFICIENCY

1) Tear replacement approaches

a) Artificial tear substitutes

Artificial tear substitutes are considered the base of treatment in DED. The general properties of the lubricants currently available in the Nordic countries are presented in Table 3. 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 individualized, 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 individualized. Some of these patients will also need to use ointment at bedtime.

i) Viscosity agents

Macromolecules are added to the artificial lubricants to stabilise the lubricants and make them viscous. The viscosity-enhancing agents used in tear supplement formulations include carbomer 940 (polyacrylic acid), carboxymethyl cellulose (CMC), dextran, hyaluronic acid (HA), HP-guar, hydroxypropyl methylcellulose (HPMC), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP) and polyethylene glycol. HA is a naturally occurring anionic, non-sulfated glycosaminoglycan, and the range of commercial products that contain HA has increased in the last decade.

ii) Electrolytes

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.

iii) Phosphates

Dry eye products contain a wide variety of buffers to control pH value, including citrate, phosphate and borate buffers. The concentration of such buffers is critical, as reports exist of corneal calcification following extensive use of a dry eye product preserved with elevated levels of calcium phosphate (Lyndon Jones, et. al. 2017) The use of dry eye products containing phosphates should therefore be used with caution and it is recommended to use dry eye products without phosphate if the treatment is long term.

Management and therapy of dry eye disease

iv) Osmotic agents and osmoprotectants

As the core mechanisms of dry eye disease are driven by tear hyperosmolarity and tear film instability, hypoosmotic artificial tears have been developed. Furthermore, recent formulations also provide protection against the adverse effects of increased osmolarity (osmoprotection). Osmoprotectants such as trehalose, L-carnitine, erythritol, and betaine may directly protect cells against hyperosmolarity and thereby break the vicious circle of DED. It is therefore recommended to use hypoosmolar eyedrops in the treatment of dry eye disease.

v) 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 makes the tear film unstable and decreases TBUT. 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. It is recommended to use tear substitutes without preservatives (DEWS II).

b. Biological tear substitutes

Autologous serum eye drops have advantages compared to tear substitutes. Serums lack 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.

c. Other agents

Mucolytics are a group of substances that depolymerize mucin. The mucolytic eye drop acetylcysteine may reduce subjective symptoms of DED and can be used for palliative treatment of filamentary keratitis, which is a potential complication of DED.

d. Lipid supplementation

Lipid-containing drops are formulated as emulsions. Emulsions can be broadly categorized into three types, and this is dependent upon droplet size. Different types of lipids have been proposed to try to best mimic natural meibum. The types of lipids used include phospholipids, saturated and unsaturated fatty acids, and triglycerides. Phospholipids can be neutral (zwitterionic), negatively (anionic) or positively (cationic) charged. It appears that anionic phospholipids have a greater ability to increase lipid layer thickness than zwitterionic compounds as negatively charged phospholipids contribute to a stable interface between non-polar lipids at the surface of the hydrophilic aqueous layer.

2) Tear conservation approaches

a. Punctal occlusion

i) Punctal plugs

Punctal occlusion is indicated in aqueous deficient DED. 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.

ii) Surgical punctal occlusion

Permanent surgical closure of the punctum is typically reserved for patients who are unable to retain or tolerate punctal plugs. A wide variety of surgical methods exist, however, disposable, hand-held thermal cautery is the most widely used method in clinical practice.

b. Moisture chamber spectacles and humidifiers

Moisture chamber spectacles are eyeglasses specially designed to slow evaporation of the tears, by providing a humid environment and minimizing airflow over the ocular surface. Locally placed humidifying devices have also been proposed to enhance humidity or local air quality.

3) Tear stimulation

a. Topical secretagogues

Several topical pharmacologic agents that stimulate aqueous, mucin and/or lipid secretion are commercially available in certain markets, or under development. Diquafosol is a P2Y2 purinergic receptor agonist that activates P2Y2 receptors on the ocular surface as well as P2Y2 receptors in the Meibomian glands. Diquafosol stimulates both fluid secretion from the conjunctival epithelial cells and mucin secretion from the conjunctival goblet cells. Rebamipide is a quinolinone derivative that increases the secretion of both membrane-bound mucins from corneal epithelial cells and secreted mucins from conjunctival goblet cells, and increases the goblet cell count. Rebamipide is further shown to inhibit microvilli damage and has anti-inflammatory properties by inhibition of NFκB activation.

b. Nasal neurostimulation

An intranasal tear neurostimulator has been developed to induce normal tear production via stimulation of the nasolacrimal reflex.

II. TREATMENT FOR LID ABNORMALITIES

1) Anterior blepharitis

As anterior blepharitis may result in dry eye, lid hygiene using e.g. wipes or foams is important to reduce lipid by-products and lipolytic bacteria. Using sterile lid cleaning wipes are advised to reduce the bacterial overload.

Topical antibiotics such as fusidic acid, ofloxacin or azithromycin may be applied to overcome bacterial overcolonisation. Demodex infestation is a causative factor in many cases of intractable blepharitis and is often associated with dry eye symptoms, although there is currently no evidence to show a direct association with the development of MGD. Tea tree oil is a natural, essential oil from steamed *Melaleuca alternifolia* leaves that exhibits antimicrobial, anti-inflammatory, antifungal, and antiviral properties, and is toxic to Demodex. Tea tree oil may be toxic to the cornea. There are products on the market that contain terpinen-4-ol, the active compound extracted from Tea tree oil, but without the harmful Tea tree oil ingredients.

2) Meibomian gland dysfunction

a. General

The International Workshop on Meibomian Gland Dysfunction (Geerling et al.,2011), presents an evidence-based treatment algorithm for MGD with four stages of disease as shown in Table 2. 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

b. Meibum quality

Meibum quality is assessed in each of the eight glands which are located in the central third of the lower lid. The meibum quality from each gland is then graded using a scale from 0 to 3:

0, clear;

1, cloudy;

2, cloudy with debris (granular);

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

c. Expressibility

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.

d. Oxford staining

Oxford staining is s obtained by summing the scores of the exposed cornea and conjunctiva with score range, 1–5;

e. 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 as described above.

f. Eyelid warming and massage

Eyelid treatment consists of mechanical lid hygiene, eyelid warming, and massage of the eyelids on a regular basis, and is performed to improve the quality and quantity of the tear film lipids. Eyelid warming is applied to melt pathologically altered Meibomian lipids. Heat may be delivered using a warm compresses, eye warmer masks (Blephacura, TherapearI, Blepha Eyebag), or eyelid warming devices (Blephasteam).

g. Tetracyclines and azithromycin

The antibacterial and anti-inflammatory properties of tetracyclines and azithromycin are found to be beneficial in the treatment of MGD. A three month course of 250 mg of tetracycline is recommended to bring MGD under control. Furthermore, treatment with azithromycin 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.

h. Physical treatments

i. Debridement scaling

Debridement of the mucocutaneous junction and the keratinized lid margin removes accumulated debris and keratinized cells from the eyelid margin to allow increased flow of meibum into the tear film.

ii. Intraductal probing

Intraductal probing using probes (Maskin) of various lengths is a procedure to reopen blocked Meibomian glands and has been shown to improve symptoms and signs in DED.

iii. Forceful expression

Forceful expression of the Meibomian glands following topical anesthetics has been shown to improve symptoms, meibum quality, and lipid layer thickness.

iv. Intense pulsed light (IPL)

IPL (Eye-Light, E-Eye) delivers light within the infrared zone to the lower eyelid and is postulated to stimulate the parasympathetic nerve branches innervating the Meibomian glands.

v. Thermal pulse therapy

Thermal pulse therapy (LipiFlow) is designed to loosen, liquefy and express the hardened meibum that has blocked the Meibomian glands..

3) Treatment for corneal exposure

a. Entropion and ectropion

Management of both entropion and ectropion include tightening the canthal tendons and removing a cicatrix or other mechanical reasons for eyelid malposition.

b. Contact lenses

i. Therapeutic soft contact lenses (bandage lenses)

The purpose of a bandage contact lens (silicone hydrogel) is to improve ocular comfort and reduce the effects of an adverse environment. It has been suggested that bandage contact lenses may stabilize the tear film and assist with the restoration of epithelial cell turnover, and potentially aid in the management of corneal pain by insulating sensitized corneal nerves from environmental stimulation.

ii. Rigid gas permeable scleral lenses

Rigid gas permeable scleral lenses may play an important role in the management of moderate to severe DED, possibly due to the fact that they can provide a repository of tears between the lens and the ocular surface.

III. ANTI-INFLAMMATORY THERAPY

1) Topical glucocorticoids

Corticosteroids are effective anti-inflammatory agents in DED. Corticosteroids are found to significantly decrease ocular irritation symptoms, fluorescein and lissamine staining presumably by suppressing MMP-9, inflammatory cytokine expression and mitogen-activated protein kinase activation in the corneal epithelium. Studies have advocated steroid pre-treatment before the initiation of long-term topical cyclosporine, as steroids have provided faster symptom relief and improvement in ocular signs than topical cyclosporine alone. The long-term use of steroids is not without risk of complications and include ocular hypertension, cataract and opportunistic infections, even after short periods of use.

Preservative-free Hydrocortisone is recommended due to the low risk of side effects.

The penetration into the interior chamber is very low and an increase of the intraocular pressure is rarely seen compared to other steroid drops.

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2) Non-glucocorticoid immunomodulators

a. Cyclosporine

Cyclosporine is pivotal in the long-term treatment of the ocular surface inflammation underlying DED circumventing the potential side effects of steroids. Cyclosporine inhibits the calcineurin phosphatase pathway responsible for the transcription of T-cell–activating cytokines (such as IL-2). Cyclosporine also inhibits cytochrome c–mediated apoptosis and increases tear production (via the immunosuppressive activity) and increases goblet cell density. Cyclosporine is found to significantly decrease ocular irritation symptoms, conjunctival rose Bengal/lissamine staining, superficial punctate keratitis, and the expression of immune and inflammation activation markers.

b. Tacrolimus

Tacrolimus also inhibits the calcineurin phosphatase pathway responsible for the transcription of T-cell–activating cytokines and is a viable alternative for patients with intolerance to topical cyclosporine or in patients where the response to topical cyclosporine is poor.

c. Non steroidal anti-inflammatory drugs

Clinical trials have shown that NSAIDs may reduce ocular discomfort in patients with DED, but NSAIDs should be used with caution due to the risk of corneal melting in individuals with severe DED.

IV. SURGICAL APPROACHES

1. Tarsorrhaphy

Tarsorrhaphy is mainly performed in cases of persistent epithelial defects and reserved for severe dry eye that is refractory to medical treatments and punctal occlusion.

2. Lower lid blepharoplasty

Lower lid laxity and ectropion are most commonly treated with transcutaneous lower lid blepharoplasty.

3. Conjunctival surgery and amniotic membrane grafts

Individuals with conjunctival disorders such as pterygium, pingueculae, Stevens-Johnson syndrome, and mucous membrane pemphigoid often develop dry eye disease and may benefit from removal of the inflamed tissues and conjunctival reconstruction. Amniotic membrane grafts could be considered for persistent epithelial defects in cases of ocular cicatricial pemphigoid, Stevens-Johnson syndrome and other severe OSD.

4. Treatment for conjunctivochalasis

In severe cases of conjunctivochalasis that do not respond to ocular lubricants, topical cyclosporine or punctal occlusion, resection of the excessive conjunctival tissue may be considered.

5. Major salivary gland transplantation

In severe dry eye, the parotid gland and the submandibular gland may be transplanted to the subconjunctival space.

V. DIETARY MODIFICATIONS

There is growing evidence that diet and nutritional supplementation play a role in DED.

Essential fatty acids (EFA) administered orally are found to significantly decrease ocular irritation symptoms and ocular surface staining. However, the role of ω-3 and/or ω-6 EFA supplementation for treating DED is not yet completely understood. The DREAM study assessing the efficacy and safety of fish oil versus olive oil (placebo) demonstrated that dry eye symptoms and signs improved in both fish oil and olive oil users during the study. Surprisingly, improvement was not significantly different between the groups. The study was, however, criticized for its design e.g. the choice of olive oil as placebo and the potential confounding due to additional specific dry eye therapy including anti-inflammatory treatment. Clearly, further research is warranted

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Management and therapy of dry eye disease

VI. LOCAL ENVIRONMENTAL CONSIDERATIONS

a. Systemic medications

Dry eye has been reported in individuals using antihistamines, beta-blockers, antidepressants, diuretics, anxiolytics, antipsychotics, anti-Parkinsonian drugs, isotretinoin, estrogen therapy and systemic chemotherapy. The strategies to reduce or eliminate systemic drug-induced side effects include dose adjustments, discontinuation of the drugs, switching to another medication or more aggressive management of the induced dry eye.

b. 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, Air conditioning in the car or air from outside if car windows are open, or with the heating fan in the car pointing directly at the face), cigarette smoke, and evaporation of 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.

References

1. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007). The ocular surface 2007;5:163-78.

2. Geerling G, Tauber J, Baudouin C, et al. The international workshop on Meibomian gland dysfunction: report of the subcommittee on management and treatment of Meibomian gland dysfunction. Invest Ophthalmol Vis Sci 2011;52:2050-64.

3. Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. Ocul Surf. 2017 Jul;15(3):575-628.

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

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

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); and 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;

Tear supplementation: Lubricants

DROPS									
		Supplement of:							
Product	Viscosity	Water	Lipid	Mucin	Contact lens Yes or No	Use after open. mth.	Preser-vatives	Phos-phates	Pack-age
CLASS: Carboxymethylcellulose (CMC)									
Cellufluid	Low	Yes	No	Yes	Yes	Unidosis	-	No	Pipette
Celluvisc	Low	Yes	No	Yes	Yes	1	-	No	Pipette
Optive	Low	Yes	No	Yes	Yes	6	Purite	No	Bottle
Optive Plus	Low	Yes	Yes	Yes	No	3	Purite	No	Bottle
Optive Fusion	Low	Yes	No	Yes	Yes	3	Purite	No	Bottle
Refresh Tears	Low	Yes	No	Yes	Yes	6	Purite		Bottle
CLASS: Hydroxypropyltrimethylammonium (HPMA) + Povidone									
Tears Naturale II	Low	Yes	No	Yes	Yes	1	Polyquad	No	Bottle
						Unidosis	-	No	Pipette
CLASS: Hydroxymethylcellulose (HPMC)									
Artelac	Middle	Yes	No	Yes	After 15 min.	1	CTRM*	Yes	Bottle
					Yes	Unidosis	-	Yes	Pipette
Bion Tears	Low	Yes	No	Yes	Yes	Unidosis	-	No	Pipette
Isopto Plain	Low	Yes	No	Yes	No	1	BAC	Yes	Bottle
						Unidosis	-	Yes	Pipette
Dacriosol	Low	Yes	No	Yes	Yes	1	BAC	No	Bottle
Hyprosan	Low/middle	Yes	No	Yes	Yes	1	-	Yes	Bottle
Viscous eye drops	Low	Yes	No	No	Yes	1	BAC	Yes	Bottle
CLASS: PEG + Sodium Hyaluronate									
Blink Intensive Triple Action	High	Yes	Yes	Yes	Yes	3	PHMB	No	Bottle
Blink Intensive Tears	Low/middle	Yes	No	Yes	Yes	1.5	OcuPure	No	Bottle
						Unidosis	-	No	Pipette
Blink Intensive Tears Plus	Middle/high	Yes	No	Yes	Yes	1.5	OcuPure	No	Bottle
CLASS: HP Guar + PE/PEG									
Systane Ultra	Low/middle	Yes	No	Yes	Yes	3	-	No	Bottle
CLASS: HP Guar + PE/PEG + Sodium Hyaluronate									
Systane Hydration	Middle	Yes	No	Yes	Yes	1-3	-	No	Bottle
						3	Polyquad	No	Bottle
CLASS: Polyvinyl alcohol (PVA)									
Refresh Classic	Low	Yes	No	Yes	No	1	BAC	No	Bottle
Sincon	Low	Yes	No	Yes	No	Unidosis	-	No	Pipette
CLASS: Povidone									
Oculac	Low	Yes	No	Yes	No	1	BAC	No	Bottle
					Yes	Unidosis	-	No	Pipette

* CTRM: Cetrimide

Tear supplementation: Lubricants

DROPS (continued)									
		Supplement of:							
Product	Viscosity	Water	Lipid	Mucin	Contact lens Yes or No	Use after open. mth.	Preser-vatives	Phos-phates	Pack-age
CLASS: Sodium Hyaluronate									
Hyabak	Low	Yes	No	Yes	Yes	3	-	No	Bottle
Hylo-Comod	Middle	Yes	No	Yes	Yes	6	-	No	Bottle
Hylo-Gel	High	Yes	No	Yes	Yes	6		No	Bottle
OsmoTears Low	Low	Yes	No	Yes	Yes	3	-		Bottle
OsmoTears Ultra Low	Low	Yes	No	Yes	Yes	3	-		Bottle
Oxyal	Low/middle	Yes	No	Yes	Yes	2	Oxyd	No	Bottle
Tearsagain Eye drops	N/A	Yes	No	N/A	Yes	3	-	No	Bottle
Blink Contacts	Low	Yes	No	Yes	Yes	1.5	Ocupure	No	Bottle
Comfort Shield MDS		Yes	No	Yes	Yes	6	No	Yes	Bottle
Comfort Shield SD		Yes	No	Yes	Yes	Unidosis	No	Yes	Pipette
CLASS: Sodium Hyaluronate + Dexpanthenol									
Hylo-Dual Care	Middle	Yes	No	Yes	Yes	6	-	No	Bottle
CLASS: Sodium Hyaluronate + Ectoin									
Hylo-Dual Intense	High	Yes	No	Yes	No	6	-	No	Bottle
CLASS: Sodium Hyaluronate + Euphrasia Officinalis									
Hylo-Fresh	Low	Yes	No	Yes	Yes	6	-	No	Bottle
CLASS: Lipids									
Thealipid	Low	Yes	Yes	No	15 min. after administration.	3	No	No	Bottle
CLASS: Trehalose									
Thealoz	Low	Yes	No	Yes	Yes	3	-	No	Bottle
CLASS: Trehalose + Sodium Hyaluronate									
Thealoz Duo	Low	Yes	No	Yes	Yes	6	-	No	Bottle
Oxyal Trehalos Duo Ac.	Middle	Yes	No	Yes	Yes	6	-	Yes	Bottle
Oxyal Trehalos Trp. Ac.		Yes	Yes	Yes	Yes	6	-	No	Bottle
Piiloset Biodrop MD plus	Middle	Yes	No	Yes	Yes	6	-	Yes	Bottle
Puro Teho	Middle	Yes	No	Yes	Yes	6	-	Yes	Bottle

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Tear supplementation: Lubricants

GELS (continued)									
		Supplement of:							
Product	Viscosity	Water	Lipid	Mucin	Contact lens Yes or No	Use after open. mth.	Preser-vatives	Phos-phates	Pack-age
CLASS: Carbomer									
Oftagel	High	Yes	No	Yes	Yes	1	BAC	No	Bottle
						Unidosis	-	No	Pipette
Viscotears	High	Yes	No	Yes	30 min. after administration	1	Cetrimid	No	Tube
						Unidosis	-	No	Pipette
Lakrimont	High	Yes	No	Yes	30 min. after administration	1	Cetrimid	No	Tube
CLASS: Carbomer + Dexpabthenol									
Oxyal Care Gel	High	Yes	No	Yes	15 min. after administration	1.5	Cetrimid	No	Tube
CLASS: HP Guar + PE/PEG									
Systane Gel drops	Middle/high	Yes	No	Yes	Before & After	3	Polyquad	No	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	-	No	Bottle
Vita-Pos Eye Oientm.	High	Yes	No	Yes	No	6	-	No	Bottle
CLASS: Trehalose + Sodium Hyaluronate + Carbomer									
Thealoz Duo Gel	High	Yes	No	Yes	30 min. after administration	Unidosis	-	No	Pipette
EvoTears	Low	No	Yes	No	No	6	-	No	Bottle

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** PNE: Phenoxyethanol

Tear supplementation: Lubricants

GELS (continued)									
		Supplement of:							
Product	Viscosity	Water	Lipid	Mucin	Contact lens Yes or No	Use after open. mth.	Preser-vatives	Phos-phates	Pack-age
OIL EMULSION									
CLASS: Mineral oil and glycerol									
Cationorm	Low	Yes	Yes	Yes	Yes	3	-	No	Bottle
CLASS: HP Guar + PE/PEG + Lipitech									
Systane Balance	Low	Yes	Yes	Yes	Before & After	6	Polyquad	Yes	Bottle
CLASS: Triglycerides + Sodium Hyaluronate + Carbomer + Glycerol									
Oxal Triple Action	Middle	Yes	Yes	Yes	15 min. after administration	6	-	No	Bottle
CLASS HP Guar + PE + Nanosized lipid droplets									
Systane Complete	Low/middle	Yes	Yes	Yes	Before & After	3	Polyquad	Yes	Bottle
LIPOSOMAL SPRAY									
CLASS: Phospholipid Liposomes									
Oxyal Total Care Spray	n/a	Yes	Yes	Yes	Yes	6	-		Bottle
Oxyal Triple Action Spray	n/a	Yes	Yes	Yes	15 min after administration	6	-	No	Bottle
Tearsagain	-	No	Yes	No	Yes	6	PNE**	No	Bottle
Tearsagain Sensitive	-	No	Yes	No	Yes	6	-	No	Bottle
CLASS: Perfluorohexyloctane									
EvoTears	Low	No	Yes	No	No	6	-	No	Bottle
CLASS: Phospholipid liposomes + hyaluronic acid + perilla seed									
Zalispray/Zaspray	Low	Yes	Yes	Yes	No	3	No	No	Bottle

** PNE: Phenoxyethanol