Diagnosis and treatment of dry eye disease: an overview

Abstract

Dry eye disease (DED) is a multifactorial condition that is complex to diagnose and treat. Our knowledge of how to define and diagnose different types of DED has increased over the last five to six years, but outdated or obsolete methods of looking at the problem prevent many patients from getting the correct diagnosis and treatment. By keeping up to date with new research and reports, healthcare professionals can provide the right diagnosis, information and treatment to patients suffering from the condition. To define and diagnose DED involves taking a thorough history and performing an examination of the eye. This article aims to provide a better understanding of DED and advice on how to define and diagnose DED correctly.

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Background

Dry eye disease (DED) is a major public health problem and one that will doubtless intensify in the future as a result of the ageing population and modern lifestyles (Aquavella, 2013; Schein et al, 1997; Moss et al, 2004).

Recent improvements in our understanding of this condition hold promise for the development of new technologies to aid in the diagnosis and treatment of DED, and improve quality of life for dry eye sufferers (Niimi et al, 2013).

DED is caused by conditions that increase evaporation of the tear film or decrease tear production (Tomlinson et al, 2006). The resulting increase in tear film osmolarity (hyperosmolarity) leads to ocular surface inflammation, damage and symptoms such as dryness, burning or stinging, ocular grittiness, foreign body sensation, blurred or fluctuating vision, watery eyes and photophobia (Tsubota et al, 1999) (*Table 1*).

It is clear that this previously underappreciated condition needs to be diagnosed correctly and treated effectively.

Table 1. Typical symptoms of dry eye disease

- Burning sensation
- Stinging
- Grittiness
- Foreign body sensation
- Blurred vision
- Watery eyes
- Photophobia

DED is a common problem and epidemiological studies show wide differences in prevalence. Historically, estimating the prevalence of DED has been problematic due to the lack of consensus on diagnostic criteria. Tomlinson et al (2006) state that DED affects up to 20% of the population in North America. A dry eye workshop (DEWS Research Committee, 2007) provided researchers and clinicians with a well anchored and modern definition of DED. According to a recent study (Nichols and Gaume Giannoni, 2012) the rate was even higher at 35% (±18.8).

Dry eye is further recognised as a disturbance of the lacrimal functional unit (LFU), a structured system comprising the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands) and lids, and the sensory and motor nerves that link them (Stern et al, 1998) (*Figure 1*). An important part of the LFU are the trigeminal sensory fibres, which arise from the ocular surface and run to the superior salivary nucleus in the pons, from which efferent fibres pass on their way to the pterygopalatine ganglion.

From this area, unmyelinated fibres arise, which terminate in the lacrimal gland and vessels of the orbit. Another neural pathway controls the blink reflex, through trigeminal afferent fibres of the seventh cranial nerve. In the brain stem nuclei there is a rich supply to the epithelia and circulatory system of the glands and ocular surface.

This part of the LFU controls and regulates the components of the tear film and responds to external conditions, and endocrinological and cortical influences. Its overall function is to preserve the integrity of the tear film, the transparency of the cornea and the quality of the image projected onto the retina (Stern et al, 1998; Pflugfelder et al, 2000; Beuerman et al, 2004; Stern et al, 2004).

Defining DED

Unfortunately, in many countries the definition of DED is usually primary Sjögren syndrome (SS), but the criteria have been more clearly defined during the last decade. Generally, there are two principal groups: aqueous tear-deficient dry eye (ADDE) and evaporative dry eye (EDE). These will be described below.

Aqueous tear-deficient dry eye (ADDE)

ADDE is caused by a malfunction of lacrimal tear secretion. In any form of dry eye due to lacrimal acinar destruction or dysfunction, dry eye is a result of reduced tear secretion and bulk (Zegans et al, 2002; Sommer, 2003). A consequence of reduced tear secretion is hyperosmolarity from the ocular surface. Although the water evaporates from the ocular surface in the normal way, it comes from a reduced tear pool. This causes dehydration of the ocular surface epithelial cells and stimulates a cascade of inflammatory outcomes (Li et al, 2004; (Luo et al, 2005). ADDE has two major sub-classes: Sjögren syndrome dry eye (SSDE) and non-SSDE (NSSDE).

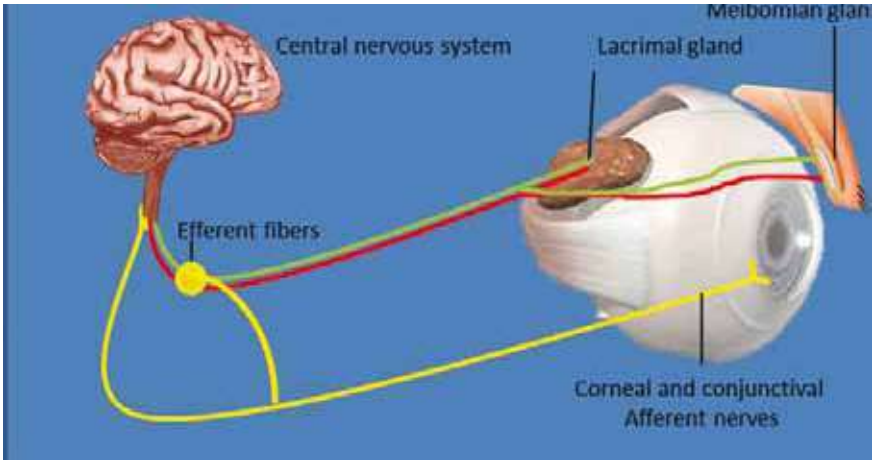

Figure 1. Schematic picture over the lacrimal functional unit (LFU)

Primary Sjögren syndrome

This syndrome is an exocrinopathy, where the lacrimal and salivary glands are exposed to an auto-immune process. The glands are penetrated by T-cells, which cause cell death and hyposecretion of the tears and/or saliva. Primary SS involves the occurrence of ADDE in combination with symptoms of dry mouth, as well as the presence of auto-antibodies and a positive score on salivary gland biopsy (Vitali et al, 2002).

Secondary SS

Secondary SS has the characteristics of primary SS, but with the features of an auto-immune connective disease, such as rheumatoid arthritis, which is often the primary cause. Other auto-immune diseases, such as systemic lupus erythematosis and polyarteritis nodosa, may also be involved (Kosrirukvongs et al, 2012).

Non-Sjögren syndrome

NSSDE is similar to primary SS; it is an ADDE caused by lacrimal dysfunction, but without the systemic auto-immune characteristics. The most common form is age-related DED. NSSDE comes in different forms and some of the most common are described below.

Primary lacrimal gland deficiencies

Along with normal age-related physiological changes in human beings, an increase in ductal pathology may promote lacrimal gland dysfunction, causing an obstructive effect (Damato et al, 1984; Obata et al, 1995). Damato et al (1984) state that mild dacryoadenitis could be the result of systemic infections or conjunctivitis, or sub-clinical conjunctivitis might be causing stenosis in the excretory ducts.

Secondary lacrimal gland deficiencies

Lacrimal secretion may be obstructed due to inflammatory infiltration of the gland, as in sarcoidosis, lymphoma, AIDS, lacrimal gland ablation and lacrimal gland denervation (Heath, 1948; Whitwell, 1958; James et al, 1964; Scherz and Dohlman, 1975; Itescu et al, 1990).

Obstruction of the lacrimal gland ducts

Any form of cicatrising conjunctivitis may lead to an obstruction of the ducts of the main palpebral and accessory lacrimal glands, causing ADDE. In such cases it is not uncommon for conjunctival cicatrising to cause an obstructive meibomian gland dysfunction (MGD). Cicatrising can also result in lid deformity, causing the tear film to spread by affecting lid collocation and dynamics. Conditions causing this kind of lid deformity can include trachoma, cicatricial pemphigoid, and chemical and thermal burns (Lemp, 1992; Guzey et al, 2000; Dart, 2005).

Reflex sensory block

During the day, there is an increased reflex sensory drive from the exposed areas of the eye. If a diminution in sensory drive from the ocular surface occurs, it can cause dry eye by decreasing reflex-induced lacrimal secretion and reducing the blink rate, thus causing hyperosmolarity (Battat et al, 2001). Several mechanisms can contribute to reflex sensory block; for example, contact lenses, especially in extended wear and in hard lenses.

Here, a decreasing of the corneal sensitivity occurs, followed by reduced blink rate and tear secretion, contributing to dry eye symptoms (Nichols and Sinnott, 2006). Other mechanisms contributing to reflex motor block are refractive surgery and cataract surgery; in both cases, reduced sensitivity is induced when incisions or ablating via laser cuts a

Table 2. Common causes of reflex hyposecretion

- Cataract surgery
- Keratoplasty
- Refractive surgery
- Photorefractive keratectomy (PRK)
- Laser-assisted in situ keratomileusis (LASIK)
- Topical anaesthesia
- Systemic medications
- Chronic contact lens wear
- Diabetes mellitus
- Ageing

large portion of the corneal nerves (Roberts and Elie, 2007; Murakami and Manche, 2012).

Diabetes

Diabetes mellitus has been recognised as a risk factor for dry eye in several studies, including large population studies (Goebbels, 2000; Kaiserman et al, 2005). Kaiserman et al (2005) suggest an association between poor glycaemic control and frequency of drop use, possibly due to diabetic sensory or autonomic neuropathy, and/or microvascular changes in the lacrimal gland.

Reflex motor block

Loss of lacrimal secretomotor function can occur due to blockage of signals from the seventh cranial nerve, which, via the nervus intermedius, carries fibres to the lacrimal gland. In reflex motor blockage, systemic drugs have, in several studies, been proven to be associated with dry eye, such as antihistamines, betablockers, antispasmodics, diuretics and antidepressive agents, which decrease lacrimal secretion (Moss et al, 2004) (*Table 2*).

Evaporative dry eye (EDE)

In contrast to ADDE, in EDE hyperosmolarity occurs from the exposed ocular surface in the presence of normal lacrimal function. Reasons for this could be due to intrinsic as well as extrinsic causes.

Meibomian gland dysfunction (MGD) is the most common reason for EDE (Foulks and Bron, 2003; Bron and Tiffany, 2004; Bron et al, 2004). Its causes are multiple, and various sources propose that MGD in a high degree is associated with an an insufficient tear film lipid layer and hyperosmolarity. Several methods exist to grade the degree of MGD, including measuring the degree of gland dropout (meibography) (Robin et al, 1985; Bron et al, 1991) and these will be discussed later in this article.

According to the International Workshop on Meibomian Gland Dysfunction, the recommended definition of MGD is as follows.

'Meibomian gland dysfunction (MGD) is a chronic, diffuse abnormality of the meibomian glands, commonly characterised by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion. This may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease.' (Nelson et al, 2011)

The term 'blepharitis' is often used in MGD but the term is a general one, describing inflammation of the lid as a whole. A more correct term would be 'marginal blepharitis', which is used to describe inflammation of the lid margin and comprises both anterior and posterior blepharitis.

Another cause of EDE is an increase in the exposed evaporative surface. This can occur due to endocrine exophthalmos or craniostenosis, and also a low blink rate during tasks of concentration; for example, working or playing at a computer. It has been reported that in healthy subjects the spontaneous eye blink rate (SEBR) during a conversation is approximately 21 blinks per minute (Doughty, 2001). Playing games at a computer lowers the SEBR to 5.32 blinks per minute (Freudenthaler et al, 2003).

Further causes of EDE are extrinsic; for example, vitamin A deficiency, which can cause lacrimal acinar damage and hence dry eye symptoms. Topical drugs can not only contribute to reflex sensory blockage but also to ocular surface disorders due to their formulations, and induce a toxic response from the ocular surface. The use of preserved drops is a significant cause of dry eye signs and symptoms, for example, in glaucoma patients; however, this can be reversed by switching to non-preserved formulations (Pisella et al, 2002). Therefore, frequent use of preserved tear lubricants should be avoided.

Contact lens wear is a common reason for extrinsic dry eye symptoms and several studies have shown that 50% of contact lens wearers report dry eye symptoms (Doughty et al, 1997; Nichols et al, 2006). Pre-lens lipid layer thickness and poor lens wettability are probably a basis for hyperosmolarity during lens wear. Further, there is evidence that chronic ocular surface diseases, such as allergy, destabilise the tear film, causing dry eye symptoms (Abelson et al, 2003).

From the above discussion, we can conclude that a number of essential mechanisms in the dry eye process can initiate, exaggerate and alter the tear film, causing an ADDE or an EDE. This can further expose the ocular surface to epithelial damage, disturbance of the glycocalyx and the mucin-producing goblet cells and releasing of inflammatory mediators. To acquire the necessary understanding of DED, it is vital

not only to understand the core mechanisms of the problem, but also how to examine and diagnose dry eye. Below we will discuss a number of techniques used to diagnose dry eye.

Diagnosing DED

A comprehensive eye examination to determine the cause of dry eye should always start with a thorough medical history, which includes a complete history of overall health, as well as eye health. In addition to the medical history, the clinician may provide the patient with a dry eye questionnaire before the examination. If the information provided, in conjunction with other clinical data from the medical history, raises the suspicion of DED, then obtaining a tear osmolarity test may be necessary. This can be performed as a laboratory test, or by the professional with a commercial instrument that is now available. A clinical osmometer, which requires an extremely small tear sample, can be used to provide a biomarker for disease severity (*Figure 2*). This test should always be performed before any invasive test to prevent bias from a disturbed tear film.

Arguably, the measurement of tear film osmolarity offers the best way of establishing, in a single parameter, the balance of input and output of the tear system (Tomlinson et al, 2006). However, no 'gold standard' exists for the diagnosis of dry eye, and to determine whether the patient has ADDE or EDE, a further test should also be performed.

Tests to diagnose ADDE

Schirmer's test uses paper strips inserted into the eye to determine lacrimal production. Both eyes are tested at the same time, for 5 minutes (*Figure 3*). The test is interpreted by measuring the number of mm wetted (Hanson et al, 1997):

1. Normal: ≥15 mm wetting of the paper
2. Mild: 14–9 mm wetting of the paper
3. Moderate: 8–4 mm wetting of the paper
4. Severe: <4 mm wetting of the paper.

It should be noted that Schirmer's test is an invasive method, generating increased neural lacrimation. Some practitioners administrate local anaesthesia to counteract this, but this causes motor reflex blockage. A less invasive method to measure lacrimation is the phenol red thread (PRT) test. This causes less reflex tearing and, perhaps more importantly, it is less time consuming to perform (15 seconds in comparison to 5 minutes for Schirmer's test).

In PRT, the thread should be placed at a point approximately one-third of the distance from the lateral canthus of the lower eyelid (*Figure 4*). Each eye is individually tested, with the eyes open, for 15 seconds. When in contact with tears, the thread turns red and the entire length of the red portion is measured in mm; less than 10 mm is considered dry.

Figure 2. Collection of a sample from the tear film with an osmometer

Figure 3. The application of Schirmer strips

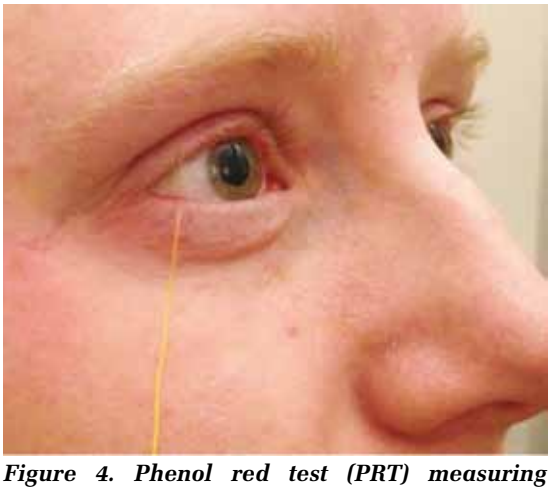

Figure 4. Phenol red test (PRT) measuring lacrimation

Measurement of the tear meniscus height (TMH) is another way to estimate the output of lacrimation (*Figure 5*). Although meniscus is found in both the upper and lower eyelid, the most common way to measure the height is by looking at the lower lid. The measurement can be performed with several instruments and techniques, such as cameras, optical coherence tomography (OCT), and slit lamps. In a

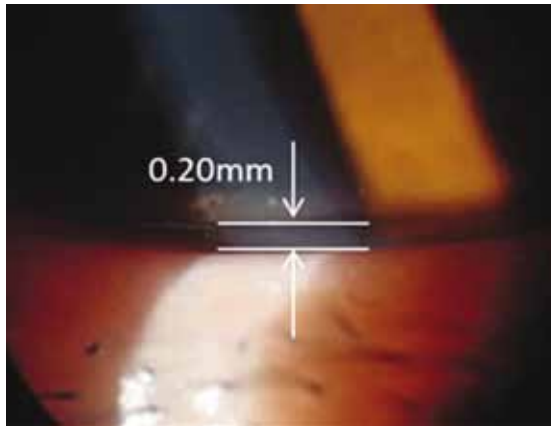

Figure 5. Normal values in all ages range between 0.2–0.4 mm but a lower meniscus than 0.2 is considered to be a sign of a low lacrimation

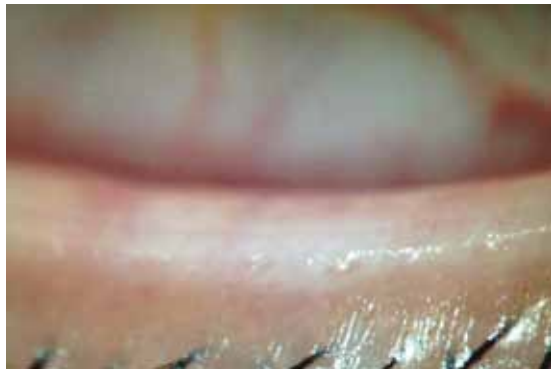

Figure 6. Healthy lid margin with meibomian orifices

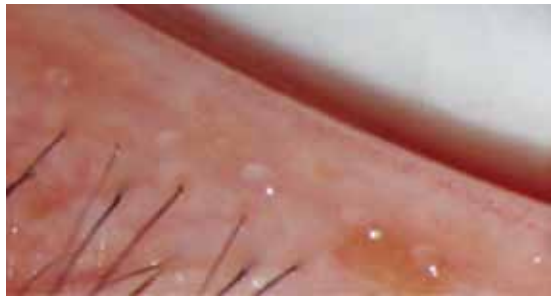

Figure 7. Meibomian gland lipids contend

Figure 8. Note the turbid toothpaste-like secretion from the meibomian glands, often causing inspissation

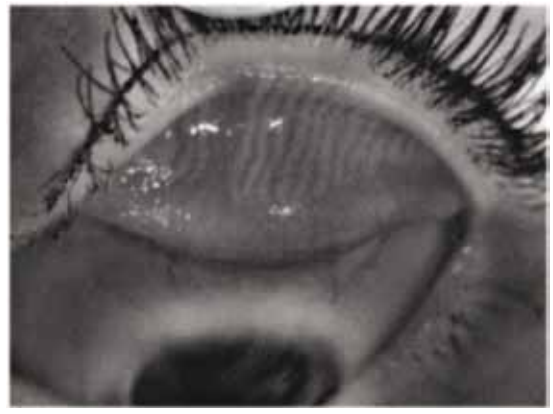

Figure 9. Upper and lower eyelid showing the meibomian glands in a normal subject

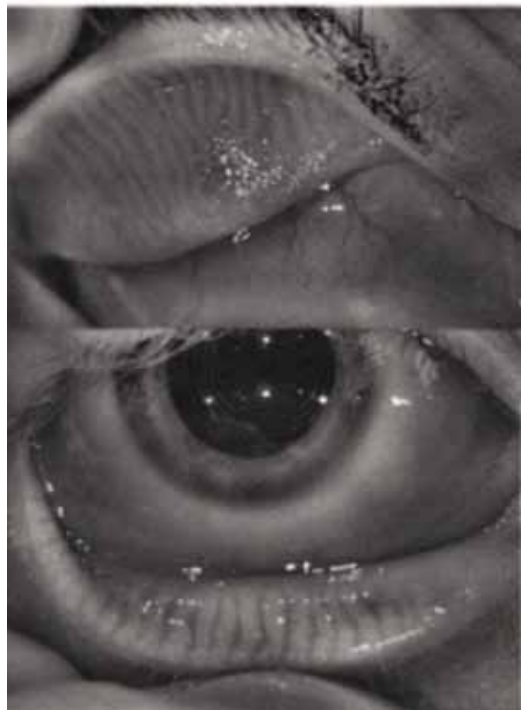

Figure 10. Drop-outs of MG in the superior part of the upper eyelid in a silicone hydrogel lens wearer with extended wear

clinical setting, the most comfortable test uses the slit lamp. Some clinicians use fluorescein sodium to better view the meniscus, but as this has been demonstrated to give a higher TMH (Lim and Lee, 1991), its use is not recommended. A normal height is considered to be 0.20 mm or greater.

Tests to diagnose EDE

When considering tests for EDE, the focus should be on the quality of the tear film and the reasons to disturbance hereof. Inspection of the meibomian glands (*Figures 6–8*) is of great importance in EDE. MGD, primarily synonymous with blepharitis, is mainly caused by an obstructive mechanism in

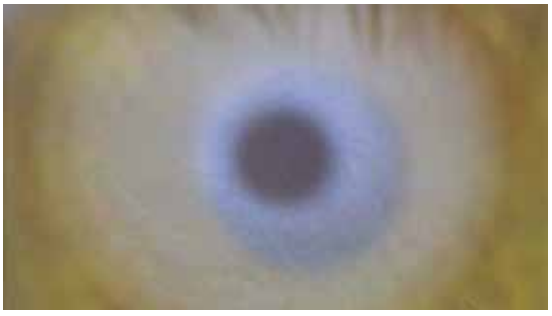

Figure 11. Open meshwork: very thin lipid layer, Itchy, gritty eyes (dry eye symptoms)

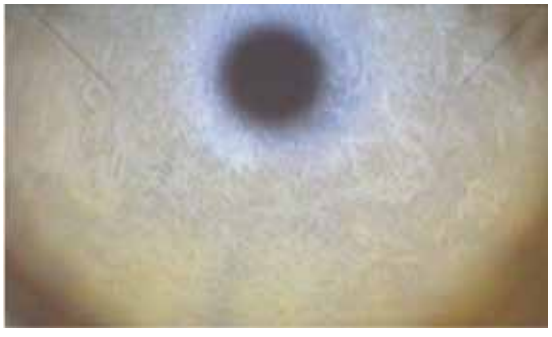

Figure 12. Closed meshwork: still thin lipid layer but does not present dry eye symptoms

Figure 13. Wave: representing the average lipid layer in around 30% of the population. Does not present dry eye symptoms

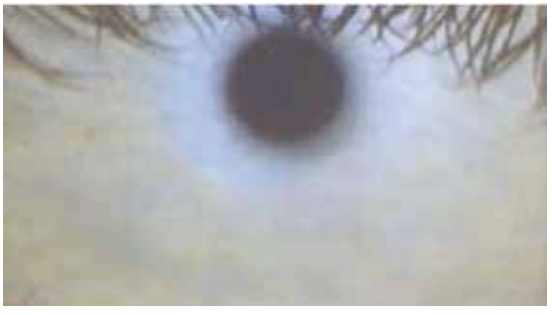

Figure 14. Amorphus: thick lipid layer (80–90 mm). Does not present dry eye symptoms

Figure 15. Colour fringes type 1: thick lipid layer (90–140 mm). Does not present dry eye symptoms

Figure 16. Colour fringes type 2: abnormal lipids linked to affected meibomian glands. Itchy, gritty eyes (dry eye symptoms)

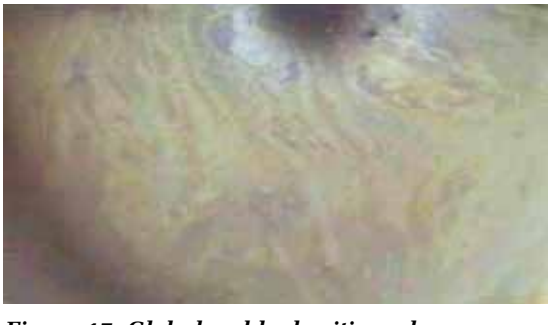

Figure 17. Globular: blepharitis and over secretion of lipid, meibomian gland dysfunction (dry eye symptoms)

the glands. Careful investigation of the eyelids and lid margins with eversion should, therefore, be performed (Nichols et al, 2011). Particularly important is the inspection of the Meibomian orifices. This is preferably performed with the slit lamp.

The everted lids should be inspected for any form of irritation or cicatrising, which can lead to an obstruction of the ducts of the main palpebral and accessory lacrimal glands. Everted lids can also be inspected with infra-red irradiating (Srinivasan et al, 2012). New techniques allow us to produce high-quality gross images of the meibomian glands (*Figures 9 and 10*).

Evaluation of tear film lipid layer thickness to differentiate between a normal and abnormal tear film can be performed in several ways, such as slit lamp and different interferometers (Bron et al, 2004) (*Figures 11–17*).

A variety of other tests can be performed to verify the ocular surface condition. Fluorescein sodium has been used since the end of the 19th Century and is one of the most frequently used methods for studying dry eye. As superficial punctate epithelial erosions

may have several causes (for example, drug toxicity and laser-assisted in situ keratomileusis (LASIK)-induced neurotropic epitheliopathy), corneal fluorescein staining cannot be considered a specific sign of dry eye; nor can it be considered a very sensitive measure, as it is only detected in around 10% of dry eyes (Schiffman et al, 2000; Nichols et al, 2004).

Rose bengal staining (RB) can give us an idea of how damaged the ocular surface is, but the connection between RB staining and dry eye has not been fully established, as RB staining can also be seen in asymptomatic patients (Schein et al, 1997; Khan-Lim and Berry, 2004), and seems to lack a clearly defined relationship with subjective symptoms (Schein et al, 1997; Lin et al, 2005).

Lissamine staining (LG) is nearly identical to RB and the two are usually considered to be interchangeable (Norn, 1973; Manning et al, 1995; McCulley et al, 2003). However, experimental studies have shown significant differences between LG and RB——LG does not stain healthy corneal epithelial cells, nor does it affect their viability (Kim and Foulks, 1999).

Break-up time (BUT) is frequently used to assess tear film stability by measuring the tear break-up time (TBUT) – the time between a complete blink and the first appearance of a dry spot in the precorneal tear film after fluorescein instillation. However, the fluorescein method is invasive and presents biased measurements. Furthermore, this method has been criticised as imprecise and not reproducible (Vanley et al, 1977). A large range of normal values, lack of a standardised routine for fluorescein appliance to the tear film and poor association with subjective symptoms have further strengthened this concept (Nichols et al, 2004). In a clinical setting, if using BUT, it is better to measure a non-invasive break-up time (NIBUT).

Techniques can vary, but using a keratoscope it is possible to determine the NIBUT simply by looking at changes in the projected placido rings, indicating the BUT of the tear film (*Figure 18*).

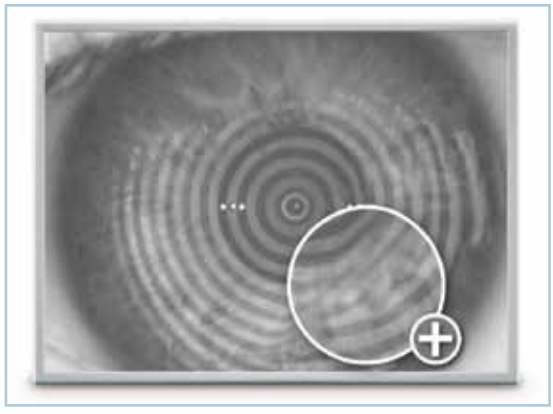

Figure 18. Placido rings projected at the cornea with a keratoscope

Conclusion

DED is a multifactorial condition and is complex to both treat and diagnose. However, with better knowledge of how to define and diagnose DED, health professionals can prevent ocular disease and improve quality of life for dry eye sufferers. IJOP

Conflict of interest: none declared

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Key points

- Dry eye disease (DED) is a multifactorial condition that is complex to both treat and diagnose
- DED has been an under-appreciated condition, but it should be diagnosed correctly and treated effectively
- A number of essential mechanisms in the dry eye process can initiate, exaggerate and alter the tear film, producing either aqueous tear-deficient dry eye (ADDE) or evaporative dry eye (EDE)
- A wide variety of techniques are accessible and ready for use to diagnose DED
- With better knowledge of how to define and diagnose DED, we can prevent ocular diseases and improve quality of life for dry eye sufferers

• Dry eye disease (DED) • Aqueous tear-deficient dry eye (ADDE) • Evaporative dry eye (EDE) • Osmolarity • Meibomian glands

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