OPHTHALMIC DOCTORATE

The predictive ability of clinical tests for contact lens induced dry eye

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THE PREDICTIVE ABILITY OF CLINICAL TESTS FOR CONTACT LENS INDUCED DRY EYE

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Summary:
Approximately half of current contact lens wearers suffer from dryness and discomfort, particularly towards the end of the day.
Contact lens practitioners have a number of dry eye tests available to help them to predict which of their patients may be at risk of contact lens drop out and advise them accordingly. This thesis set out to rationalize them to see if any are of more diagnostic significance than others.

This doctorate has found:

(1) The Keratograph, a device which permits an automated, examiner independent technique for measuring non invasive tear break up time (NITBUT) measured NITBUT consistently shorter than measurements recorded with the Tearscope. When measuring central corneal curvature the spherical equivalent power of the cornea was measured as being significantly flatter than with a validated automated keratometer.

(2) Non-invasive and invasive tear break-up times significantly correlated to each other, but not the other tear metrics. Symptomology, assessed using the OSDI questionnaire, correlated more with those tests indicating possible damage to the ocular surface (including LWE, LIPCOF and conjunctival staining) than with tests of either tear volume or stability. Cluster analysis showed some statistically significant groups of patients with different sign and symptom profiles. The largest cluster demonstrated poor tear quality with both non-invasive and invasive tests, low tear volume and more symptoms.

(3) Care should be taken in fitting patients new to contact lenses if they have a NITBUT less than 10s or an OSDI comfort rating greater than 4.2 as they are more likely to drop-out within the first 6 months. Cluster analysis was not found to be beneficial in predicting which patients will succeed with lenses and which will not. A combination of the OSDI questionnaire and a NITBUT measurement was most useful both in diagnosing dry eye and in predicting contact lens drop out.

Key words: Dry eye; NITBUT; cluster analysis; OSDI; Keratograph

Dedication

This doctorate is dedicated to my wife Laura and my son William Connor.

Acknowledgement

The Keratograph was kindly loaned to the authors by the Birmingham Optical Group, UK.

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Abbreviations

ARDE	Age related dry eye
ADDE	Aqueous deficient dry eye
BUT	Break Up Time
CLDEQ	Contact Lens Dry Eye Questionnaire
CLIDE	Contact Lens Induced Dry Eye
CoF	Coefficient of Friction
DES	Dry Eye Syndrome
EDE	Evaporative dry eye
FBUT	Fluorescein Break Up Time
LIPCOF	Lid Parallel Conjunctival Folds
LFU	Lacrimal Functioning Unit
LWE	Lid Wiper Epitheliopathy
MGD	Meibomian Gland Dysfunction
NITBUT	Non Invasive Break Up Time
NIKBUT	Non Invasive Keratograph Break Up time
OCI	Ocular Comfort Index
OSDI	Ocular Surface Disease Index
PLTF	Pre Lens Tear Film
PL-NITBUT	Pre Lens Non Invasive Break Up Time
POLTF	Post Lens Tear Film
SiH	Silicone Hydrogel
SS	Sjögren’s syndrome
SSDE	Sjögren’s syndrome dry eye
BUT	Break up time
TMH	Tear Meniscus Height

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1. Introduction

Approximately half of current contact lens wearers suffer from dryness and discomfort, particularly towards the end of the day (Morgan and Efron, 2008) and a significant number are not satisfied with their contact lenses and are at risk of discontinuation (Richdale *et al*., 2007). This risk of discontinuation has been shown to be higher with new wearers than it is for experienced wearers (Morgan *et al.,* 2005). Prior to fitting their patients with contact lenses there are a number of tests available to the practitioner to assess the quality and quantity of tears, to allow advice to be given on an individual's suitability for contact lenses and to recommend the most appropriate modality of wear. Traditionally these tests have included non-invasive tear break up time (NITBUT), invasive or fluorescein break up time (BUT), corneal and conjunctival staining, bulbar hyperaemia, tear prism height measurement, phenol red test and various questionnaires. More recently the diagnostic ability of metrics such as lid parallel conjunctival staining (LIPCOF) and lid wiper epitheliopathy (LWE) have been promoted. Most of these tests are subjective and reasonably variable, so new, more objective assessment of the tear film is desirable. One such test, the Keratograph, digitises the image of a Placido disc reflected from the tear film, to provide an objective assessment of NITBUT. In addition, a new device is now available to the community optometrist which allows determination of tear osmolarity (the measurement of total solute concentrate in patients' tears). This increase in osmolarity, when water is lost from the aqueous phase of the tear film leaving behind the solutes such as metal ions, draws moisture out of the cornea in an attempt to restore equilibrium, causing dessication. This can cause a reduction in mucous production, leading to further tear loss. As a result, higher tear film osmolarity has also been shown to cause ocular surface inflammation (Gilbard 2005, Luo *et al.,* 2005) which can result in symptoms of ocular discomfort. Tear hyperosmolarity can

be regarded as the main feature which characterises dry eye disease (DEWS Report 2007), therefore the ability to directly measure this parameter is of great clinical significance.

In 2000 a survey was carried out to determine the preferred tests for dry eye diagnosis of a number of eye care practitioners with an interest in the tear film (Korb, 2000). If given only one test, the majority (28%) chose a dry eye questionnaire. The second most frequently chosen test was fluorescein break up time (19%), followed by fluorescein staining (13%) and rose bengal (10%). A more recent study (Smith *et al*., 2008) of dry eye experts found that symptom assessment, again with questionnaires, the preferred tests alongside tear break up time, corneal staining, tear film assessment, conjunctival staining and Schirmer test. Most practitioners used a multiple of tests (medial 6).

1.2. Literature review

1.2.1 Tear film function

The tear film performs a number of functions (Milder, 1987):

(1) Optical - maintenance of an optically uniform corneal surface

(2) Mechanical - flushing cellular debris from the cornea and conjunctival sac

(3) Nutritional - nourishing the cornea

(4) Bactericidal - antimicrobial properties to reduce the likelihood of corneal infection

(5) Lubricant - ensuring a smooth movement of the eyelids over the globe during the blink

1.2.2 Tear film structure

The tear film was classically believed to be composed of three distinct layers (Figure 1.1).

1. An outermost superficial oily layer derived from the meibomian glands which reduces the rate of evaporation of the aqueous layer and also forms a barrier along the lid margins to prevent the overflow of tears onto the skin.
2. A middle aqueous layer which hydrates the epithelial cells and provides metabolites to them.
3. An innermost mucous layer secreted by the goblet cells of the conjunctiva and the squamous cells of the cornea and conjunctiva. This coats the inherently hydrophobic corneal epithelium rendering it more hydrophilic and allowing the aqueous layer to "wet" it.

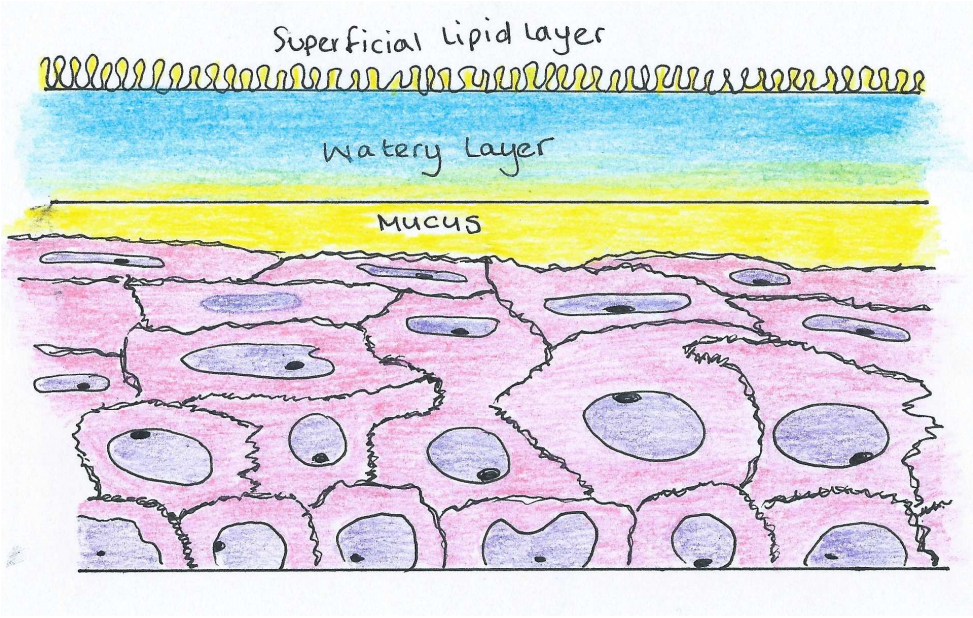


Figure 1.1: Anatomy of the tear film

Over the years scientists have disagreed about the thickness and degree of separation of these layers. In 1946 Wolff suggested a tri-laminar structure that is about 7μm thick and is composed of an outer lipid layer (approximately 0.1μm thick), an intermediate aqueous phase (7μm), and an inner mucous layer (0.05μm) (Wolff,

1946). Other researchers disagreed, disputing the proposed thickness of the mucous layer of the Wolff model and argued that the tear film should be thought of as being as much as 34-45μm thick (measured by laser confocal microscopy technique), but with the same tri-laminate structure (Prydal *et al.,* 1992). However, setting aside the uncertainty as to its true thickness in recent models, the general opinion is that the tear film is composed of an outer lipid layer, a mucous-aqueous layer and an underlying mucous-layer (glycocalyx) that covers the corneal and conjunctival epithelium (Argueso and Gipson 2001; Gipson, 2004). The three components of the tear film work together to maintain the integrity of the tear film. The functions and origins of the tear film are summarised below (Table 1.1):

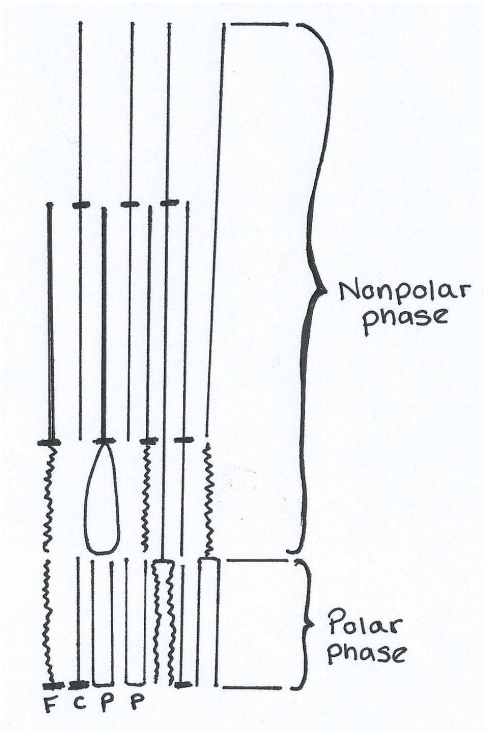
Structure	**Origin**	**Major components**	**Functions**
Lipid layer	Meibomian glands	Cholesterol esters Ester waxes	Avoids evaporation Provides optically smooth surface
Aqueous layer	Lacrimal glands	Water, protein, salts	Bacteriostasis Debris flushing Maintenance of epithelial hydration
Mucin layer	Conjunctival goblet cells Glands of Moll and Krause	Glycoprotein	Renders epithelial surface hydrophilic for aqueous to wet

Table 1.1: Structure and function of the tear film

1.2.3 Lipid layer

The lipid layer is produced by the meibomian glands located in the tarsal plates of the eyelids; its role is to reduce tear film evaporation, enhancing tear film stability (Mishima *et al.,* 1961). Rapid and forceful blinking has been shown to increase the

thickness of the lipid layer (Korb *et al.,* 1994). The secretion from the meibomian glands is known as meibum and consists of both polar and non-polar lipids. The polar element of the meibomian layer is comprised mainly of phospholipids and acts like a surfactant, spreading over the aqueous layer. The non-polar element of the meibomian layer lies at the air-lipid interface (Greiner *et al.,* 1996; Figure 1.2).



HC: Hydrocarbon
WE: Wax ester

CE: Cholesterol ester
TG: Triglyceride (mono & diunsasurated)

F: Fatty acid
C: Cerebroside
P: Phospholipid

_ Carbroxyl or ester group
~~~~ Unsaturated
____ Saturated

Figure 1.2: Composition of the lipid layer (Adapted from McCulley and Shine, 1997)

The absence of a lipid layer in rabbits has been shown to increase tear film evaporation by a factor of 10 (Mishima and Maurice, 1961). Increased tear film evaporation will result in tear film hyperosmolarity. The lipid layer varies in thickness It is estimated by observation of interference patterns, to measure between 0.06-0.18 microns in the open human eye (Korb 1998) and it extends from the opening of the meibomian glands to cover the tear film. It can be regarded as independent from
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other aspects of the tear film as it does not flow from lateral to medial canthi, nor does it enter the conjunctival sac (Ruskell and Bergmanson, 2007).

1.2.4 Aqueous layer

The aqueous layer is produced by the lacrimal gland and the accessory lacrimal glands of Krause and Wolfring under the influence of the sympathetic and parasympathetic nervous system and various hormones (Walcott *et al.,* 1994). The aqueous layer has a number of functions:

- transporting atmospheric oxygen to the cornea
- carrying nutrients to the cornea
- flushing away desquamated epithelial cells
- providing a smooth refracting surface to the cornea (Montes-Mico , 2007)
- antibacterial effects of lysozyme against gram +ve bacteria (Lal and Khurana, 1994)
- antibacterial effects of lactoferrin against gram -ve bacteria (Flanagan and Wilcox, 2009)
- anti-inflammatory effects of lactoferrin (Veerhuis and Kijlstra, 1982)

The aqueous layer of tears contains many proteins but there are 3 major protein components: lysozyme (24-47%), lactoferrin (23-29%) and tear lipocalin (15-33%) (Fullard, 1988). Immunoglobulin A (IgA) becomes the predominant protein when the lids are closed for prolonged periods (Sack 1992; Sack 2000). The aqueous contains a number of growth factors including epidermal growth factor, human growth factor and transforming growth factor-alpha (Van Setten *et al.,* 1990) important for cell growth, proliferation and differentiation. A decrease in aqueous production will result in a reduction of these growth factors in the tears (Van Setten *et al.,* 1992).

1.2.5 Mucous layer

The mucous layer comprises of mucins, immunoglobulins, urea, salts, glucose, leukocytes, cellular debris and enzymes (Nichols *et al.,* 1985). It has a number of functions including (McKenzie *et al.,* 2000):

- rendering the corneal epithelium hydrophilic
- preventing corneal desiccation
- protecting the epithelium from shear forces
- reducing bacterial contamination of the cornea

Corneal and conjunctival epithelial cells synthesise membrane bound mucins (MUC 1, MUC 4, MUC 16), which constitute part of the glycocalyx and aid in ocular surface wetting (Gibson and Inatomi, 1998). The glycocalyx (composed of glycoproteins and glycolipids) covers the conjunctival and corneal epithelium microvilli and microplicae (Dilly, 1994). The mucous layer of the tear film then attaches to the glycocalyx. Secretory mucins (MUC 2, MUC 5AC, MUC 5AB, MUC 6) are found in aspects of the aqueous component and confer non-Newtonian thixotropic properties. These thixotropic properties allow the tear film to be thicker and more viscous in nature under normal conditions but to become thinner and to flow more readily when agitated. This reduces damage from shearing forces generated during eye movements and blinking (Berry *et al.,* 2004). The bulk of the mucous layer is secreted by conjunctival goblet cells which can be stimulated to secrete mucin by histamine, antigen or blinking (Chandler and Gillette, 1983).

Mucins exist as a network distributed in the aqueous body of the tear film and covered by 2 layers of lipid (Chen *et al.*, 1997). Nichols, in 1985, described a mucin

layer that measures 2-7 microns above the corneal surface and is intimately associated with corneal microvilli and presumably anchored to the glycocalyx of the conjunctiva. Prydal in 1992 suggested from measurements by laser confocal microscopy, that the human aqueous-mucin layer may be much thicker than first estimated at between 41 and 46 microns.

1.3.Tear film production

Normal production of tears requires a healthy Lacrimal Functional Unit (LFU). This is an integrated system comprising the lacrimal glands, cornea, conjunctiva, meibomian glands, lids and sensory and motor nerves (DEWS Report 2007).

Basal tear flow is a reflex response to afferent impulses arising mainly from the ocular surface. The cornea is innervated by the ophthalmic division of the trigeminal nerve. These nerve fibres enter the corneal periphery close to the middle of the stroma before dividing and forming a dense sub-epithelial plexus. They then deviate upwards, penetrating Bowman's layer and terminating in the corneal epithelium. These afferent sensory nerves run to the superior salivary nucleus in the pons, efferent fibres then pass in the nervus intermedius to the pterygopalatine ganglion. Post-ganglionic fibres terminate in the lacrimal gland and nasopharynx (Quinto 2008). Any interruption of this neural loop will result in reduced tear output (Stern, 1998) as is often seen in post LASIK patients.

The secretory components include the lacrimal gland, accessory lacrimal gland, meibomian glands and conjunctival goblet cells. The corneal and conjunctival epithelia are continuous via ductal epithelia with the acinar epithelia of the main and accessory lacrimal glands and the meibomian glands (DEWS Report 2007). The

accessory lacrimal glands of Krause are located in the stroma of the palpebral conjunctiva with approximately 20 in the upper fornix and 8 to 10 in the lower fornix. The accessory glands of Wolfring occupy the upper part of the superior tarsal plate.

1.4. The tear film in dry eye

In 2007 the International Dry Eye Workshop (DEWS 2007) produced the following definition of dry eye syndrome (DES):

> "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."

Symptoms include visual disturbances, grittiness, dryness, burning, stinging and discomfort (Behrens *et al.,* 2006). These symptoms can worsen with tasks associated with reduced blink rate e.g. driving or computer work and tend to worsen as the day progresses or in dry warm environments (Paschides *et al.,* 1998, Tsubota and Nakamori, 1993) . Signs of dry eye include bulbar conjunctival redness, superficial punctate corneal staining, lid parallel conjunctival folding, reduced tear break up time, reduced team meniscus height, lid wiper epitheliopathy and increased tear osmolarity (Toda 2007). It is not uncommon for signs and symptoms in dry eye patients to correlate poorly (Lemp, 1995); for example in one study 48-59% of post LASIK patients had dry eye symptoms while punctate keratitis was present in only 2-6% (Hovanesian, 2001).

The dry eye workshop classifies dry eye into two major subgroups (Figure 1.3), aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE).

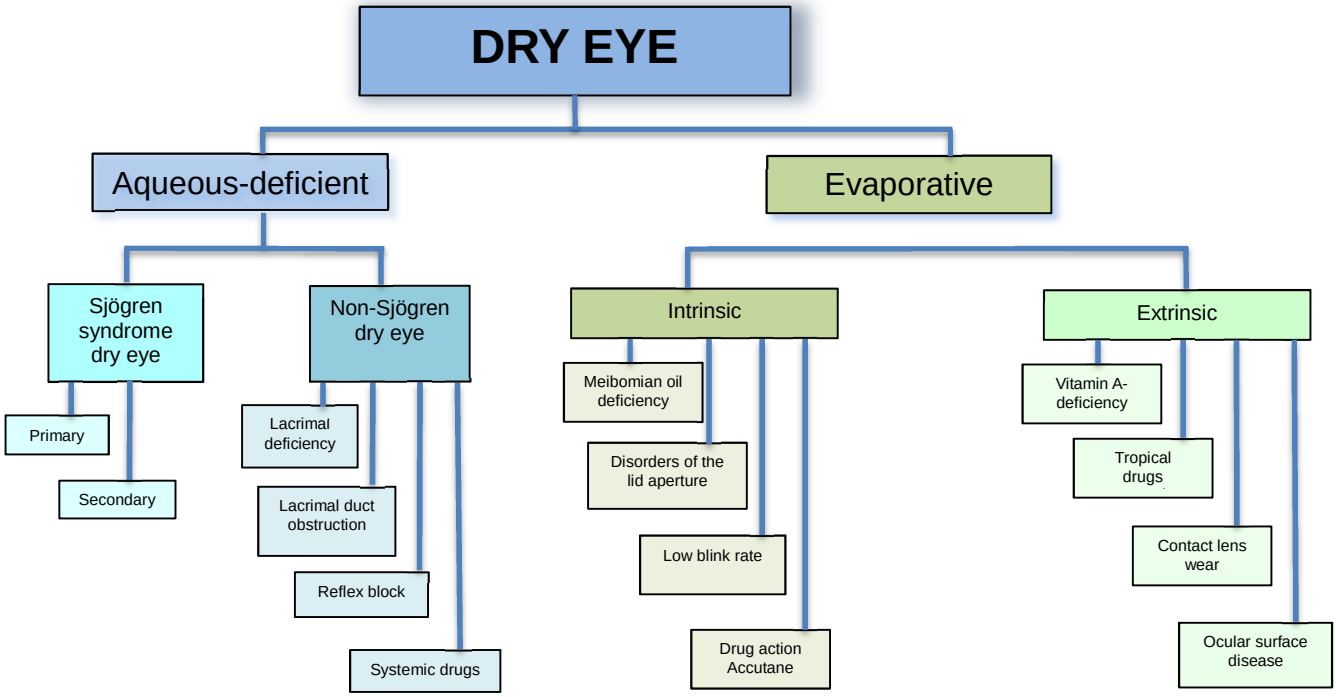

Figure 1.3: Dry eye definition and classification (Adapted from DEWS 2007)

1.4.1 ADDE

ADDE is a dry eye resulting from a reduction of lacrimal tear secretion. Tear evaporation will continue at a normal rate resulting in tear hyperosmolarity. This causes hyperosmolarity of the corneal epithelial cells and stimulates an inflammatory cascade and the generation of inflammatory cytokines, tumour necrosis factor and matrix metallo-proteinases (mmp-9) (Li *et al.,* 2004; Luo *et al.,* 2005; De Pavia *et al.,* 2006).

ADDE is further classified into Sjögren's syndrome dry eye (SSDE) and non Sjögren's syndrome (SS) dry eye. SSDE is further classified into primary SS, this is ADDE combined with a dry mouth and specific auto-antibodies (Vitali *et al.,*1996; Fox *et al.,* 1986) and secondary SS in which the patient also has features of autoimmune

disease, for example rheumatoid arthritis. The ocular dryness in SSDE is due to inflammatory changes in the lacrimal gland, together with the presence of inflammatory mediators in the tears and within the conjunctiva (Jones *et al.,* 1994). This results in lacrimal hyposecretion. Patients with SS appear more likely to suffer from meibomian gland dysfunction (MGD) suggesting excessive tear film evaporation may exacerbate their dry eye (Shimazaki *et al.,* 1998). Non SSDE is a form of ADDE where the autoimmune features of SS are not present - the most common form of this sub-type is age related dry eye (ARDE). As we age, a number of changes occur in the LFU including preductal fibrosis, inter-acinar fibrosis and acinar atrophy (Damato *et al.,* 1984). Other causes of non SSDE include :

- Secondary lacrimal gland deficiencies e.g. secondary to sarcoidosis or AIDS
- Obstruction of lacrimal gland ducts by cicatrising conjunctivitis e.g. in trachoma (Guzey *et al.,* 2000)
- Reflex hyposecretion - lacrimal tear secretion results from trigeminal sensory input from the naso-lacrimal passages and the eye. Reduced sensory input will decrease lacrimal secretion and reduce the blink rate increasing tear evaporation (Battat *et al.,* 2001). This can occur in wearers of certain contact lens materials, diabetics and post LASIK treatment (Albietz *et al.,* 2005).
- Neurotrophic keratitis-causing sensory denervation of the anterior segment

1.4.2 EDE

EDE is the term used for conditions where there is normal tear production but a loss of tear constituents due to excessive evaporation. It can result from intrinsic or extrinsic causes.

1.4.2.1 Intrinsic causes of EDE

- MGD - this is the most common cause of EDE (Bron, 2004). There are many causes of MGD and if present to a sufficient degree it is associated with a reduction in the thickness of the lipid layer, increased tear evaporation and evaporative dry eye (The International Workshop On Meibomian Gland Dysfunction, 2011).
- Disorders of lid aperture or lid globe interaction - high myopes or proptosed eyes will experience increased evaporation of the tear film (Gilbard *et al.,* 1983). It can also occur with prolonged upgaze, for example a security guard viewing a bank of monitors above head height.
- Low blink rate - drying of the ocular surface will be caused when the time between blinks increases. This can occur during certain visual tasks e.g. display screen use (Nakamori *et al.,* 1997) or be a feature of diseases such as Parkinson's disease (Lawrence *et al.,* 1991).

1.4.2.2 Extrinsic causes of EDE

- Ocular surface disorders - any disease resulting in imperfections on the ocular surface will reduce the ability of the tears to wet the eye causing a more rapid break up of the tear film and excessive evaporation. Vitamin A is important for goblet cell production and glycocalyx formation (Tie *et al.,* 2000) so vitamin A deficiency can lead to EDE. Topical drugs and preservatives e.g. benzalkonium chloride can cause a toxic response on the cornea reducing surface wettability. For this reason non-preserved tear preparations are preferable to preserved ones. The acne medication, Isotretinoin, has also been associated with an increased risk of dry eye.

- Contact lens wear - the pre-lens lipid layer thickness has been shown to be reduced in contact lens wearers experiencing dry eye symptoms (Nichols and Sinott, 2006) which could result in increased evaporation of the tears. Another mechanism which could increase EDE in contact lens wearers is the predilection for hydrophobic lipids, produced by the meibomian glands, to the surface of silicone hydrogel contact lenses (Lorentz *et al.,*2007) .

Irrespective of the aetiology of the dry eye two mechanisms seem to result which cause ocular surface damage and symptoms; these are tear hyperosmolarity and tear film instability.

1.4.3 Tear Hyperosmolarity

Hyperosmolarity of the tear film can result from either reduced aqueous production or excessive evaporation; in practice these two events often occur together. Hyperosmolarity stimulates a cascade of inflammatory events in epithelial surface cells and the generation of inflammatory cytokines and matrix metallo-proteinases (Li *et al.,* 2004; Tsubota and Yamada*,* 1992). These inflammatory events result in increased apoptosis of both goblet cells and corneal and conjunctival epithelial cells (Yeh *et al.,* 2003). Reduced goblet cell density has been shown to correlate with reduced levels of MUC 5AC in dry eye patients (Argueso *et al.,* 2002). In the initial stages of dry eye, patients with normally functioning lacrimal glands may experience reflex tearing secondary to ocular surface damage. This may help to reduce the degree of tear hyperosmolarity. Although tear flow in these patients may be higher than normal, they do demonstrate reduced tear break up time and increased ocular surface staining (Shimazaki *et al.,*1998).

Inflammatory mediators such as tumour necrosis factor A and interleukin-1 result from a hyperosmolar state also detrimentally affect the nerve supply to the cornea (Acosta *et al.,* 2007) resulting in reduced tear flow and mitigating the potential benefits of reflex tearing in the longer term (Figure 1.4). This will reinforce the pre-existing reduced tear flow in ADDE and could reduce tear volume in a previous high volume EDE. For this reason a person with ADDE and hyperosmolar tears may see a reduction in goblet cell density and secondary increased tear film evaporation - EDE. Conversely a patient with primary EDE, for example secondary to MGD, will experience reduced corneal sensitivity and a subsequent reduction in tear production resulting in a form of ADE. For this reason differentiating between ADDE and EDE in a clinical setting may be problematical.

Figure 1.4: Aetiology of dry eye disease (DEWS 2007).

1.4.4 Tear Film Instability

As discussed above, tear film instability can result from hyperosmolarity of the tear film and the subsequent effect on mucin cell density, it can also be the cause of dry eye. In a normal patient the tear film break up time (TFBUT) is longer than the blink interval (although it is generally accepted that a TFBUT < 10 seconds is abnormal; Lemp, 1995). When break up occurs within the blink interval, hyperosmolarity of the tears will result with all of the sequelae discussed in the section above (Figure 1.4). These sequelae will further destabilise the tear film, causing a vicious circle to ensue. This sequence of events can be seen in patients with Vitamin A deficiency (xerophthalmia) as a result of reduced goblet cell density (Sommer and Emran,

1982). The common preservative Benzalkonium Chloride can also cause tear film instability and reduced goblet cell density (Rolando *et al.,* 1991).

1.5. The effect of a contact lens on the tear film

Approximately 50% of contact lens wearers report experiencing dry eye symptoms (Nichols *et al.,* 2002) and contact lens wearers are 12 times as likely than emmetropic non contact lens wearers to report dry eye (Nichols *et al.,* 2005). A contact lens will divide the tear film in two, the pre-lens tear film (PLTF) and the post-lens tear film (PoLTF). Both of these are approximately half the normal tear film thickness (3.5µm each; DEWS Report, 2007), but have to support a contact lens which is typically approximately 10 times this thickness. It is suggested that the PLTF relates to comfort and the PoLTF to the lens fit (Little and Bruce, 1994b). With hydrogel and silicone hydrogel lenses the PLTF has to maintain a wettable front surface as well as maintain the hydration of the lens itself (Guillon, 1998b). The insertion of a contact lens into an eye can affect the integrity of the tear film and result in ocular discomfort.

The pre lens non-invasive break up time (PL-NITBUT) is much shorter than the NITBUT when no lens is present. Tear break up on the front surface of a hydrogel contact lens occurs after 3-10 seconds (Young and Efron, 1991) resulting in reduced image quality (Tutt *et al.,* 2000). Researchers have found that pre lens tear film (PLTF) thinning time is shorter in symptomatic contact lens wearers than asymptomatic ones. It is not completely clear whether this is due to more rapid evaporation of the tears or de-wetting as a result of hydrophobic regions on the lens surface. The pre-lens lipid layer is also thinner in symptomatic contact lens patients. This finding correlated with the reduced PLTF thinning time (Nichols *et al.,* 2005) and

it was hypothesised that lipids bind to the surface of the lens resulting in increased hydrophobicity and de-wetting. The PoLTF maintains lubrication of the back surface of the contact lens and as well as flushing away tear film debris and by-products of corneal metabolism. Thinner PoLTF's are associated with lower tear exchange (Brennan *et al.,* 2001). The thicker the pre-ocular tear film prior to contact lens fitting the more likely it is that a stable lipid layer will be able to form over the contact lens (Craig, 2002).

Tear film osmolarity was found to be higher in a symptomatic group of contact lens wearers, possibly resulting from reduced lipid layer thickness allowing increased evaporation of tears. Hyperosmolarity of the tear film can subsequently cause changes in both the quantity and quality of mucins. Yasueda and colleagues demonstrated in 2005 that the density of mucin cells decreases in contact lens wearers. Mucins are responsible for lubrication of the ocular surface which is important in contact lens comfort. Surface mucins lubricate and anchor the tear film to surface epithelia. Studies looking at the effect of contact lenses on goblet cell density have produced varying results. Some have shown reduced goblet cell density with hydrogel lens wear (Knop and Brewit, 1992) while others have shown an increase (Connor *et al.,* 1994). According to the DEWS report 2007 the evidence is not yet conclusive as to whether changes in goblet cell density predispose a patient to CLIDE. Mucin expression may be up-regulated during the early years of contact lens wear, with long-term lens wear, mucin expression may return to normal levels or sub-normal levels, although this is not well understood. Further, the polar nature of mucins may be associated with their affinity for contact lens surfaces making them a component of contact lens deposition. This has potential implications in the wettability

and tolerability of contact lenses, and may be influenced by surface coatings, polymer characteristics, or care solutions.

1.6. Contact lens discontinuation

The fact that approximately 50% of contact lens wearers in the UK will cease lens wear as a result of discomfort suggests that optometrists and contact lens opticians are not identifying these patients adequately on initial presentation. Dryness is the single most common reason for lens discontinuation (Richdale *et al.,* 2007) with contact lens wearers being 12 times more likely to report symptoms of dry eye than non wearers (Nichols and Sinnott*,* 2006). Studies have also shown that symptomatic contact lens wearers tend to report an increase in symptoms towards the end of the day (Fonn *et al., 1999;* Guillon and Maissa, 2005a). There are a number of potential causes of contact lens induced dry eye (CLIDE) which can relate to patients or lens properties. For example, lenses with higher water content have been associated with an increased risk of CLIDE (Nichols and Sinnott, 2006).

There has been considerable debate on the effect that the fitting of silicone hydrogel lenses has had on these comfort related issues. While silicone hydrogel lenses have been shown to have a shorter pre lens break up time than hydrogel lenses (Nichols *et al*., 2005), other studies have demonstrated improved comfort for contact lens wearers when switching from hydrogel to silicone hydrogel lenses (Long and McNally, 2006; Schafer, 2006) In another study, patients wearing monthly (SiH) extended wear lenses reported symptoms of dryness less frequently than those wearing weekly (hydrogel) extended wear lenses (Chalmers *et al.,* 2002). A recent study found that 40% of contact lens wearers had lapsed for at least four months with

the primary reasons for discontinuation being discomfort (24%) and dryness (20%). (Dumbleton *et al*., 2013).

With regards to the modality of lens wear, those patients choosing to wear lenses on a continuous wear basis were found to experience more adverse events than those wearing on a daily wear basis but the incidence of discontinuation was similar with both modalities (Santodomingo-Rubido *et al*., 2007). A recent study by Young and colleagues found that CLIDE was more likely among toric lens wearers than spherical lens wearers (Young *et al*., 2011) though corneal staining was not found to differ between the two groups (Nichols *et al*., 2002).

Advances in contact lens material, design, replacement frequencies and care systems have improved the prospects for avoiding lens-related discomfort and for continuing contact lens wear. In a study by Young and colleagues in 2002, 236 lapsed contact lens wearers (of whom 51% cited discomfort as the principal reason for dropping out) were subsequently refitted. 77% of these lapsed wearers were still wearing lenses after one month with a further 73% of this group still wearing lenses after 6 months (Young *et al.,* 2002). The highest success in refitting was found to be with two weekly and monthly soft spherical lenses, lower rates were found with soft torics and soft bifocals. A more recent study found that, flowing an initial adaptation period, comfort scores of subjects wearing daily disposable silicone hydrogel lenses were equivalent to non-lens wearers (Morgan *et al.,* 2013). (A summary of research into contact lens discontinuation is provided in Table 1.2)

There are a large number of dry eye tests available to the practitioner. This may cause a degree of uncertainty amongst practitioners regarding which combination of

these tests is most adequate at discriminating between patients who will become successful long term wearers and those who will drop out. In this context, the availability of a simple, quick, comfortable battery of tests which could help to predict these patients would be very useful to community optometrists and contact lens opticians. This may influence the choice of lens material, modality and care system.

Author	Number of participants	Comments
Young *et al.,* 2002	236	A high proportion of lapsed contact lens wearers can be successfully refitted with contact lenses
Chalmers *et al.,* 2002	658	Symptoms of dryness are less likely with extended wear of silicone hydrogel lenses than extended wear of hydrogel lenses
Morgan PB *et al.,* 2005	100	Experienced wearers are less likely to discontinue contact lens wear compared with neophytes
Richdale K *et al*., 2007	730	62% of subjects were current or previous lens wearers. 26.3% of these reported contact lens dissatisfaction and 24.1% had discontinued lens wear.
Santodomingo-Rubido *et al*., 2007.	51	A similar incidence of discontinuation was found with daily and continuous wear modalities
Dumbleton *et al*., 2013	4207	23% of those surveyed had discontinued lens wear permanently. Primary reasons for discontinuation were discomfort (24%) and dryness (20%).
Morgan *et al.,* 2013	74	Comfort scores were equivalent for a group of contact lens wearers compared to a group of non contact lens wearers.

Table 1.2: Studies investigating contact lens discontinuation

1.7 Contact lens properties and their relationship to CLIDE

1.7.1 Modulus

The modulus of a contact lens is a measure of its "stiffness"; in general silicone hydrogel (SiH) materials have higher moduli than hydrogels (Jones *et al.,* 2006). Increasing a lens modulus can bring advantages, for example increased durability and easier handling (Jones *et al.,* 2002a). However, higher moduli have also been associated with an increase in mechanical complications such as Superior Epithelial Arcuate Lesions (SEALs; Figure 1.5) and papillary conjunctivitis (Dumbleton, 2003; Figure 1.6). The contribution of lens modulus to CLIDE is still not clear (Sindt and Longmuir, 2007).

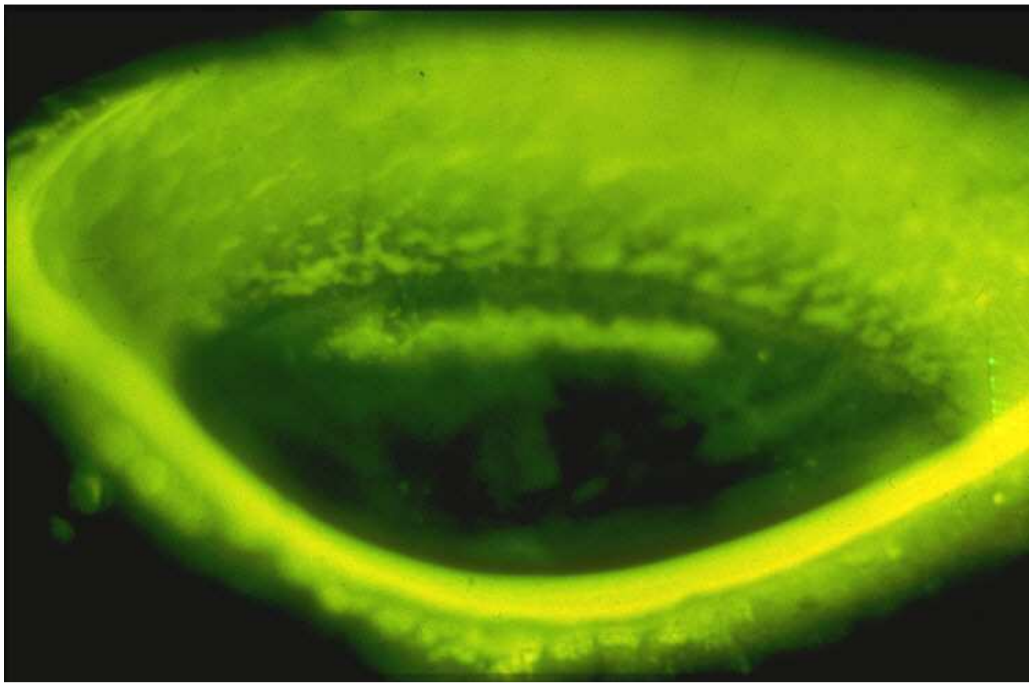

Figure 1.5: Superior Epithelial Arcuate Lesion

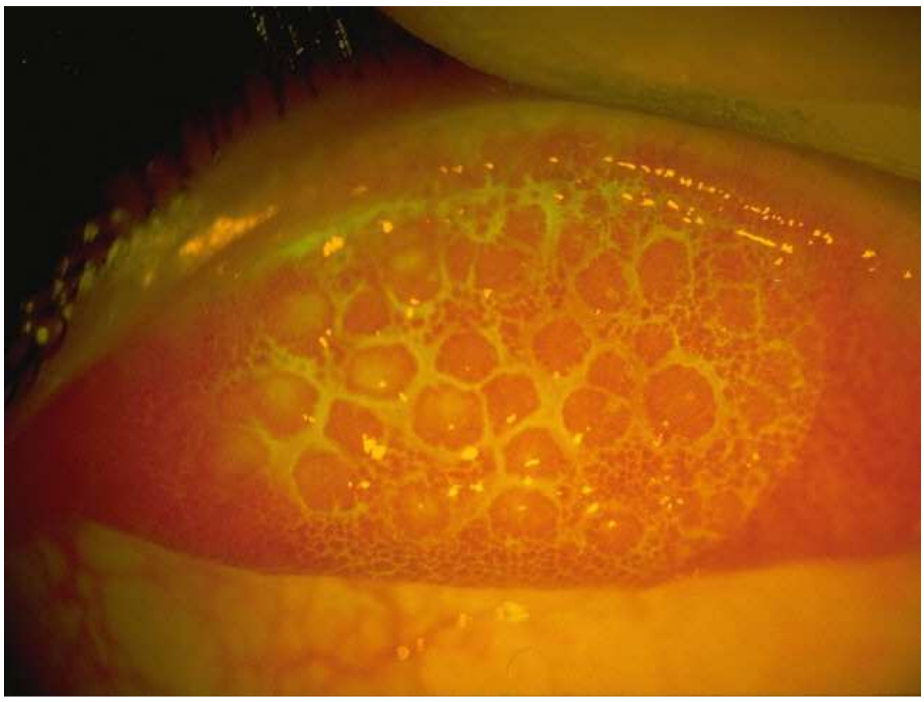

Figure 1.6: Contact lens associated papillary conjunctivitis

1.7.2 Wettability

Surface wettability is a measure of how the tear film spreads across the contact lens material during a blink. The standard method employed in-vitro to measure wettability of a contact lens is the captive air bubble technique. In theory, lower contact angles (better wetting) should result in reduced CLIDE and symptoms of dryness have been shown to be closely related to the surface wettability of a contact lens (Tonge *et al.,* 2001). SiH lenses have poorer wettability than hydrogels because silicone is inherently hydrophobic (Cheng *et al.,* 2004). Manufacturers have adopted a number of different approaches to try to overcome this problem and render their lenses more wettable (Jones *et al.,* 2006). Bausch & Lomb surface treat their lenses in a reactive gas plasma chamber transforming the silicone components into hydrophilic silicate islands. These isolated hydrophilic areas on the lens surface bridge the underlying hydrophobic surface improving wettability (Valint *et al.,* 2001). Alcon (formerly Ciba

Vision) apply an extremely thin, uniform hydrophilic plasma coating onto the surface of their SiH lenses following manufacture (Lopez *et al.,* 2002) to improve wettability. Johnson & Johnson do not use surface treatments to improve wettability of their SiH lenses; instead their materials contain polyvinyl pyrollidone (Jones *et al.,*2006), a wetting agent designed to minimise on-eye dehydration (Osborne and Keys, 2005). Coopervision's Comfilcon A employs neither a surface coating nor an internal wetting agent. It utilises long chain silicone polymers to produce a wettable material. The Sauflon Clariti lens also adopts a non surface-coated approach. The manufacturer claims that a process, known as “Aquagen” allows the lenses to maintain a low wetting angle for the wearing time of the lens, but no research papers are currently available on this lens.

1.7.3 Oxygen transmissibility

The relationship between oxygen transmissibility of a contact lens and CLIDE is disputed. Studies have demonstrated improved comfort for contact lens wearers when switching from hydrogel to SiH lenses (Long *et al.,*2006; Schafer *et al.,*2006) but it is not clear what role increased oxygen permeability plays in this. These studies switched hydrogel lens wearers to SiH lenses, with no masked control group so there is the potential for bias. There seems to be a consensus of opinion that any increased comfort experienced on switching from hydrogel to SiH lenses is more likely to be attributable to other factors such as the maintenance of the lens hydration and lubricity than to oxygen permeability (Nichols, 2004a; Ross, *2005;* Long *et al.*, 2006; Riley *et al*., 2006) . Studies have shown that wearers of low Dk hydrogel lenses demonstrate reduced corneal sensitivity (Liesegang, 2002) resulting in a reduction in tear production by the lacrimal gland (Bourcier *et al.,* 2005).

1.7.4 Lubricity

The lubricity of a contact lens is a measure of how well the material resists friction (French and Jones, 2008). The coefficient of friction (CoF) of a lens gives an indication of the friction experienced by an eyelid when it moves over the surface of the contact lens and is influenced by properties such as lubricity, wettability and deposition rate. (Ross, 2005). Recently a protocol has been developed to measure the CoF of contact lenses (Roba *et al.,* 2011). The table below (Table 1.3) shows the CoFs for a range of currently available soft contact lenses.

Table 1.3: CoF values for a range of contact lens materials (Roba M *et al.,* 2011)

A human cornea has a CoF of 0.05 ± 0.02 (whereas soft contact lenses can be as high as 8 times this (Cobb *et* al., 2008; Table 1.3).The lower the CoF (higher lubricity) the less irritation of the lid wiper may be expected. "Comfort enhancing" contact lenses may have lower CoF compared to their counterparts (Ross and Tighe, 2010).

1.7.5 Deposition

Surface wettability will be reduced if a lens surface is deposited, particularly by lipids which are hydrophobic (Lorentz and Jones, 2007). In the period between blinks the lens surface can dry out, non-wetted areas will then attract hydrophobic components from the tear film, these will further disrupt the tear film and can cause further drying and deposition (Tighe and Franklin, 1997). The tear film protein lysozyme deposits significantly less on SiH lenses than hydrogels, particularly group IV materials (Senchyna *et al.,* 2004). On the other hand, lipid deposition on SiH lenses is considerably higher than on hydrogels (Ghormley *et al.,* 2006) requiring patients to comply with rub and rinse steps to maintain the optimum levels of both vision and comfort (Ghormley and Jones, 2006). A more frequent replacement schedule may also benefit patients with troublesome lipid deposition (Carney *et al.,*2008).

1.8 Evaluation of tear film and the ocular surface

1.8.1 Non Invasive Break Up time (NITBUT)

An accepted method of assessing tear film quality is to project a grid onto the cornea and observe its reflection. Traditionally this grid has been observed by a practitioner for any disruption which would indicate tear film break up. This method has been used by the Tearscope (Keeler) and now by the Keratograph (Oculus) (Figure 1.7). The Tearscope uses a cold cathode light source which is designed to be as far away from the eye as possible, combined with a heat sink which draws the heat away from the light via the handle. This design reduces any heat related drying effect. The Tearscope can be used with or without a slit lamp; slit lamp observation allows higher

magnification and a more sensitive assessment of the tear film (Guillon 1998a, Guillon 1998b, Elliott *et al.,* 1998).

Figure 1.7: Keratograph (Oculus)

The above image was kindly provided by Birmingham Optical Group

The Keratograph illumination system consists of 200 red LEDs (wavelength 653nm), these emit little heat, minimising thermally induced alterations to the tear film. An illuminated ring pattern is projected onto the cornea in the form of a Placido disk consisting of 22 rings. Once the patient is correctly aligned the software prompts the practitioner to ask the patient to blink twice. The second blink triggers the video recording and measurement. The measurement finishes when one of two events occurs; either the subject blinks or significant distortion of the reflected image of the Placido rings occurs (Figure 1.8). The following information is then presented to the practitioner (Figures 1.9 and 1.10):

- a video recording of the reflected mires

- time to first break up (1/100ths of a second)
- total measuring time (1/100ths of a second)
- a tear map showing when tear break up occurred across the cornea adjacent to a colour coding scale

Dry patches which break up early are indicated in red, areas of longer break-up (>15 seconds) or where no break-up has been detected after 30.4 (the maximum recording time) seconds are indicated by varying shades of green. The colour coded tear map is a very useful tool when discussing tear film quality with patients. NITBUT was determined using a Tearscope Plus (Keeler Ltd, Windsor, UK) with a fine grid insert (Guillon, 1998b). This grid was observed by a practitioner for any disruption which would indicate tear film break up with the NIBUT recorded as the time measured, in seconds, between the a complete blink and the first observed break in the tear film or an uncontrollable blink caused by discomfort. Three consecutive readings separated by at least 60 seconds were taken and the median recorded.

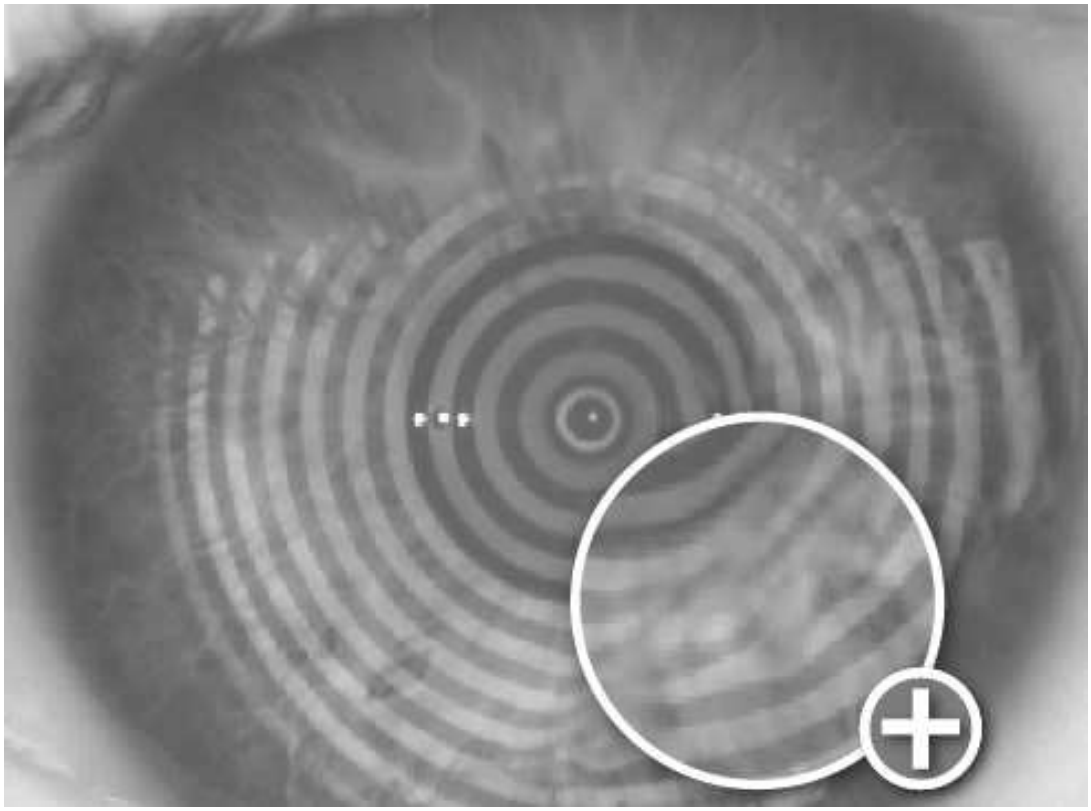

Figure 1.8: Distortion of the Placido disc rings can be seen in the large white circle. This represents areas of tear film break up.

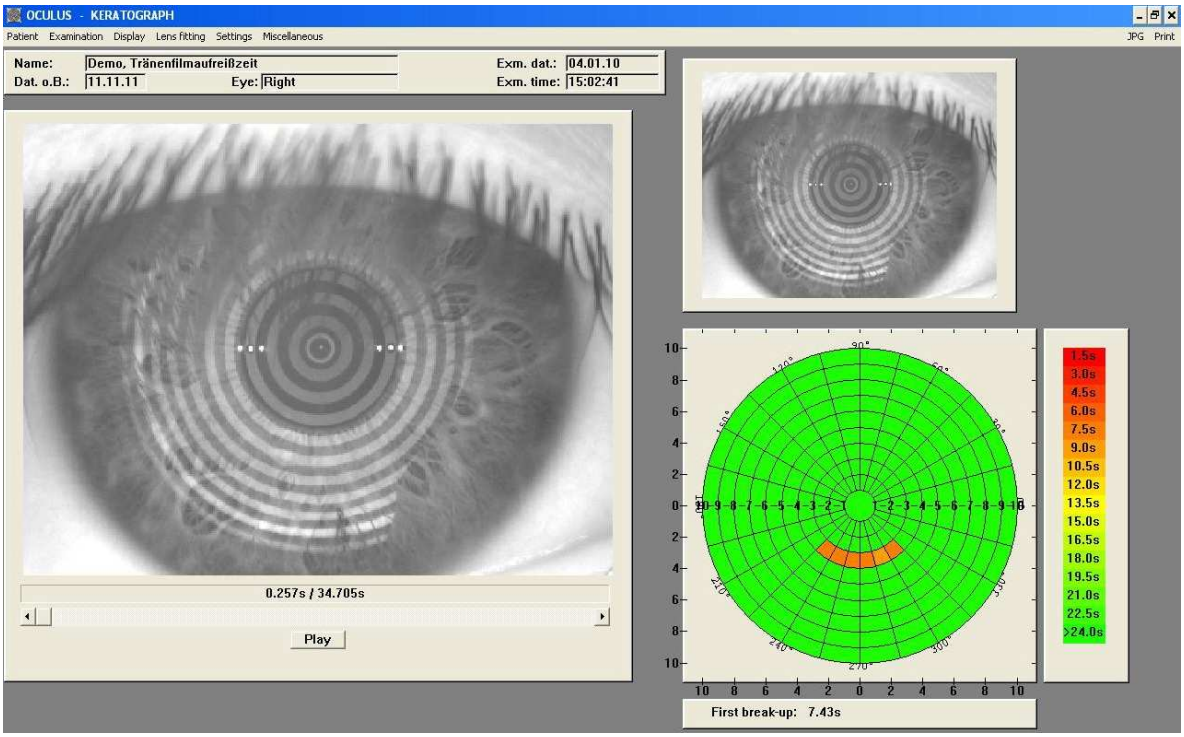

Figure 1.9: Information provided to the practitioner by the Keratograph. The image on the left hand side is a video which can be replayed to allow the practitioner to view the tear film break up. The times beneath indicate the time to first tear film break up and the time the instrument stopped recording. The colour image in the bottom right hand corner gives allows practitioners' to see where and when break up occurred.

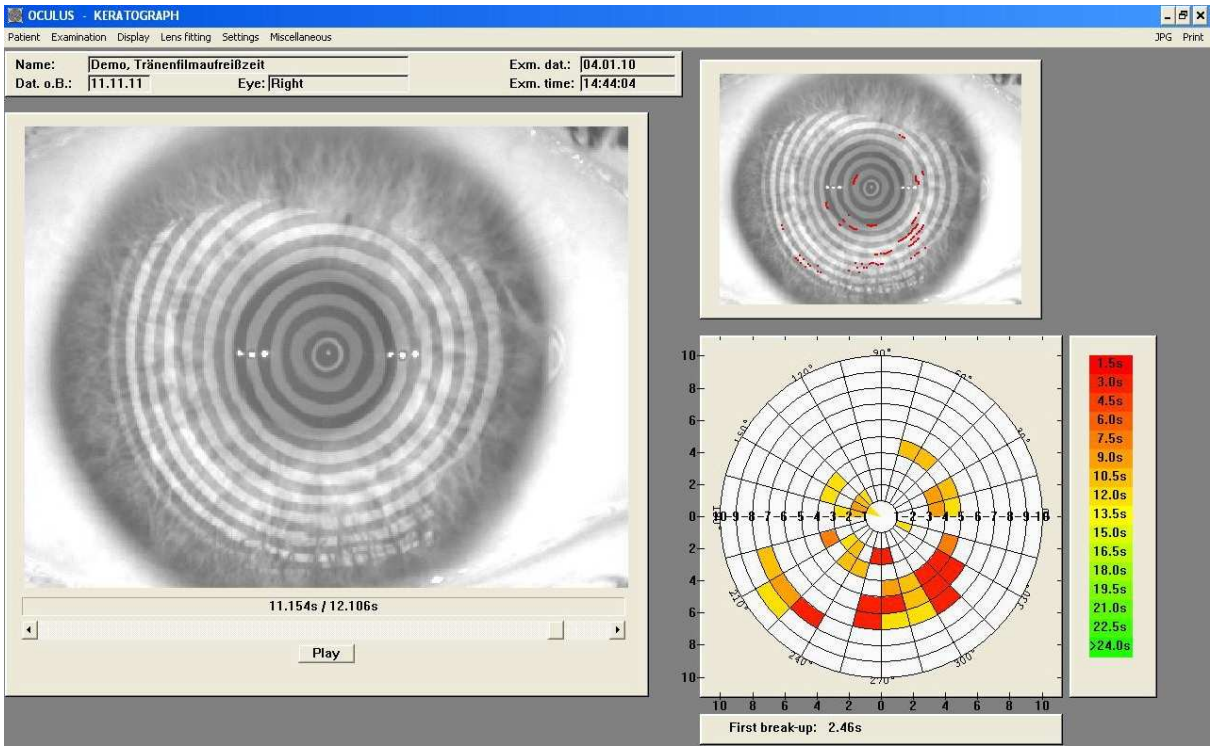

Figure 1.10: Information provided to the practitioner by the Keratograph. The image on the left hand side is a video which can be replayed to allow the practitioner to view the tear film break up. The times beneath indicate the time to first tear film break up and the time the instrument stopped recording. The colour image in the bottom right hand corner gives allows practitioners' to see where and when break up occurred.

Figures 1.8, 1.9 and 1.10 were kindly provided by Birmingham Optical Group

Successful contact lens wearers show a median break-up time of approximately 20 seconds and intolerant wearers 13 seconds (Glasson *et al,* 2003). Other investigators assumed that NIBUT or BUT are poorly related to patient symptoms (Nichols *et al,* 2004). However, NIBUT is recommended by the International Dry Eye Workshop (DEWS), who define the threshold as <10secs (DEWS, The Ocular Surface, 2007).

1.8.2

Tear meniscus height

A normal pre-ocular tear film should be continuous over the cornea, conjunctiva and lid margin (Figure 1.11). The height of the tear meniscus can give some indication of tear volume. Slit lamp cameras allow the tear meniscus to be photographed and measured accurately using the camera's software. Another method is to rotate the slit beam until it is horizontal and adjust the width of the slit until it matches the height of the tear prism. The tear meniscus height (TMH) should be measured directly below the pupil centre. Tear meniscus height is classified as follows: good: > 0.2 mm; normal: = 0.2 mm; poor < 0.2 mm (Kawai *et al*., 2007).

Many studies demonstrate athe good correlation between TMH and symptoms of dryness (Glasson *et al*., 2003; Mainstone *et al.,* 1996; Golding *et al.,* 1997) .
Tear meniscus height was measured in millimetres using the tear analysis software on the Keratograph at the centre of the lower lid. Three consecutive readings were taken and the median recorded. (This method of TMH measurement has not been previously validated).

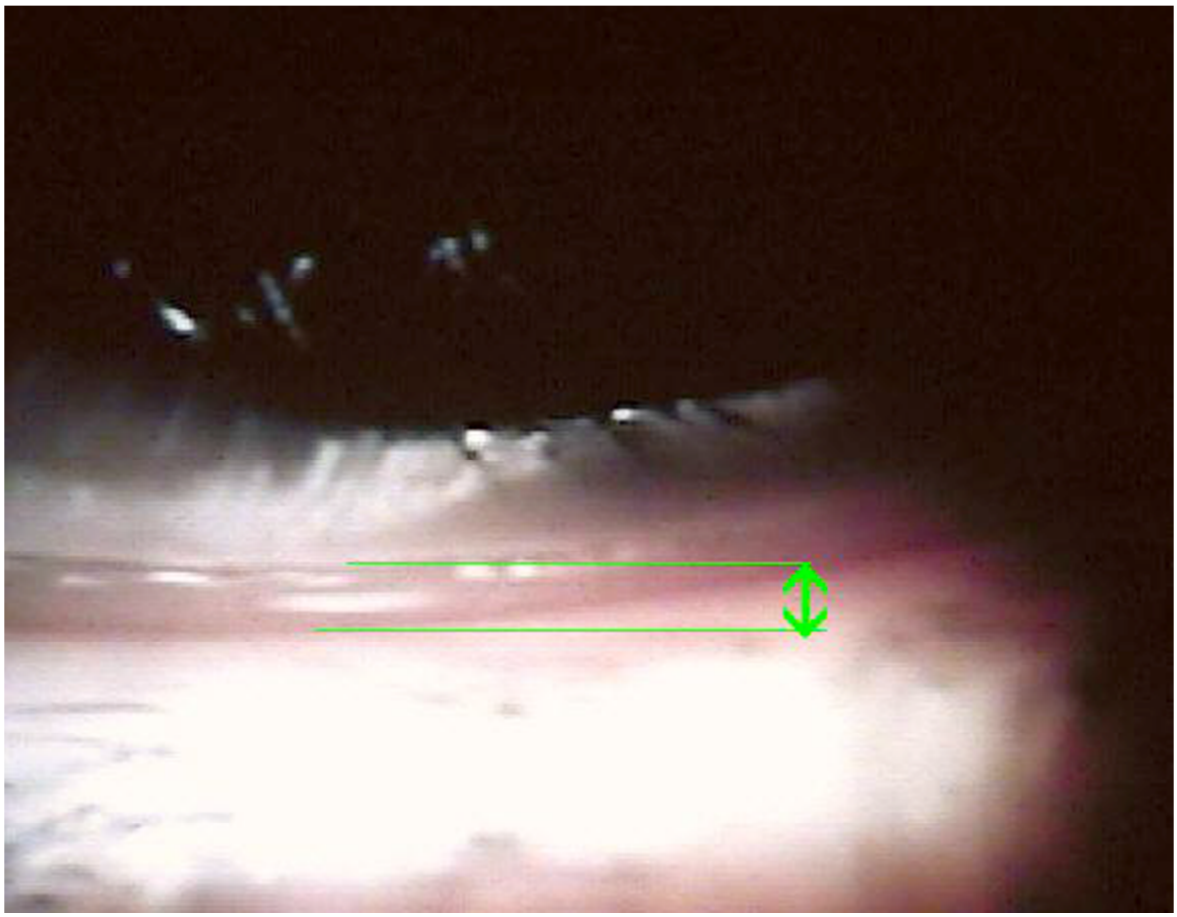

Figure 1.11: Tear meniscus of the lower lid, observed with a slit lamp microscope in 12x magnification. The horizontal green lines indicate the upper and lower edges of the tear meniscus. Tear meniscus height is classified as good: > 0.2 mm; normal: = 0.2 mm; poor < 0.2 mm

The above image was kindly provided by Dr Heiko Pult

1.8.3

Bulbar and limbal hyperaemia

Bulbar or limbal hyperaemia is a common clinical finding in optometric practice associated with a large number of causes including infection, allergy, contact lens wear and foreign body reactions (Papas, 1998).. Bulbar hyperaemia is normally associated with general ocular factors (Brennan *et al.,* 2002) while limbal hyperaemia

tends to be associated with corneal insult (Efron, 2004). The relationship between dry eye and ocular hyperaemia is not clear (Solomon, 2001; Dumbleton *et al.,* 2006). Soft lens wearers tend to demonstrate more limbal hyperaemia (Figure 1.12) than RGP wearers (McMonnies and Chapman-Davies, 1987a) but this has been shown to reduce when patients are re-fiited with high Dk silicone hydrogel contact lenses (Papas *et al.,* 1998) suggesting that the limbal hyperaemia is a response to corneal hypoxia.

Bulbar and limbal hyperaemia were evaluated through a slit lamp microscope using 16x magnification and a diffuse white light (Dundas et al., 2001). They were graded using the Cornea and Contact Lens Research Unit (CCLRU) grading scale interpolated in 0.1 increments (Bailey *et al.,* 1991).

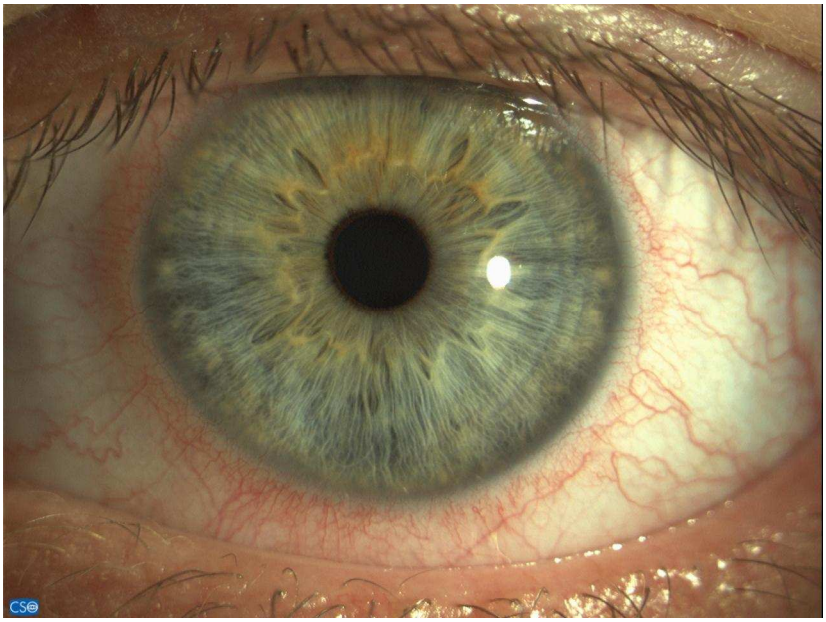

Figure 1.12: Soft hydrogel lens wearer demonstrating limbal hyperaemia

1.8.4

Lid parallel conjunctival folds (LIPCOF)

LIPCOF are folds in the lower conjunctiva parallel to the lower lid margin (figure 1.13) (Pult and Sickenberger, 2000), which have been shown to be predictive of dry eye symptoms in contact lens wearers (Pult *et al.,* 2008). They were evaluated without the instillation of fluorescein using a 2-3 mm wide vertical slit located along the temporal limbus at an angle between the observation and illumination system of 20-30 degrees, viewed at 25X magnification. The slit lamp beam should run from the temporal limbus to the inferior bulbar conjunctiva just above the lower lid margin. LIPCOF was graded using a four point scale according to table 1.43.2 below :

Grade 0	No parallel fold
Grade 1	1 parallel fold
Grade 2	2 parallel folds with a height of <0.2mm
Grade 3	Several parallel folds with a height of >0.2mm

Table 1.4: LIPCOF grading scale (Pult H and Sickenberger W, 2000)

LIPCOF graded ≥ grade 2 is likely to be associated with dry eye symptoms (Begley, 2003).

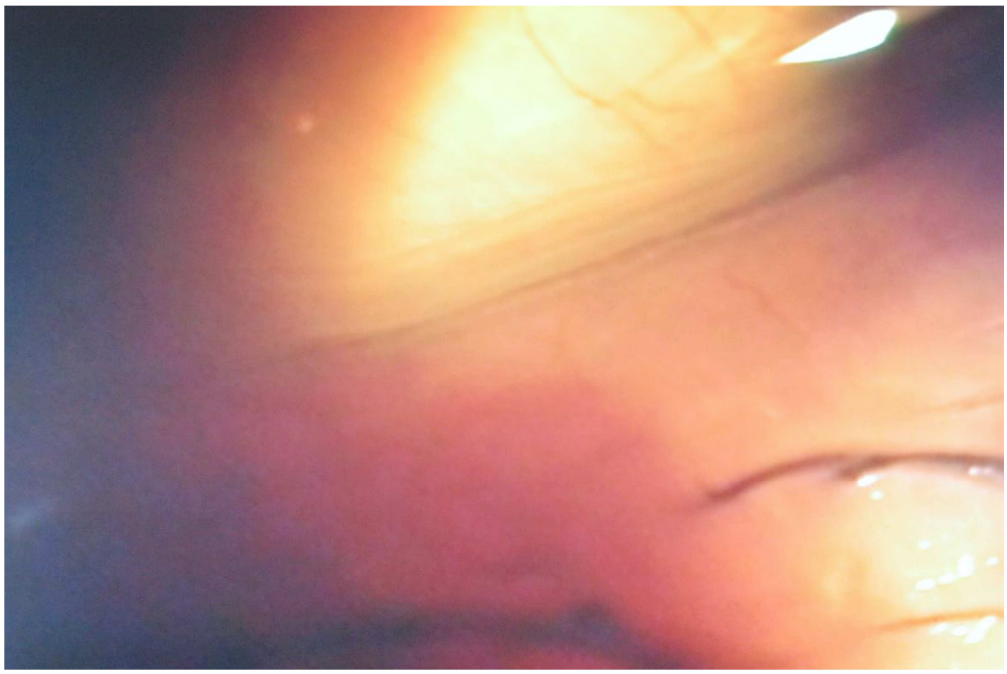

Figure 1.13: Grade 3 LIPCOF (more than 2 parallel folds are visible)

The above image was kindly provided by Dr Heiko Pult

It is believed that friction between the upper eyelid and bulbar conjunctiva interferes with conjunctival lymphatic flow resulting in dilation and ultimately folds (Meller and Tsang, 1998).

1.8.5

Osmolarity

The tears of patients with dry eyes generally have a higher osmolarity than normal patients (Gilbard, 1986), this hyperosmolarity being a primary cause of the inflammation seen in dry eye patients resulting in both ocular discomfort and surface damage (Farris *et al.,* 1983, Gilbard *et al.,* 1978). Hyperosmolarity can be the trigger for an inflammatory cascade resulting in the production of inflammatory cytokines (Li *et al.,* 2004) which can lead to increased apoptosis of corneal and conjunctival epithelial cells and conjunctival goblet cells. A reduction in goblet cells will result in reduced mucin production (Argueso *et al.,* 2002) and increased tear film instability

(DEWS Report 2007). For many years scientists have believed that tear film osmolarity is likely to have the ability to be highly diagnostic of dry eye disease. Tear film osmolarity is a single biophysical measurement that can provide much information about the balance between tear production, retention and elimination (Tomlinson *et al.,* 2006).

Tear osmolarity has traditionally been measured by laboratory based research scientists. A complex and lengthy procedure was involved to calibrate the devices and collect tear samples. One method measured tear osmolarity by observing the change in the freezing point of tear samples (Gilbard and Farris, 1979; Farris *et al.,*1983). This required approximately 0.2 microlitres of tears, a high level of training by the user and constant equipment maintenance. Errors could occur due to tear sample evaporation (Nelson and Wright, 1986; Tomlinson *et al.,* 2006). Electrical conductivity of the tear film can also be used to measure tear osmolarity (Ogasawara *et al.,* 1996) but it requires a sensor to be placed onto the ocular surface which could precipitate reflex tearing.

The Tearlab (TearLab Ltd, San Diego, CA, USA) is an osmometer that offers a relatively expertise-free method for tear osmolarity measurement (Figure 1.14). It requires only a very small volume of tears so can be used in subjects with relatively dry ocular surfaces. It can be used by non-professional staff and technicians (Srinivasan *et al.,* 2010). Osmolarity is determined by measuring the impedance of an electric current passed through a very small sample of tears (< 50 nanolitres). (Sullivan, 2005). A tear collection device known as a "Tearlab Osmolarity System Pen" was placed lightly onto the patient’s lower tear meniscus from where it draws tears into the test card. An audible signal allows the user to know that sufficient tears

have been collected. The "pen" was then transferred to the "Tearlab Osmolarity System Reader" which automatically converted the tear fluid sample data into an osmolarity measurement which it displays on its LCD.

Figure 1.14: Tearlab

(kindly provided by Birmingham Optical Group)

In 2006 Tomlinson and colleagues performed a meta-analysis on published data for tear osmolarity in samples of both normal eyes and different subtypes of dry eye. Their study showed that a value of 316 mOsmol/L had a sensitivity of 59%, specificity of 94% and a predictive accuracy of 89% for diagnosing dry eye disease. In 1978 Gilbard and colleagues chose 312 mOsmol/L as an osmolarity referent for keratoconjunctivitis sicca to avoid under-diagnosis. This figure gave a sensitivity of 94.7% and a specificity of 93.7%, but its high sensitivity may in part be attributable to the fact that osmolarity was included in selection criteria for the subjects, introducing selection bias (Knottnerus *et al*., 2002).

In 2010 researchers demonstrated a strong correlation (r=0.904; p=0.006) between the Tearlab and the Clifton osmometer (Tomlinson *et al*., 2010). They obtained values with the Tearlab of 308±6 mOsmol/L for the control group and 321±16 mOsmol/L for dry eye patients. Another study (Versura *et al.,* 2010) found a stepwise increase in osmolarity directly proportional to the severity of dry eye. The control group had tear osmolarity of 296.5±9.8 mOsm/L. The mild dry eye group had tear osmolarity of 298.1±10.6 mOsm/L, the moderate dry eye group had tear osmolarity of 306.7±9.5 mOsm/L while the severe dry eye group were found to have osmolarity 314.4±10.1 mOsmol/L. In another study, the single best indicator of dry eye disease severity across different dry eye categories has been shown to be osmolarity (Sullivan *et al.,* 2010) but the same study found that traditional clinical tests including corneal staining, conjunctival staining and the Schirmer test were also useful in diagnosing severe dry eye disease.

1.8.6

Phenol red thread

The phenol red thread test is used to assess tear quantity. The phenol red thread test is less invasive than the Schirmer test and as a result it should result in less reflex tearing. The test consists of a cotton thread treated with the pH indicator phenol red (phenolsulfonphthalein) which is initially yellow in colour, but changes to light red on contact with tear fluid. The folded end of the thread was placed in the inferior temporal conjunctival sac (Figure 1.15) and left in position for 15 seconds. The patient was instructed to look ahead and blink normally. The thread was then removed and the entire length of the red portion measured by a ruler to the nearest 0.5mm, including the folded section. This test has been shown to be repeatable and the results should be interpreted as follows (Little and Bruce, 1994a):

- < 11 mm wet suggests low tear secretion
- 11-16 mm wet suggests borderline secretion
- >21 mm wet suggests normal tear flow

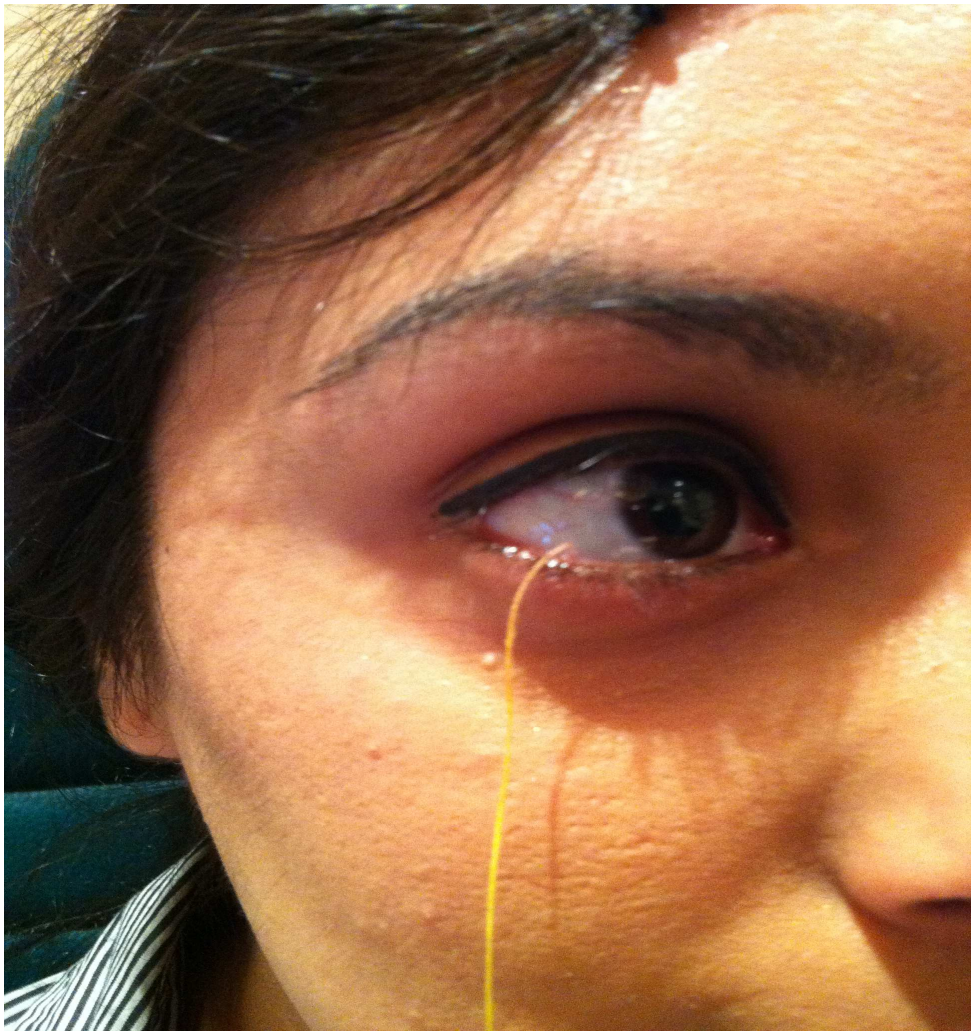

Figure 1.15: A phenol red thread in situ

1.8.7

Fluorescein break up time (TBUT)

Traditionally tear film quality has been assessed by measuring the time it takes the tear film to ‘break-up’. Assessing this property of the tear film is difficult as the tear film is transparent, so fluorescein dye can be introduced into the tears to make observation of the tear film break up easier. Following instillation the patient is asked to blink a few times to spread the dye over the surface of the eye. The uniform green film is observed and the time recorded for black patches to start to appear, as these are signs of the tear film breaking up (Figure 1.16).

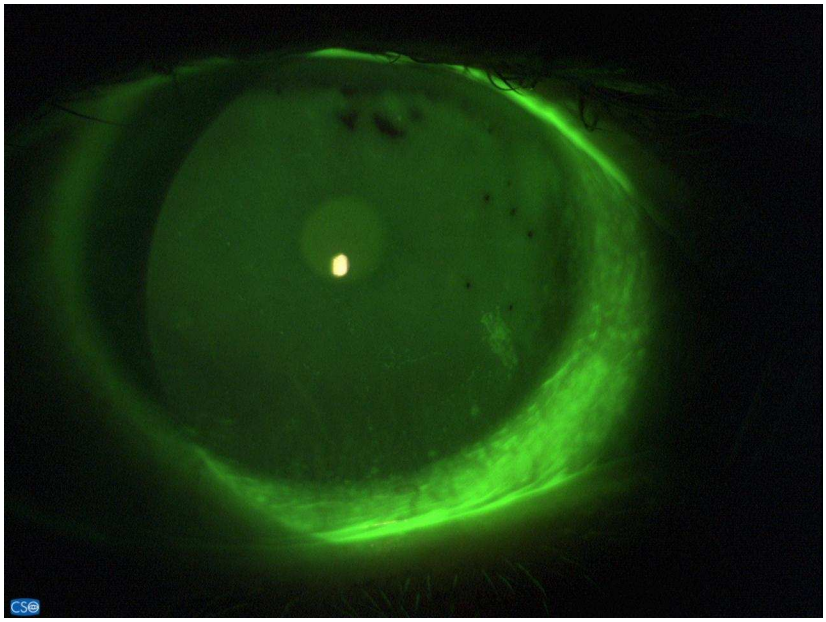

Figure 1.16: Black patches, demonstrating tear film break up, are visible superiorly and nasally on this right cornea.

A FBUT less than 10 seconds is usually considered abnormal (Lemp,1995). The main problem with this procedure is that once the dye has been introduced into the tear film it is no longer "normal" and may react differently than it would have done

had the dye not been introduced. In this study, tear film TBUT was measured following the instillation of fluorescein into the temporal lower palpebral conjunctiva by a moist fluoret. The cornea was then observed under blue light to excite the fluorescein molecules, through a yellow enhancement filter (Peterson *et al.,* 2006). The patient was instructed to blink and the time in seconds to the first observed tear film break-up or the first uncontrollable blink measured. Three consecutive readings were taken and the median recorded.

1.8.8

Corneal staining

In patients with dry eye the corneal or conjunctival surfaces and/or the intracellular surfaces become compromised (Korb, 2002), staining agents allow these changes to be viewed. The most commonly used stain in optometric practice is sodium fluorescein**.** Sodium fluorescein is a pH-dependent indicator dye which derives its functionality from its fluorescent properties (Morgan and Moldonado-Codina, 2009). At a typical ocular surface pH (6.5-8) the colour of fluorescence remains a constant green (Wang *et al.,* 2002). When exposed to light of a wavelength of 495nm, maximum excitation of fluorescein is obtained. A blue filter is placed in the illumination system, this blocks the wavelengths that don't excite fluorescein molecules so only useful light is shone onto the eye. A Kodak Wratten 12 barrier or equivalent yellow filter in the viewing system will absorb the unwanted reflected light and transmit only the longer wavelengths emitted by the fluorescein, when excited by the blue light. Peterson and colleagues (2006) demonstrated that a moistened fluoret, shaken to remove excess saline, provided a peak intensity of fluorescence after about 1 minute, a reasonable time to wait in optometric practice. Though the

reasons why are poorly understood, an increase in corneal staining has been shown to occur with sequential doses of fluorescein (Korb and Herman, 1979). It has been shown that low levels of fluorescein can enter healthy corneal epithelium through tight cell junctions but at insufficient levels to be detected with a slit lamp (McNamara *et al.,* 1998).

Corneal staining is believed to be observed when fluorescein enters damaged epithelial cells (Wilson *et al.,*1995) though there is evidence that fluorescein can diffuse into adjoining cells (Kanno and Loewenstein, 1964). Some degree of staining is found in up to 79% of corneas in healthy non contact lens wearing patients (Dundas *et al.,* 2001). The cornea's stem cells are located at the limbus and the process of corneal and limbal epithelial cell proliferation has been shown to be affected by contact lens wear. Both daily and overnight wear cause a reduction in the number of exfoliating cells (Ladage *et al.*, 2001) and that this could result in increased corneal staining. There are a number of different corneal staining patterns commonly seen in contact lens wearers. Superior epithelial arcuate lesions are associated with poor fitting, high modulus lenses (Figure 1.17). Desiccation staining on the inferior cornea of a soft lens wearer is sometimes referred to as a smile stain (Figures 1.18 & 1.19) whilst solution staining can be diffuse or annular (Figure 1.20). Once the cause has been removed corneal staining can resolve very quickly, overnight in the case of superficial staining.

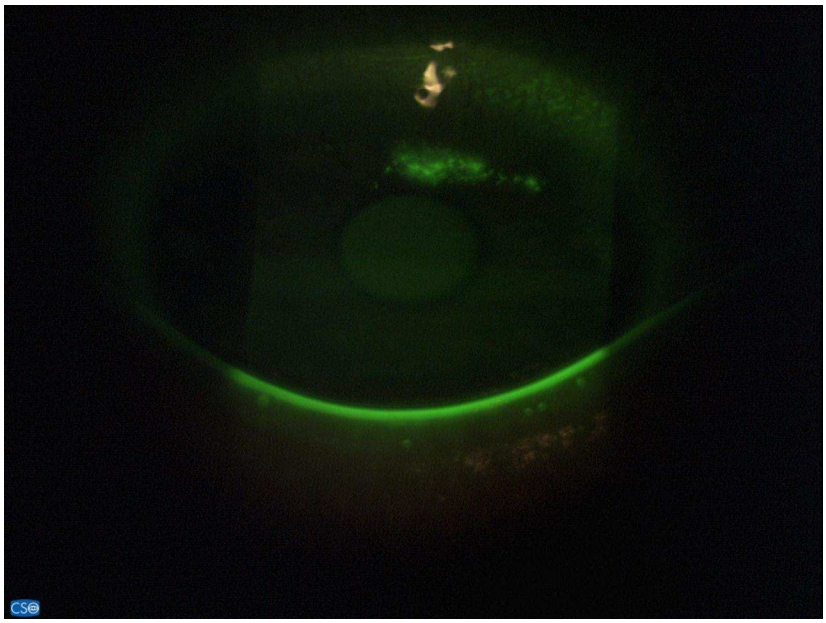

Figure 1.17: Superior epithelial arcuate lesions which are associated with high modulus poor fitting lenses.

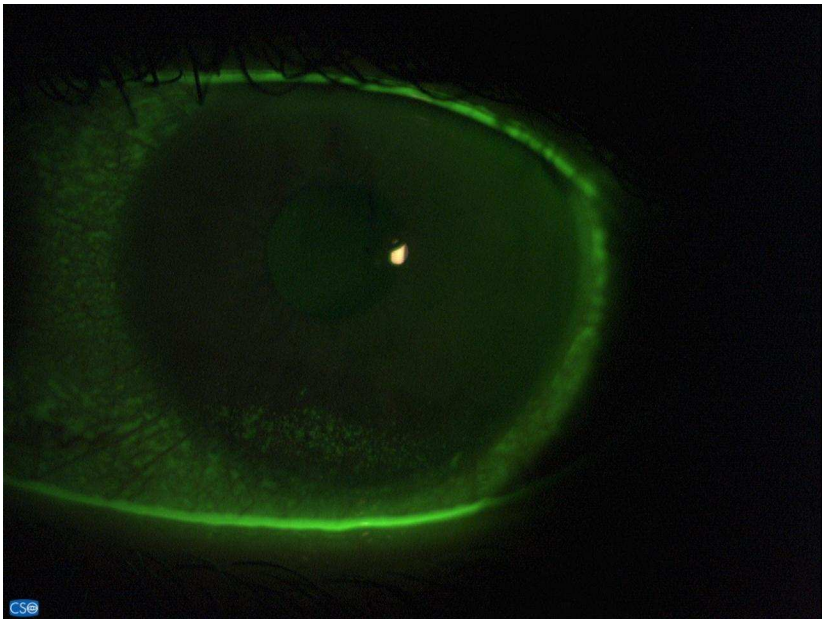

Figure 1.18: Superficial inferior punctate staining, often associated with incomplete blinking and dry eye.

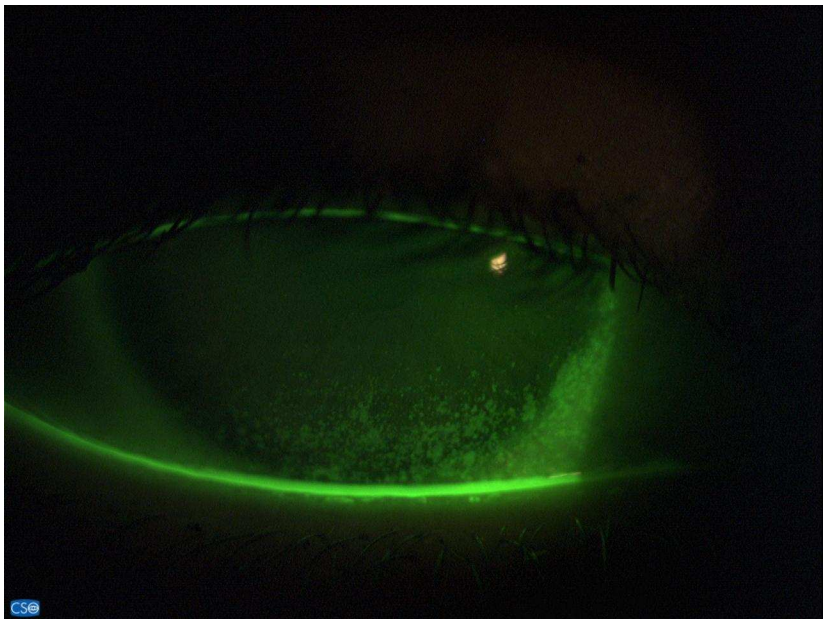

Figure 1.19: Inferior punctate staining, often associated with incomplete blinking and mild dry eye.

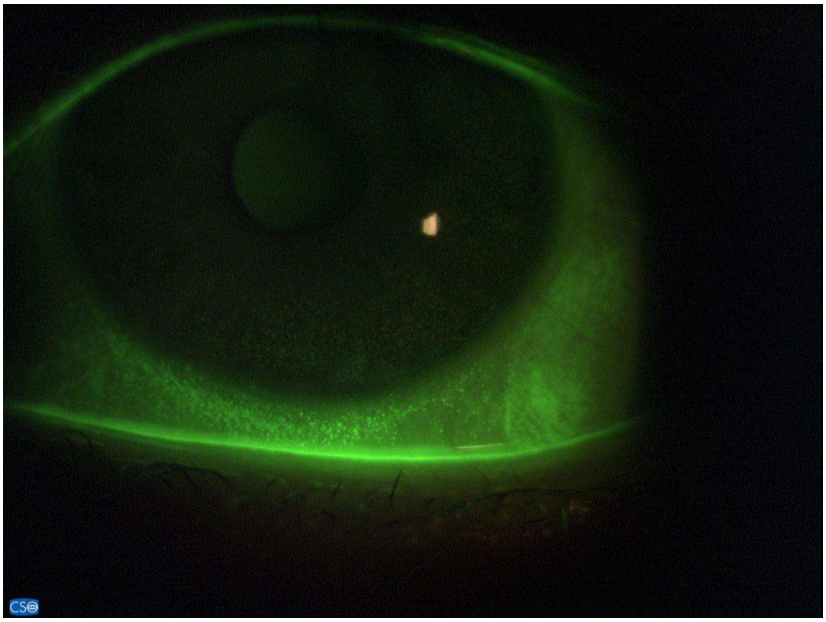

Figure 1.20: Diffuse annular staining associated with solution staining.

Corneal staining was visualised under blue light to excite the fluorescein molecules, observed through a yellow enhancement filter to optimise visualisation following the instillation of fluorescein and its extent classified using the CCLRU grading scale interpolated to 0.1 intervals (Bailey *et al.,* 1991, Peterson *et al.,* 2006).

1.8.9

Conjunctival staining

Lissamine green is primarily a conjunctival dye which stains dead and degenerate cells (Feenstra *et al.,* 1992) and areas of the conjunctiva not protected by mucus. It now seems to be replacing rose bengal as the preferred dye for conjunctival staining due to better availability and causing less discomfort (Machado *et al.,* 2009). It is instilled using impregnated paper strips containing 1.5mg of the dye. A drop of sterile saline is added to the strip before it is placed into the lower fornix of the eye. A relatively large volume should be instilled (10-20 microlitres) and a Wratten 25 filter or equivalent red can be used to enhance the staining contrast against the white sclera (Figure 1.21). Uchiyama and colleague suggested in 2007 that conjunctival staining with lissamine green could show up prior to corneal staining with fluorescein in patients with early dry eye.

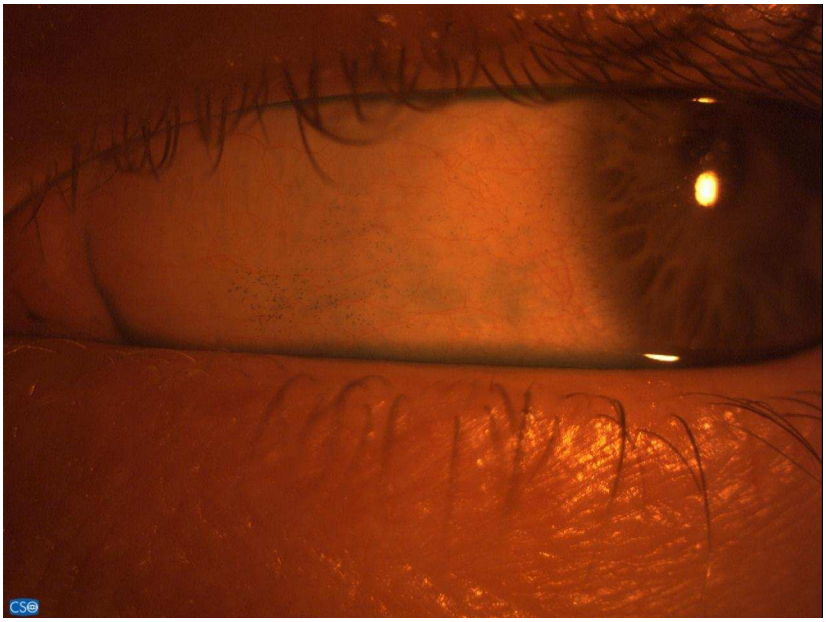

Figure 1.21: Conjunctival staining visible following instillation of lissamine green

In this study, conjunctival staining was visualised through a Wratten 25 red filter following the instillation of lissamine green and classified using the CCLRU grading scale interpolated to 0.1 intervals (Bailey *et al.,* 1991).

1.8.10

Lid wiper epitheliopathy

The lid wiper is the region of the marginal conjunctiva of the upper eyelid that wipes over the cornea and conjunctiva during blinking (Korb *et al.,* 2002a). Lid wiper eitheliopathy (LWE) has been shown to occur in both contact lens wearers and non contact lens wearers with dry eye symptoms (Korb *et al.,* 2002a). In a study by Korb and colleagues in 2005 LWE was found to be present in 76% of patients with symptoms suggestive of dry eye states but who had normal fluorescein break up times, normal Schirmer scores and no corneal staining. The lid wiper region, unlike the rest of the palpebral conjunctiva, consists of stratified squamous epithelium

(Ehlers, 1965), a characteristic finding in other parts of the human body tissues that experience frequent rubbing. The blink rate ranges from 3 to 15 times per minute or up to 5 million blinks per year (Monster *et al.,* 1978) so the benefit of having a lubricated interface is obvious. In a healthy eye the tear film will provide this lubricating effect, in a dry eye insufficient lubrication at the lid wiper-ocular surface interface can result in friction and damage to the ocular surface. Once the lid wiper is damaged and inflamed the very act of blinking can cause discomfort and further micro trauma and a vicious circle can ensue.

In this study Lissamine Green was used to stain the lid wiper. Care was taken to differentiate the staining associated with Marx's line (Figure 1.22) from staining of the lid wiper (Korb *et al.,* 2002a). In 1992 when discussing Marx's line Norn and colleagues (Norn, 1973) noted that: "*The line runs along the lid margin in relation to the base of the tear meniscus just behind the orifices of the meibomian glands. It forms an imprint, as it were, of the course of the streaming lacrimation."*

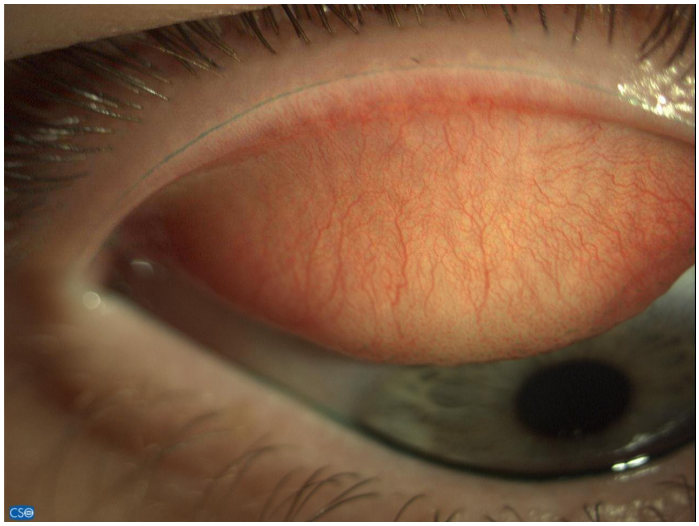

Figure 1.22: Marx's line

Following the instillation of the lissamine green, the upper eyelid was everted and the length and sagittal width of any staining present were measured. The sagittal width of the lid wiper extends from just proximal to the line of Marx to the sub-tarsal fold. The staining was graded as follows (Korb *et al.,* 2002a):

Staining length:	Staining width
<2mm = grade 0	<25% = grade 0
2-4mm = grade 1	25-50% = grade 1
5-9 mm = grade 2	50-75% = grade 2
>9 mm = grade 3	>75% = grade 3

The individual grades for each of these two characteristics were averaged for a final grade for LWE. For example if a patient demonstrated 4 mm of LWE (grade 1) with a staining width estimated as 60% of the lid wiper (grade 2) the overall LWE would be graded as the average of these two numbers i.e. 1.5. An example of a grade 3 LWE is shown in figure 1.23.

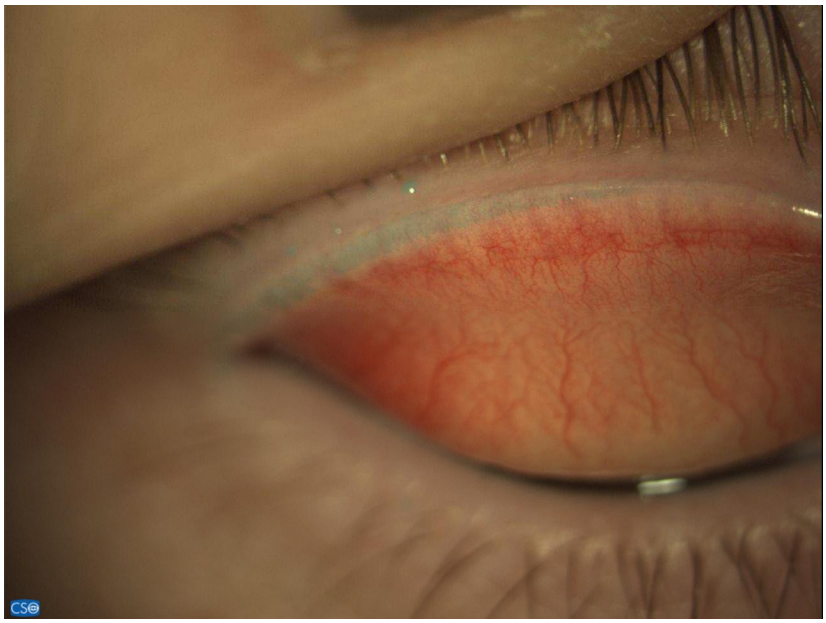

Figure 1.23: Grade 3 LWE. The image above shows LWE extending from the outer canthus to roughly the centre of an adult eyelid eyelid, approximately 12 mm. This equates to staining length grade 3. The LWE extends from Marx's line to the sub-tarsal fold (>75%) equating to staining width grade 3. The average of staining length and staining width is grade 3 LWE overall.

1.8.11

Symptoms

Dry eye questionnaires have been shown to be useful (Begley *et al.,* 2002, Nichols *et al*., 2004b) in assessing the following:

- the severity of the condition
- the success or otherwise of therapy
- identifying environmental triggers
- measuring end points in clinical trials

Any dry eye questionnaire should fulfil the following requirements (Pult *et al.,* 2008):

- The questionnaire has to be appropriate for both current contact lens wearers and for naive contact lens wearers.

- The questionnaire has to be understandable by patients as well as practicable in normal contact lens practice (length and type of questions).

- The results of the questionnaire should present a high degree of prediction for the severity of the patient's symptoms in contact lens wear.

- The questionnaire has to have been validated with the appropriate population.

- The questionnaire has to be available and appropriate for normal practitioners.

There are a number of dry eye questionnaires available to the clinician, the most well-known are the McMonnies Dry Eye Index (McMonnies and Ho, 1987b), Ocular Comfort Index (OCI), Ocular Surface Disease Index (OSDI) and the Contact lens Dry Eye Questionnaire (CLDEQ). The OSDI is a dry eye questionnaire which utilises a 12 question 5-item Likert scale design to assess both the level of discomfort and how dry eye interferes with daily living activities. Five of the twelve questions relate to ocular symptoms, four to functional tasks and three to environmental triggers (Schiffman *et al.,* 2000). Advocates of this questionnaire suggest that the OSDI score is proportional to symptom intensity. Schiffman and colleagues (2000) defined a mean score of 4.5 ± 6.6 as normal, 18.1 ±17.1 as mild-moderate and 36.3 ±23.1 as severe dry eye, a cut-off value for all dry eye patients of 6.0 and severe dry eye patients of 15.0.

The OSDI was chosen over other alternative dry eye questionnaires for the following reasons:

- McMonnies is long and asks some questions which may be difficult or embarrassing for the patient to answer.
- The OCI has not been validated for contact lens wearers (Johnson and Murphy, 2007).
- The CLDEQ diagnoses subjects as either dry eye or normal and can be used for grouping subjects while the OSDI is able to evaluate dry eye symptoms in non-lens wearers as well as contact lens wearers and can monitor symptoms in prospective studies.

Therefore the OSDI was suggested as the preferred questionnaire for naive contact lens wearers, while the CLDEQ is perhaps better suited to experienced lens wearers only (Appendix 2)

The OSDI questionnaire was used to measure patients' symptoms on their initial visit and again after 6 months of contact lens wear (Schiffman *et al.,* 2000).

(N.B. The median of 3 readings was favoured to the mean when recording some of the above tear metrics as with such small samples mean values can be distorted by a single unusually high or low value).

Conclusion

Depending on the definition used, the prevalence of dry eye varies from just over 5% to nearly 34%. The high prevalence of dry eye among the older age group will result in ever increasing numbers of sufferers in the future as a result of increasing longevity. There are a number of tests used to diagnose and monitor dry eye but no "gold standard" exists for its diagnosis and many of the currently available tests are

both subjective and variable. Dry eye is a multifactorial disease, a person with ADDE and hyperosmolar tears may see a reduction in goblet cell density and secondary increased tear film evaporation resulting in some degree of EDE. Conversely a patient with primary EDE, for example secondary to MGD, will experience reduced corneal sensitivity and a subsequent reduction in tear production resulting in a form of ADE. For this reason differentiating between ADDE and EDE in a clinical setting may be problematical and clinically dry eye tends to be treated as if it were one disease. If we were better able to classify our dry eye patients according to their presenting signs and symptoms a more targeted treatment could be recommended or a more appropriate contact lens type or modality prescribed.

Approximately half of current contact lens wearers suffer from dryness and discomfort, particularly towards the end of the day. This inevitably leads to dissatisfaction and possible discontinuation of lens wear. Dryness is the single most common reason for lens discontinuation with contact lens wearers being 12 times more likely to report symptoms of dry eye than non wearers. Women were found to report dry eye more frequently than men (DEWS 2007) with pre-existing dry eye patients requesting to be fitted with lenses particularly problematical (Pritchard, 2001; Sindt and Longmuir, 2007). There has been little research into which tear film characteristics might predispose an individual to contact lens induced dry eye.

Therefore, this study evaluated a new objective instrument for assessing NITBUT. It examined which tear film tests contributed independently to determining the status of the tear film, and whether there are distinct clusters of patients with different forms of dry eye. If practitioners can classify their patients into particular clusters they can recommend the most appropriate dry eye products or advise on the most appropriate

contact lens material or modality. Finally, the new instrumentation, relationship between tear film tests and dry eye cluster identified groups were used to examine a group of contact lens neophtyes fitted with silicone hydrogel, frequent replacement contact lenses to determine how this knowledge would predict those dropping out of contact lens wear.

Chapter 2:

Clinical evaluation of the Oculus Keratograph

2.1 Introduction

In optometric practice corneal curvature is routinely measured with a keratometer prior to rigid lens fitting. A keratometer is an instrument used to examine the central 3.0–3.5mm of the cornea providing information on the radii of curvature, the directions of the principal meridians, the degree of corneal astigmatism and the presence of any corneal distortion. Keratometers only assesses the central corneal curvature, but most corneas flatten towards the periphery as prolate ellipses (Guillon *et al*., 1986).

Videokeratoscopes, generally known as topographers, typically assess corneal curvature over a wider (up to 10mm diameter) region of the cornea by reflecting an illuminated placido disc of known proportions off the tear film and comparing this to the imaged reflection. Image processing software detects the location of the rings objectively in multiple meridians and displays the data in the form of contour maps along with simulated keratometry readings in the principal axes. As well as providing generally more reliable information on corneal topography over a wider corneal area the reflection quality of the placido mires indicates the quality of the tear film over time. Whilst this has been utilised in a research setting (Goto *et al*., 2004), until now no commercial devices have been available to objectively assess non-invasive tear break-up time. Objectively analysing the Placido reflections from the tear film over time after a blink has been shown to have higher sensitivity, but similar specificity in predicting symptomatic dry eye than fluorescein break-up time (Goto *et al*., 2004).

Tear stability is routinely assessed in clinical practice to aid in the diagnosis of dry eye disease and to help predict the likelihood of contact lens induced dry eye in neophyte contact lens wearers. There have been no studies published indicating which tests community optometrists are currently using to assess dry eyes but dry eye specialists often assess the tear film break up time (BUT) (Korb 2000; Smith *et al.*, 2008), a measurement of the time which elapses between a patient blinking and their tear film beginning to break up or a subsequent uncontrollable blink occurring. It is often assessed following the instillation of sodium fluorescein dye into the tears and observation with a slit lamp microscope using blue light and a yellow enhancement filter (Peterson *et al*., 2006). There is concern that the presence of fluorescein in the tear film will destabilise the tears and for this reason it is preferable to measure tear film non-invasively without first instilling fluorescein (Mengher *et al*., 1985; Mengher *et al*., 1986; DEWS, 2007). This type of tear film measurement is referred to as non-invasive tear break-up time (NITBUT) although it should be noted that changes in meniscus curvature have been observed even with this minimally invasive technique suggesting it is easy to induce minor degrees of reflex tearing (DEWS, 2007).

The repeatability of measurements with one of the main subjective devices for assessing NIBUT, the Tearscope (Keeler, Windsor, UK) appears to be more reliable that other techniques such as observations through a slit lamp or of video keratoscope mires, although Tearscope measures are still quite variable (Elliott *et* al., 1998) and there is considerable inter-examiner variability (Nichols *et al*., 2002). The Diagnostic Methodology Subcommittee of the International Dry Eye Workshop stated it was important to develop objective analysis methods of NIBUT to help standardise

tear film examination methods and improve comparability of measurements (DEWS, 2007).

The Keratograph (OculusOptikgerate GmbH, Wetzlar, Germany) is the first commercially available device with software (“Tear Film Scan”) which permits an automated, examiner-independent technique for measuring NITBUT. The aim of this study was to determine the validity and reliability of the measurement of corneal curvature and NITBUT measures using the Keratograph.

2.2 Methods

One hundred consecutive patients with no known anterior eye disease (average age 37±13 years, range 19–67 years; 65 female, 35 male) were randomly recruited from the staff and patients of a community optometric practice in the North East of England over a period of 1 month. Consent was obtained after explanation of the study and possible consequences of taking part. The study was approved by the ethical committee of Aston University and conformed to the Declaration of Helsinki. Due to the similar nature of the two eyes, data from only right eyes were analysed to avoid statistical bias. A single keratometry reading was captured with a validated Tonoref II (Software version 1.05; Nidek, Nagoya, Japan) (Chelhab *et* al., 2011) following alignment of the instrument head with the centre of the pupil and after the patient had been asked to blink. Two further topography images of the patient's right eye were subsequently captured with the Oculus Keratograph (software version 2.73r19). All measurements were taken by a trained optometrist or contact lens optician and took approximately 30s. Both instruments were calibrated by their manufacturers immediately prior to the study.

NITBUT was measured on the same patients with the Keeler Tearscope (average of 3 reading) by one researcher and then, within 5 minutes twice with the objective Keratograph (average of 3 readings) by another masked researcher, in random order to prevent bias. Once the Keratograph assessment drops below an unspecified level, the instrument stops measuring and this time was also recorded. The Tearscope was hand-held and the tear film observed through the magnifying lens attachment. The Ocular Surface Disease Index questionnaire (OSDI) was then completed to relate the tear film stability to the subjective comfort of the eye.

2.2.1 Statistical analysis

Validity was assessed by applying Bland–Altman analysis to the comparison between the instruments with the average reading plotted against the difference for each subject (Bland and Altman, 1986). Reliability was determined from the 95% confidence interval of the difference between the repeated Keratograph measurements. Normally distributed components were compared by *t*-test.

Assessing variance in cylindrical components can be problematical (Bullimore *et al*., 1998) so the cylinder and axis component were converted into a vector representation (Thibos *et al*., 1997).

•a spherical lens of power mean spherical equivalent (MSE=sphere+(cylinder/2))

•Jackson cross-cylinder power at axis 0° (J_0=−[cylinder/2]cos[2×axis])

•Jackson cross-cylinder power at axis 45° (J_{45}=−[cylinder/2]sin[2×axis])

The Ocular Surface Disease Index (OSDI) is a 12 item, 5-category Likert scale that investigates symptoms, triggers and consequences of dry eye. OSDI scores were converted to a 100 point scale (Schiffman *et al*., 2000) and correlated with NITBUT to assess the discrimination of the devices.

2.3. Results

2.3.1. Topography

The average corneal curvature was 7.74±0.29mm with an average difference between the flattest and steepest meridians of 0.14±0.15mm (auto-refractor-keratometer-tomoneter (ARKT) measures). On average the mean spherical equivalent (MSE) as measured by the Keratograph was found to be more positive than the ARKT (MSE difference: +1.83±0.44*D*, $p<0.001$; Figure 2.1). However, there was no significant difference in the astigmatic components (differences, J_0=+0.01±0.27*D*, $p=0.61$; J_{45}=−0.03±0.18*D*, $p=0.13$; Figure 2.2). The Keratograph topography repeated measures were similar for MSE (difference: +0.11±0.97*D*, $p=0.35$), J_0 (difference: −0.10±1.12*D*, $p=0.29$) and J_{45} (difference: 0.10±0.60, $p=0.37$).

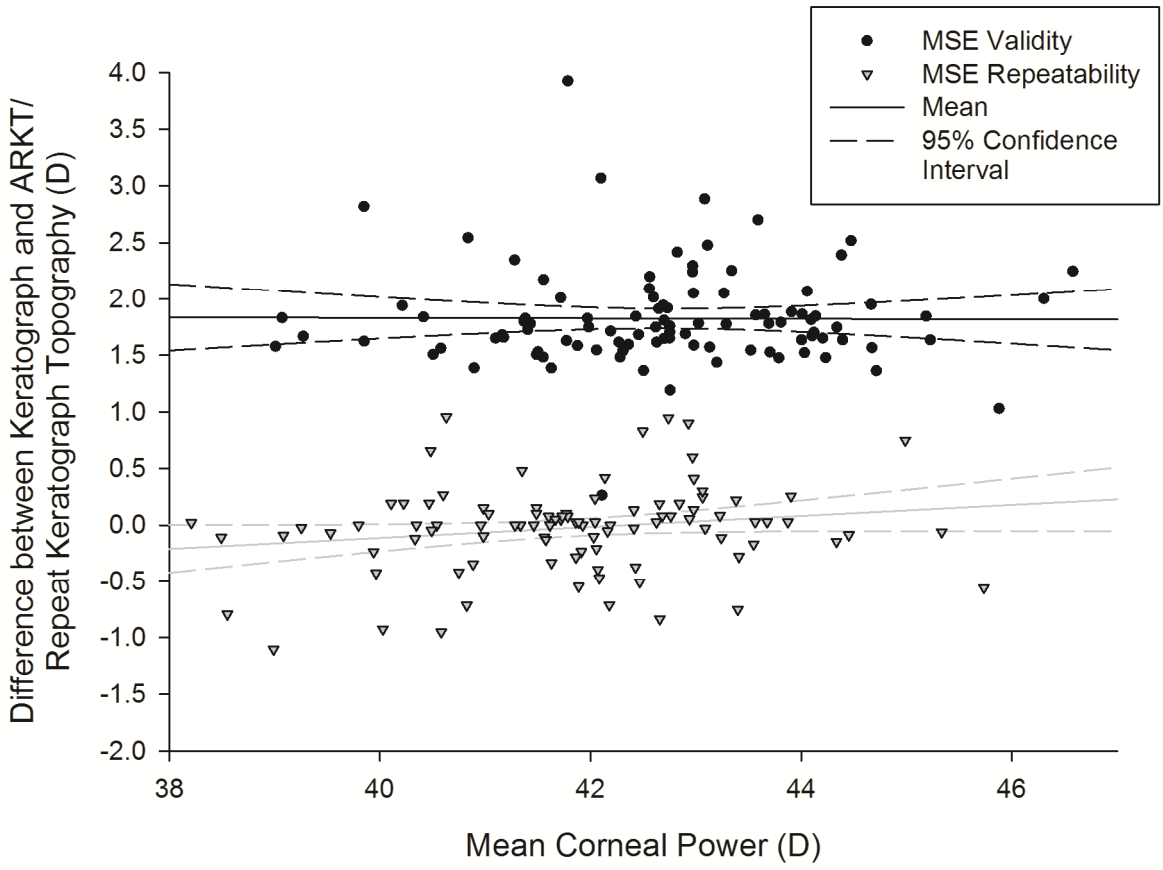

Figure 2.1: Difference in mean spherical equivalent (MSE) between the Oculus Keratograph and Nidek ARKT Tonoref II (black symbols) and repeated Keratograph measures (grey symbols) compared to the mean. *n*=100 eyes.

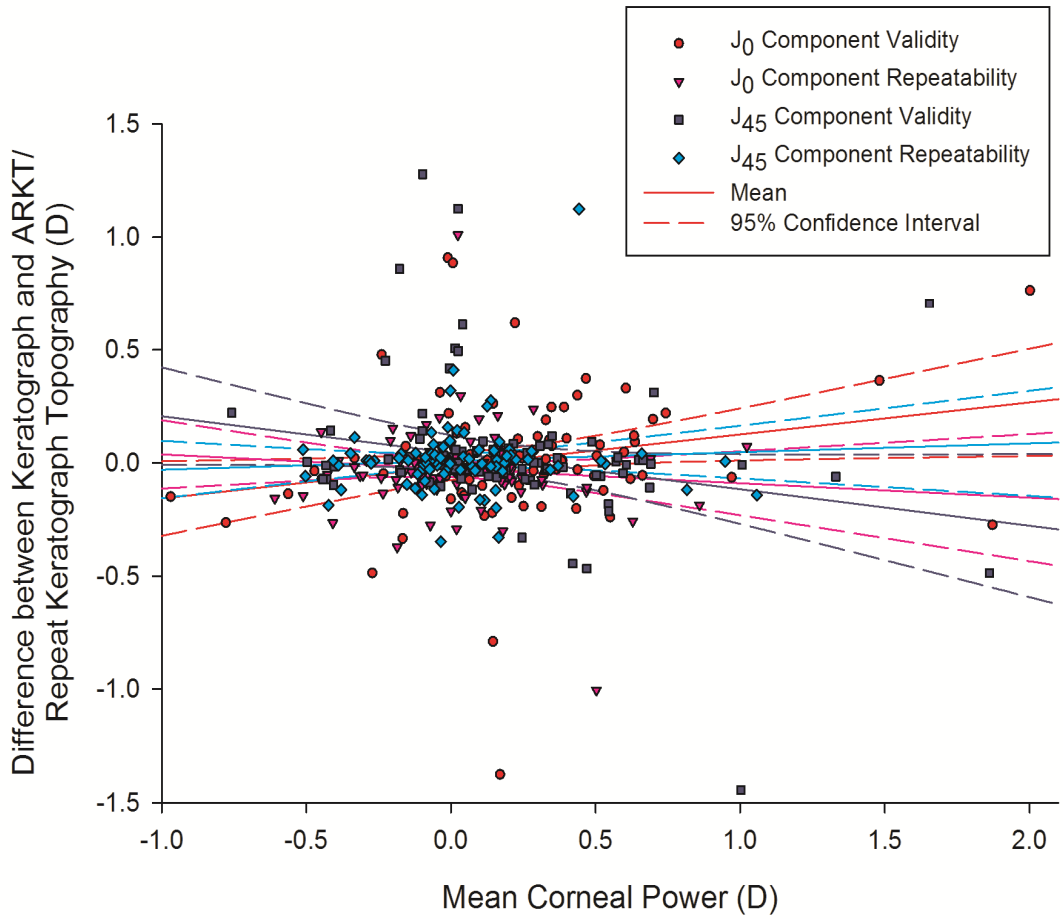

Figure 2.2: Difference in J_0 (red symbols) and J_{45} (blue symbols) astigmatic components between the Oculus Keratograph and Nidek ARKT Tonoref II (dark colours) and repeated Keratograph measures (light colours) compared to the mean. *n*=100 eyes.

2.3.2. NITBUT

NITBUT measured with the Keratograph ranged from 0.36s to 29.00s, with 63% of readings being <5s and 85% <10s. This compared to the Tearscope NITBUT range of 5.0s to 30.8s with none <5s and 15% <10s. On average the NITBUT measured by the Keratograph was 12.35s shorter than when measured with the Tearscope (SD 7.45s, $p<0.001$; Figure 2.3). The duration over which the Keratograph measured for each subject was more similar to the NITBUT of the Tearscope (1.7±3.6s longer, correlation $r=0.88$), although the difference was still significant ($p<0.001$). The second Keratograph NITBUT was on average 1.64s less than the first (SD 6.03, $p<0.01$). OSDI correlated more strongly with NITBUT measured with the Tearscope ($r=-0.32$) compared with the keratograph (NITBUT: $r=-0.19$; total measurement time: $r=-0.19$).

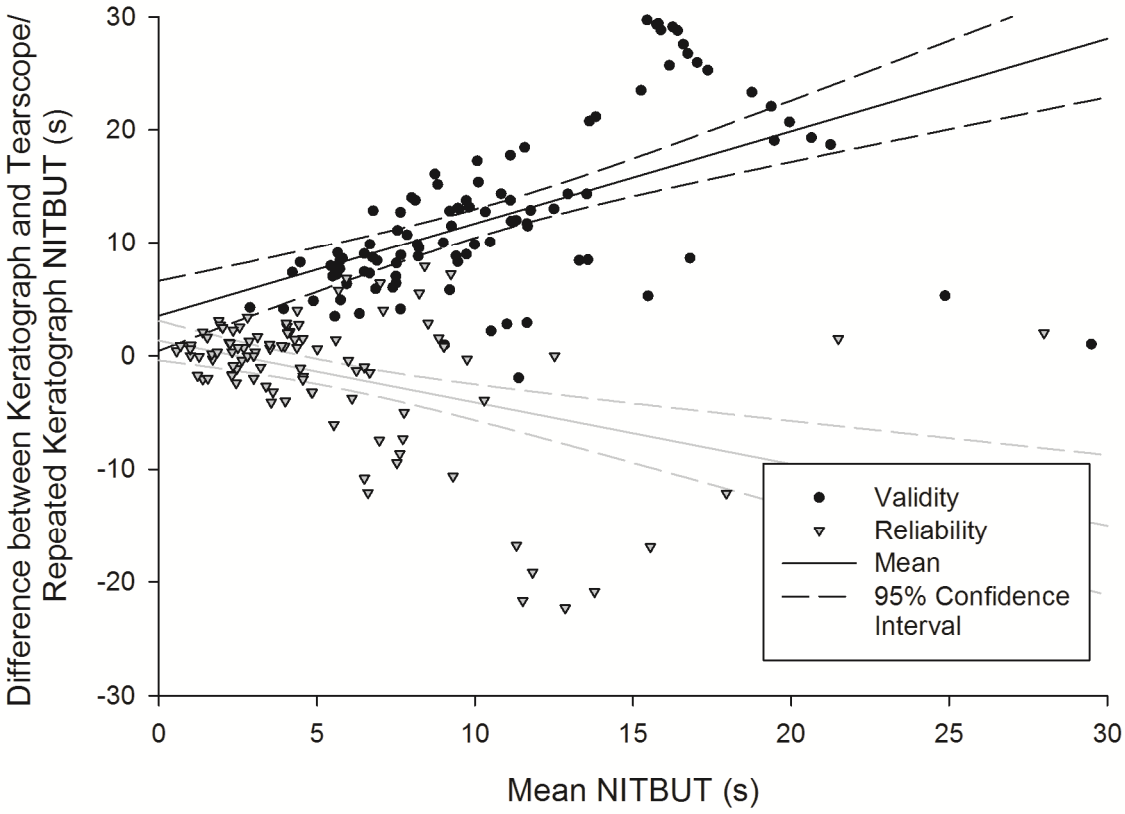

Figure 2.3: Difference in NITBUT as measured with the Keratograph when compared to the Tearscope (black symbols) and on repeated measurement with the Keratograph (grey symbols) compared to the mean. *n*=100.

2.4. Discussion

Approximately half of current contact lens wearers suffer from dryness and discomfort, particularly towards the end of the day (Morgan and Efron, 2008). This inevitably leads to dissatisfaction and possible discontinuation of lens wear. Prior to fitting their patients with contact lenses there are a number of tests available to the practitioner to assess the quality and quantity of tears. Having completed these tests advice can be given on an individual's suitability for contact lenses and to recommend the most appropriate modality and lens type. These tests include lid parallel-conjunctival folds, NITBUT, invasive break up time, corneal and conjunctival staining, lid wiper epitheliopathy, limbal hyperaemia, tear prism height measurement, phenol red test and various questionnaires (DEWS, 2007; Pult *et al*., 2008). NITBUT has been shown to be the clinical test with the highest sensitivity and specificity for dry eye (Bron and Tiffany, 2004).

NITBUT, as measured with the Keratograph was consistently shorter than measurements recorded with the Tearscope, and much more so than would be expected from the subjective observer response time. This is because the Keratograph records the first incident of break-up anywhere in the tear film irrespective of how small or transient the area of break-up. Such small or transient regions of break up would probably not be detected by an observer viewing the Tearscope mires. Alternatively the software could be detecting interference in the image capture process and interpreting this as a break in the tears. In either case, the sensitivity of the software in interpreting a tear break appears to be set too high, although it is possible that the tendency towards even a small or transient break could contribute to future end of day discomfort or contact lens induced dry eye. How the Keratograph determines when to cut short the measurement is unclear, but cut off

time was only slightly shorter than the subjectively rated NITBUT with the Tearscope and the comparison less variable than with the Keratograph NITBUT. The correlation between the Keratograph cut off time and the Tearscope was very strong (r = 0.88) suggesting that the ability of an observer using the Tearscope to measure break up time is more similar to the point at which the keratograph measures sufficient ring distortion to stop measuring. Hence this value may be more clinically valuable to clinicians until the commercially available software is altered, although the relatively poor correlation with ocular symptoms compared to the Tearscope NITBUT suggests the analysis algorithms would benefit from being adjusted. This is also the case for the measurement of central corneal curvature, where the spherical equivalent power of the cornea was measured as being significantly flatter than with a validated automated keratometer (El Chehab *et al*, 2011) . There was no significant difference found between the astigmatic components when measured with the ARKT and Keratograph and Keratograph readings were found to be repeatable.

It is important to reflect that although the Non Invasive Keratograph Break Up Time (NIKBUT) does not correlate with that subjectively measured with the Tearscope, this does not invalidate the information collected. Subjective assessment is invariably less repeatable than objective data and the video provides information not just on tear-break up in a small region, but on the location of multiple breaks, the area covered and any film reformation. Hence the technology is likely to enhance the clinician’s understanding of the patient’s tear film stability, its clinical implications and be able to use the images to better communicate with their patients.

Chapter 3:

Classification of human tear film metrics by a cluster analysis based approach to allow categorization of patients with certain tear metric combinations.

3.1 Introduction

The prevalence of dry eye has been shown to range from 8% (Schaumberg *et al.,* 2003) to 34% (Lin *et al.,* 2003), although care must be taken when comparing these figures as different definitions of dry eye are often used in studies. The prevalence of dry eye is greater amongst females than amongst males and seems to increase with age (Schein *et al.,* 1999; Schaumberg *et al.,* 2003). There also appears to be a higher prevalence amongst those of Asian ethnicity (Lin *et al.,* 2003). Mild symptoms of dry eye will be reported by as many as one in four patients presenting to an optometric practice (Doughty *et al.,* 1997). In 2007 the International Dry Eye Workshop (DEWS 2007) produced the following definition of dry eye syndrome (DES):

> "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."

Symptoms include visual disturbances, grittiness, dryness, burning, stinging and discomfort (Behrens *et al.,* 2006). These symptoms can be exacerbated by tasks associated with reduced blink rate e.g. driving or computer work and tend to worsen as the day progresses or in dry warm environments (Paschides *et al.,* 1998; Tsubota

and Nakamori, 1993). Signs of dry eye include bulbar conjunctival redness, superficial punctate corneal staining, lid parallel conjunctival folding, reduced tear break up time, reduced tear meniscus height, lid wiper epitheliopathy and increased tear osmolarity (Toda, 2007). It is not uncommon for signs and symptoms in dry eye patients to correlate poorly (Lemp, 1995); for example in one study 48% of post LASIK patients had dry eye symptoms while punctate keratitis was present in only 2-6% (Hovenasian *et al.,*2001). Although a number of studies have investigated the correlations between dry eye tests in different populations (Table 3.1), no one study has looked comprehensively at the currently recognised clinical dry eye tests and in general the population sizes examined have been limited. Therefore this study examined a wider range of clinical tests and a large patient cohort to better understand the independent contribution of each of the tests prior to later chapters which will examine how well they predict contact lens drop-out.

Author	Study population	Subjects	Age range	Height	Hyperaemia meniscus height	Hyperaemia	LIPCOF	Test	Schirmers	FBUT	Stain	stain	LWE	Symptom	NITBUT	Comments
Unlu et al 2012[11]	VDU users	n=35	mean age 29.09±6. 73 (range 20-46)						✓	✓				✓		Inverse correlation between OSDI and TBUT
Cuevas et al 2012[12]	Subjects with evaporative dry eye secondary to meibomian gland disease	n=21		✓	✓			✓		✓	✓	✓		✓		Correlation between symptoms and some clinical tests (TBUT, conj hyperaemia, TMH, conj stain)
Pult et al 2009[13]	New contact lens wearers	n=33	median age 30.5 (range 19 to 44)	✓	✓	✓	✓	✓			✓	✓	✓		✓	LIPCOF, NIBUT and OSDI are significant discriminators of contact lens induced dry eye
de Gomes et al 2012[14]	Patients with systemic sclerosis n=45,	n=45							✓	✓		✓		✓		No statistically significant correlations
Fuentes-Paez et al 2011[15]	Patients > 50 years	n=270	average age 64.5						✓	✓	✓	✓		✓		No correlation between screening questionnaire and objective tests
Pult et al 2011[16]	Non contact lens wearers	n=47	median age 45 (range 19-70)	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	NIBUT, THH, Phenol red, LIPCOF and LWE were related to ODSI scores. The strongest relationship appeared by combining NIBUT with LIPCOF
Barboza et al 2008[17]	Sjogren's syndrome patients n=42	n=42			✓				✓					✓		A weak correlation between signs and symptoms of dry eye disease
Korb et al 2005[18]	100 patients divided into those with and those without dry eye symptoms	n=100	mean age 44.3 (symptomatic), 42.8 (asymptomatic)										✓	✓		76% of symptomatic patients had lid wiper staining, 12% of the asymptomatic patients had staining of the lid wiper

Table 3.1 Studies investigating the correlation between dry eye tests in different populations

3.2 Methods

One hundred subjects (average age 49 years, range 18-71 years; 67 females) were recruited from the patients of a community optometric practice in the North East of England. Consent was obtained after explanation of the study and possible consequences of taking part. The study was approved by the ethical committee of Aston University and conformed to the tenets of the Declaration of Helsinki. The subjects were excluded from the study if they had diabetes, Sjögren's Syndrome, recent ocular infection, hay fever, use of any medications or dry eye drops known to affect the ocular surface or were pregnant. Each subject agreed to have a number of tear metrics recorded from their right eye only.

3.2.1 Clinical evaluation

The tear film metrics, evaluated in the following sequence due to the invasive nature of some tests, were:

- Non-invasive keratograph break-up time (NIKBUT)
- Non-invasive Tearscope break up time (NITBUT)
- Tear meniscus height
- Bulbar and limbal hyperaemia
- LIPCOF
- Osmolarity
- Phenol red thread
- Fluorescein break up time
- Corneal staining
- Conjunctival staining
- Lid wiper epitheliopathy
- Symptoms

Further details on all of the above tests can be found in the chapter 1

3.2.2 Statistical analysis

The relationship between tear metrics was analysed using Pearson's correlation, as were the presence of any groups of tear metrics using cluster analysis techniques. A k-means clustering algorithm was employed (where k is the number of clusters you want). The first step is to find the k centres, to do this the software will find cases that are well separated and use these as initial cluster centres. It will then begin to assign cases to the cluster closest to them based on the distance from the cluster centre. Once cases have been assigned, the cluster centres are recalculated and cases are reassigned using the new cluster centres. This process is repeated until no cluster centre changes significantly. F ratios can be calculated to describe the differences between clusters but significance levels should not be interpreted in the usual fashion as the algorithm is designed to maximise distance between clusters. Saying that, the higher the significance, the less likely it is that a variable contributes to cluster separation. The data were analysed using SPSS 20 software (IBM Corporation, New York, USA).

3.3 Results

3.3.1 Relationship between tear metrics

The data for the 100 subjects are shown in Appendix 9. LIPCOF, FBUT, conjunctival staining and LWE were all found to be related to subjective comfort as measured with the OSDI questionnaire. Limbal and bulbar hyperaemia were related to each other, bulbar hyperaemia was also related to LIPCOF. TMH and the phenol red thread test were related to each other; interestingly NITBUT measured on a Tearscope was also related to FBUT. Corneal and conjunctival staining were related to each other, as were the tear volume tests, phenol red and TMH (Table 3.2).

	T.M.H	Bulb Hyp	Limb Hyp	LIPCOF	Osmolarity	Phenol red	FBUT	Corneal stain	Conj stain	LWE	OSDI	NIBUT (T)
NIKBUT	r=-.142 p=0.158	r=-.143 p=0.157	r=-.108 p=.286	r=-0.31 p=.762	r=-.174 p=0.750	r=0.17 p=0.867	r=.210 p=.036	r=-0.034 p=.735	r=-0.12 p=.735	r=-.126 p=.210	rrr=-.029 p=.776	r=.493 p=.000
T.M.H.		r=.232 p=0.02	r=.183 p=.068	r=-.236 p=.018	r=.171 p=.460	r=.338 p=.001	r=.062 p=.538	r=.048 p=.635	r=-.149 p=.140	r=-.204 p=.042	r=.==.101 p=.317	r=-.081 p=.423
Bulbar Hyperaemia			r=.666 p=.000	r=.272 p=.006	r=.070 p=.763	r=.161 p=.109	r=.0.22 p=.831	r=.021 p=.836	r=.073 p=.472	r=-011 p=.916	r=.137 p=.174	r=-.092 p=.362
Limbal Hyperaemia				r=.025 p=.804	r=.371 p=.098	r=.155 p=.124	r=.121 p=.231	r=-051 p=.612	r=-.001 p=.992	r=-.017 p=.863	r=-.118 p=.241	r=-.003 p=.974
LIPCOF					r=.273 p=.231	r=-.073 p=.473	r=-.334 p=.001	r=-.013 p=.897	r=.235 p=.019	r=.147 p=.146	r=.217 p=.030	r=-.147 p=.143
Osmolarity						r=-.066 p=.775	r=-.291 p=.200	r=.344 p=.127	r=-.064 p=.782	r=.116 p=.615	r=.069 p=.767	r=-.069 p=.767
Phenol Red							r=-.035 p=.727	r=.055 p=.588	r=-.377 p=.000	r=-.174 r=.084	r=-.099 p=.328	r=.029 p=.773
FBUT								r=-.230 p=.021	r=.007 p=.943	r=-.214 p=.033	r=-.232 p=.020	r=.432 p=.000
Corneal staining									r=.209 p=.037	r=.000 p=1.000	r=.091 p=.370	r=-.134 p=.185
Conjunctival staining										r=.038 p=.705	r=.289 p=.004	r=-.098 p=.330
LWE											r=-212 p=.034	r=-0.99 p=.328
OSDI												r=-.193 p=.054

Table 3.2 : Correlation of tear film metrics

3.3.2 Cluster analysis

Cluster analysis was carried out for 3,4, 5 and 6 groups with the number of cases in each cluster shown below in table 3.3.

Clusters	**Number of Subjects**			
1	64	7	36	18
2	29	60	34	5
3	7	13	11	21
4		20	2	2
5			17	28
6				26

Table 3.3: the number of cases in each cluster when 3 to 6 way cluster analysis was performed.

Further analysis was carried out on the 5 way cluster as 4 of the clusters contained within it had greater than 10% of the study population. No analysis was carried out of cluster 4 within the 5 way cluster as it contained only 2 patients. The 6 way cluster analysis was excluded as it had resulted in 2 very small groups. The 3 and 4 way clusters were excluded as they each contained clusters of 60 or more patients. The mean tear metrics for clusters 1, 2 3 and 5 of the 5 way cluster analysis are shown below (Table 3.4) and those which are statistically significant are shown in red.

	Cluster 1 (n=36)	Cluster 2 (n=34)	Cluster 3 (n=11)	Cluster 5 (n=17)
NIKBUT	4.1	3.9	15.6	6.2
TMH	0.2	0.3	0.2	0.3
Bulb hyp	2.4	2.4	2.2	2.4
Limb hyp	2.0	2.2	1.9	2.3
LIPCOF	1.9	1.2	1.5	0.7
Phenol red	12.2	19.6	17.0	13.3
FBUT	6.1	8.2	8.6	18.4
Conj stain	0.2	0.4	0.2	0.0
Corn stain	1.1	0.4	0.9	0.5
LWE	0.7	0.3	0.4	0.0
OSDI	18.2	4.3	9.1	4.1
NITBUT	11.5	11.4	24.8	26.2

Table 3.4: Mean tear metrics for clusters 1, 2, 3 and 5. The statistical significance of the results of the cluster analysis was tested using an ANOVA (Table 3.5). Those tear metrics which were found to be statistically different from the same tear metrics in other clusters are indicated in red.

ANOVA

	Cluster		Error		F	Sig.
	Mean Square	df	Mean Square	df		
NIKBUT	330.203	4	11.054	95	29.871	.000
TMH	.018	4	.010	95	1.752	.145
Bulb Hyp	.165	4	.299	95	.552	.698
Limb Hyp	.510	4	.457	95	1.116	.354
LIPCOF	4.440	4	1.352	95	3.284	.014
Phenol Red	316.372	4	39.683	95	7.972	.000
FBUT	450.101	4	20.190	95	22.293	.000
Conj Stain	2.533	4	1.141	95	2.220	.073
Corn Stain	.745	4	.288	95	2.585	.042
LWE	3.216	4	1.494	95	2.153	.080
OSDI	1567.270	4	30.048	95	52.159	.000
NITBUT	1020.814	4	20.436	95	49.952	.000

Table 3.5: ANOVA of 5 way cluster analysis. F ratios can be calculated to describe the differences between clusters but significance levels should not be interpreted in the usual fashion as the algorithm is designed to maximise distance between clusters. Saying that, the higher the significance, the less likely it is that a variable contributes to cluster separation.

3.4 Discussion

There are a number of dry eye tests available but as it is impractical to conduct every test on every patient it is useful to rationalize them to see if any are of more diagnostic significance than others.

In terms of their potential linkage, the dry eye tests included in this study could be divided into 3 broad categories:

- Tear stability is assessed by break-up tests, both non-invasive (NITBUT and NIKBUT) and invasive (FBUT).
- Tests such as phenol red and tear meniscus height provide quantification of the tear volume, both from the tear prism, but differing in their level of invasiveness.
- The remainder of the tests assess provide some measure of the physiological state and irritation of the eye such as bulbar and limbal hyperaemia, LIPCOF, corneal and conjunctival staining and lid wiper epitheliopathy.

If this categorization is valid, it would be expected that tests within each group were reasonably strongly correlated with one another, but less so with tear film metrics from other categories.

The tear stability category seems to be well supported with non-invasive and invasive tear break-up times significantly positively correlated to each other, but not the other tear metrics. NIKBUT was less strongly correlated with FBUT than the Tearscope measures, presumably due to the lower range of values highlighted in chapter 2.

Tear volume was a less distinct category as although phenol red and TMH were significantly positively correlated, TMH was found to be related to LIPCOF, LWE and bulbar hyperaemia, while the phenol red test also correlated with conjunctival

staining. Tomlinson and colleagues found a lack of association between TMH and the phenol red test, although their study had fewer, and slightly younger subjects (Tomlinson *et al.,* 2001). Conjunctival and corneal staining were most strongly correlated suggesting that it may not be necessary to conduct both tests or giving validity to their joint evaluation and instillation of fluorescein and lissamine green dyes simultaneously (Korb *et al.,* 2008).

Finally, symptomology, assessed using the OSDI questionnaire, correlated better with those tests investigating possible damage to the ocular surface (including LWE, LIPCOF and conjunctival staining) than with tests of either tear volume or stability. As these tests are less common in optometric practice, the requirement for specialist dry eye clinics carrying out these specific tests is warranted. Instead of practitioners 'diagnosing' and suggesting poorly targeted treatments for dry eye based on less relevant tests carried out as a small subsection of the standard eye examination.

As discussed previously, the aetiology of dry eyes is multifactorial (DEWS, 2007). It is therefore not surprising that cluster analysis shows some statistically significant groups of patients with different sign and symptom profiles. It is difficult to determine how many groups to split a cohort into as there are clearly significant differences in all the cluster sizes examined. A five way cluster analysis was chosen based on a rationale that once the number of significant differences between metrics started to decrease, the appropriate cohort division had been passed. The analysis of variation of the five way cluster analysis showed the following tear metrics to be of statistical significance between the clusters; NIKBUT, LIPCOF, phenol red, FBUT, corneal staining, OSDI and NITBUT.

Cluster 1 (n=36) demonstrated poor tear quality with both noninvasive (DEWS 2007) (NITBUT = 11.51), and invasive tests (Lemp 1995) (FBUT = 6.12). Tear volume was also low in this group (Little SA *et al.,* 1994a) (phenol red = 12.19mm) and the patients reported more symptoms (Schiffman *et al.,* 2000) (OSDI = 18.23) These patients also had clinically significant LIPCOF (1.89).

In cluster 2 (n=34) the NITBUT (11.37s) and FBUT (8.23s) tests again indicated sub-optimal tear stability but this seemed to be offset somewhat by a higher tear volume in this group (phenol red 19.59mm) . This group of patients were considerably less symptomatic (OSDI = 4.28) and demonstrated less LIPCOF and less corneal staining. It is maybe not surprising to find that a combination of poor tear quality and low tear secretion causes more symptoms than poor tear quality alone.

Patients in Cluster 5 (n=17) seemed to have the most normal tear metrics overall, with the exception of their NIKBUT result (Best *et al.,* 2012). As might be expected they also had correspondingly low OSDI scores.

Patients in cluster 3 (n=11) had normal NITBUT but slightly reduced FBUT readings and a slightly higher OSDI reading.

Attempts have been made before to apply cluster analysis to dry eye classification. In 2004 a group of researchers evaluated 513 subjects (William *et al.,* 2004) and used cluster analysis techniques to classify blepharitis and dry eye into clinically relevant groups with common characteristics. They found that only 5 of the 13 tear variables tested were required to establish their classification system. A study into tear meniscus height (Doughty *et al.,* 2002) also used cluster analysis to separate data sets with significantly higher than average TMH readings. Cluster analysis has also been used to analyse blink rate patterns (Doughty and Naase, 2006) and to identify obstacles to medication adherence in glaucoma patients (Tsai *et al.,* 2003).

The tear metrics which showed statistical significance for each cluster are shown below in table 3.6. Tear metrics are colour coded where red is abnormal, green is normal and borderline values are shown in blue.

Tear metric	**Cluster 1** (Symptomatic with marked signs)	**Cluster 2** (Unstable tear film, asymptomatic)	**Cluster 3** (Corneal staining, mildly symptomatic)	**Cluster 5** (Mild corneal staining only)
NIKBUT	4.1	3.9	15.6	6.2
LIPCOF	1.9	1.2	1.5	0.7
PHENOL RED	12.2	19.6	17.0	13.3
FBUT	6.1	8.2	8.6	18.4
CORN stain	1.1	0.4	0.9	0.5
OSDI	18.2	4.3	9.1	4.1
NITBUT	11.5	11.4	24.8	26.2

Table 3.6: statistically significant tear metrics colour coded (red = abnormal, green = normal, blue = borderline).

The above classification for each tear metric was based on the following:

NIKBUT: <10 seconds indicates dry eye (25% above that considered borderline) (Best *et al.,* 2012*;* Dews 2007).

LIPCOF : ≥ grade 2 is likely to be associated with dry eye symptoms (25% below that considered borderline) (Pult and Sickenberger, 2000).

Phenol red: <10mm suggests low tear secretion, (25% above that considered borderline) (Hamano *et al.,* 1983).

FBUT: ≤ 10 seconds = dry eye. >10 seconds = normal (Lemp, 1995).

Corneal staining: a grading of > 0.5 on the CCLRU scale is considered abnormal (Dundas *et al.,* 2001).

OSDI: <6 = normal, >6 = dry eye, >15=severe dry eye (Schiffman *et al.,* 2000).

NITBUT: <10 seconds dry eye (25% above that considered borderline) (DEWS 2007).

In practice attention is likely to be focused on the patients in cluster 1 as they are the symptomatic group. Tear volume seems to be the key variable when differentiating between the two largest groups. Whilst poor invasive and non invasive break up times in both groups are suggestive of poor tear quality, the patients with concomitant poor tear volume appear to be more symptomatic. The Cluster two patients have poor tear quality but high tear volume and low symptoms suggesting that products which target tear volume alone may aid in reducing symptoms in the cluster one patients. The least symptomatic patients of all are found in cluster five. These patients have a similar tear volume as the Cluster one patients but much more stable tear films suggesting that products designed to reduce tear film evaporation may also be useful in reducing symptoms in Cluster one patients.

Conclusion

The ability to classify patients into a particular cluster based on their tear film metrics should allow practitioners to advise patients on the most appropriate products to manage their dry eyes. For example, our study showed that the most symptomatic patients (cluster 1) demonstrated poor tear film stability as well as reduced tear volume and so may benefit from a combination artificial tear supplements and liposomal sprays (Craig *et al.,* 2010). Those patients in cluster 3 have normal tear

volume but poor tear stability and may benefit more from a liposomal spray than ocular lubricants. Contact lens wear has been shown to reduce the pre lens non-invasive break up time (Young *et al* 1991). Patients in clusters 1 and 2 have less than optimal NITBUT measurements and may be considered at greater risk of contact lens induced dry eye. Practitioners should take this into account when considering the modality or material most likely to achieve successful contact lens wear.

Chapter 4

Predicting success with silicone-hydrogel contact lenses in new wearers

4.1 Introduction

Research suggests that approximately half of current contact lens wearers suffer from dryness and discomfort, particularly towards the end of the day (Morgan and Efron, 2008). The symptoms described by these individuals are very similar to dry eye sufferers, leading to this condition being termed contact lens induced dry eye (CLIDE) (Pult et *al.,* 2008a). This inevitably leads to dissatisfaction and is the greatest cause of discontinuation of lens wear (Pritchard *et al.,* 1999; Richdale *et al.,* 2007). There are a number of tests that are available to the practitioner for assessing the quality and quantity of tears, to allow advice to be given on an individual's suitability for contact lenses and to recommend the most appropriate modality. Traditionally these tests have included non-invasive break-up time (NITBUT), invasive fluorescein tear break-up time (TBUT), corneal and conjunctival staining, tear prism height measurement, phenol red test and various symptomatology questionnaires. Bulbar and limbal hyperaemia can give an indication of ocular surface health and more recently the degree of both lid parallel conjunctival folding (LIPCOF) and lid wiper epitheliopathy (LWE) have been added to the list of potential indicators of dry eye (Korb *et al.,* 2002a; Yeniad *et al.,* 2010; Pult *et al.,* 2011). Grade 2 LIPCOF or worse is likely to be associated with dry eye symptoms (Pult and Sickenberger, 2000).

Early silicone-hydrogel contact lenses caused small but statistically significant changes in ocular physiology and symptomatology in new contact lens wearers over

18 months wear, but these were clinically insignificant (Santodoming-Rubido *et al.,* 2006) However, no studies have examined the effect of subsequent generations of silicone-hydrogel materials in contact lens neophytes. Pult and colleagues (Pult *et al.,* 2008b) examined 61 experienced contact lens wearers and concluded that those with dryness symptoms exhibited significantly more LWE and LIPCOF (Pult *et al.,* 2008b). LIPCOF sum severity scores were the most predictive of symptoms. A further study by this researcher in 2011 concluded that NITBUT, tear meniscus height (TMH), phenol red thread test, LIPCOF, and LWE were significantly, but moderately, related to OSDI scores; the strongest relationship was achieved by combining NITBUT with nasal LIPCOF (Pult *et al.,* 2011). A number of studies have found a relationship between lid wiper epitheliopathy and CLIDE in patients wearing either hydrogel or silicone-hydrogel contact lenses (Yeniad *et al.,* 2010; Korb et *al.,* 2002; Korb *et al.,* 2005; Pult *et al.,* 2009). However, it is still not clear which clinical measures predict those new patients that will drop-out of contact lens wear.

Therefore this study assessed the effect that six months of contact lens wear by unselected new lens wearers had on their tear metrics and ocular health. It also examined the baseline characteristics of those who successfully completed 6 months wear compared with those who did not.

4.2 Methods

Subjects

Sixty subjects (average age 36 ± 14 years, range 18-67; 40 females) were recruited from the patients of a community optometric practice in the North East of England. Consent was obtained after explanation of the study and possible consequences of taking part. The study was approved by the ethical committee of Aston University and conformed to the tenets of the Declaration of Helsinki. The subjects were excluded from the study if they had diabetes, Sjögren's Syndrome, recent ocular infection, allergy, any systemic or topical medications known to adversely affect the ocular surface or were pregnant. None of the subjects had ever worn contact lenses previously and all had requested to be fitted with contact lenses. They all expressed a desire to wear lenses full time and agreed to wear their lenses for a minimum of 6 hours per day for at least 6 days per week throughout the study.

Contact Lens Fitting

Prior to contact lens fitting, each of the subjects had a number of tear metrics recorded (right eye data only was used for statistical analysis) and were then fitted bilaterally with Lotrafilcon B (Alcon, Fort Worth, Texas, USA) silicone hydrogel contact lenses in either spherical or toric (n=22) form (Table 4.1). They were instructed how to insert and remove their lenses as well as being taught appropriate cleaning procedures with Synergi (Sauflon, Twickenham, London, UK) contact lens care solution. They were instructed to return for a 2 week aftercare, a 1 month aftercare and a six month aftercare. On the six month aftercare all tear metrics were re-measured.

Property	**Air Optix Aqua**	**Air Optix Astigmatism**
Brand name	Lotrafilcon B	
Manufacturer	Alcon	
Water content (%)	33%	
Base curve/diameter (mm)	8.6/14.2	8.7/14.5
Design	Bi-aspheric	Back surface toric
Oxygen permeability (Fatt units)	110	
Centre thickness (mm) -3.00 DS	0.08	0.112
FDA group	1	
Surface treatment	Plasma Treatment	
Principal monomers	DMA, TRIS, siloxane macromer	

Table 4.1: Specifications and properties of contact lens material used in the study

DMA (N,N-dimethylacrylamide) TRIS (trimethylsiloxy silane);

4.2.1 Clinical evaluation

The tear film metrics, evaluated in the following sequence due to the invasive nature of some tests, were:

- Non-invasive keratograph break-up time (NIKBUT)
- Non-invasive Tearscope break up time (NITBUT)
- Tear meniscus height
- Bulbar and limbal hyperaemia
- LIPCOF

- Osmolarity
- Phenol red thread
- Fluorescein break up time
- Corneal staining
- Conjunctival staining
- Lid wiper epitheliopathy
- Symptoms

Further details of these tests can be found in Chapter 1

4.2.2 Statistical Analyses

Prior to statistically analysing the data, it was tested for normality using the Kolmogorov Smirnov test. Differences in tear metrics between the baseline and 6 month visits, and between those subjects who were still wearing contact lenses after 6 months and those who were not still wearing lenses after six months were analysed. We then performed either paired t-tests or the Wilcoxon t-test depending on whether the variables were normally distributed or not as assessed by the Kolmogorov-Smirnov test. The data was analysed using SPSS 18.0 software (IBM Corporation, New York, USA). A receiver operating curve of sensitivity and specificity for detecting those contact lens wearers dropping out from wear over the first 6 months was calculated.

4.3 Results

Relationship between tear metrics (baseline)

Measures of NIKBUT, NITBUT (with the Tearscope) and fluorescein break-up time tear stability tests were found to be related (Table 4.2). Tear volume (phenol red) and TMH measures were also related. Limbal and bulbar hyperaemia were related to each other and interestingly to LIPCOF. LIPCOF was also related to fluorescein TBUT. Tear volume, as assessed by the phenol-red thread test was found to be negatively correlated to lissamine green conjunctival stain. LWE and conjunctival staining was the only metric related to subjective comfort as measured with the OSDI questionnaire (Table 4.2).

Changes with 6 months lens wear

Fluorescein TBUT, LIPCOF and TMH decreased over 6 months wear whereas bulbar hyperaemia, corneal and conjunctival staining and LWE increased (Table 4.3).

Predictors of Drop-out

Twenty seven out of 60 neophyte patients had dropped out of contact lens wear within 6 months after fitting. Those who dropped out had a lower NITBUT and fluorescein TBUT at baseline than those who were still successfully wearing lenses (Table 4.3).

	NIKBUT	Tearscope NITBUT	Fluorescein TBUT	TMH	Bulbar hyperaemia	Limbal hyperaemia	LIPCOF	Osmolarity	Phenol Red	Corneal stain	Conj stain	LWE	OSDI
NIKBUT		r=0.427, p=0.001	r=0.256, p=0.049	r=-0.109, p=0.406	r=-0.035, p=0.694	r=-0.052, p=0.694	r=0.069, p=0.600	r=-0.160, p=0.221	r=0.036, p=0.0785	r=-0.036, p=0.785	r=-0.075, p=0.569	r=-0.095, p=0.471	r=0.078, p=0.551
Tearscope NITBUT			r=0.550, p<0.001	r=-0.100, p=0.447	r=-0.088, p=0.503	r=-0.102, p=0.440	r=-0.0123, p=0.348	r=0.058, p=0.661	r=0.007, p=0.955	r=-0.035, p=0.789	r=-0.125, p=0.341	r=-0.082, p=0.534	r=-0.125, p=0.342
Fluorescein TBUT				r=0.153, p=0.243	r=-0.119, p=0.366	r=-0.086, p=0.516	r=-0.257, p=0.048	r=0.061, p=0.641	r=0.011, p=0.935	r=-0.187, p=0.15	r=0.018, p=0.888	r=-0.201, p=0.124	r=-0.123, p=0.348
TMH					r=0.198, p=0.130	r=0.200, p=0.126	r=-0.226, p=0.083	r=0.189, p=0.147	r=0.463, p<0.001	r=0.079, p=0.546	r=-0.0100, p=0.448	r=-0.208, p=0.112	r=0.002, p=0.987
Bulbar hyperaemia						r=0.715, p<0.001	r=0.466, p<0.001	r=-0.054, p=0.682	r=0.154, p=0.241	r=0.051, p=0.696	r=0.217, p=0.095	r=-0.012, p=0.929	r=0.164, p=0.210
Limbal hyperaemia							r=0.276, p=0.033	r=-0.163, p=0.213	r=0.340, p=0.008	r=0.107, p=0.417	r=0.184, p=0.160	r=0.048, p=0.716	r=-0.016, p=0.903
LIPCOF								r=-0.140, p=0.286	r=-0.084, p=0.522	r=-0.054, p=0.683	r=0.249, p=0.055	r=0.211, p-0.106	r=0152, p=0.248
Osmolarity									r=-0.233, p=0.074	r=0.164, p=0.209	r=0.220, p=0.090	r=0.152, p=0.244	r=0.036, p=0.782
Phenol Red										r=0.150, p=0.254	r=-0.256, p=0.048	r=-0.257, p=0.048	r=-0.055, p=0.674
Corneal stain											r=0.038, p=0.776	r=-0.083, p=0.527	r=0.112, p=0.395
Conj stain												r=0.032, p=0.810	r=0.273, p=0.035
LWE													r=0.105, p=0.426

Table 4.2: Correlation of tear film metrics at baseline (n=60). Significant correlations are shown in red.

Measure	Normality (K-S Z)	Baseline of Successful Wearers	After 6 months Contact Lens Wear	*Significance with Wear*	Baseline of Drop-outs	*Significance with Success*
NIK-BUT (s)	1.225, p=0.099	5.9±4.3	6.2±3.5	*0.124*	4.9±4.1	*0.920*
NITBUT (s)	1.334, p=0.057	17.0±8.2	16.9±7.8	*0.306*	12.0±5.6	*0.001*
Fluorescein TBUT (s)	1.286, p=0.073	10.7±6.4	8.7±5.1	*0.027*	7.5±4.7	*0.045*
TMH (mm)	0.867, p=0.440	0.26±0.09	0.24±0.07	*0.031*	0.26±0.09	*0.689*
Bulbar Hyperaemia	0.882, p=0.419	2.5±0.5	2.7±0.3	*0.011*	2.5±0.5	*0.093*
Limbal Hyperaemia	0.854, p=0.459	2.3±0.5	2.5±0.6	*0.184*	2.3±0.7	*0.162*
LIPCOF	2.040, p<0.001	1.2±1.1	0.9±1.0	*0.011*	1.5±1.3	*0.070*
Osmolarity (mmol)	0.764, p=0.603	321±12	323±16	*0.202*	325±20	*0.514*
Phenol Red (mm)	0.609, p=0.852	16.9±6.5	19.8±9.5	*0.086*	15.5±8.4	*0.778*
Corneal Staining	3.739, p<0.001	0.21±0.51	0.86±0.79	*0.007*	0.24±0.58	0.947
Conjunctival Staining	3.424, p<0.001	0.51±0.93	1.69±1.22	*0.009*	0.51±1.04	0.954
LWE	3.464, p<0.001	0.3±0.7	1.5±1.2	*0.002*	0.7±2.0	0.826
OSDI	1.362, p = 0.0502	7.6±10.2	8.5±10.4	*0.349*	12.2±9.2	*0.255*

Table 4.3: Tear film metrics: how they change over 6 months wear of a silicone hydrogel in neophytes (n=60) and the difference in baseline between those who are successful in lens wear (n=33) and those that drop out (n=27). ± = 1 S.D. Figures in red indicate changes or differences which are statistically significant.

Receiver Operating Characteristic (ROC) curves plot the true positive rate of a test (sensitivity) against the false positive rate (1-specifity) for different cut-off points of a variable. Each point on a ROC curve represents a sensitivity/specificity pair corresponding to a particular value for the variable under investigation. The area under a ROC curve (AUC) is a measure of how well a parameter can distinguish between two groups of individuals, in this case successful contact lens wearers and those who have dropped out of lens wear (Metz, 1978; Zweig and Campbell, 1993). A test with perfect discrimination i.e. no overlap in the distribution curves of the two groups, has a ROC curve that passes through the upper left corner (100% sensitivity, 100% specificity). The closer the ROC curve is to the upper left corner, the higher the accuracy of the test (Zweig and Campbell, 1993).

ROC curve for each of the tear film metrics are plotted in figure 4.1. Those metrics which differentiated successful wearers from unsuccessful wearers ($p < 0.05$) were NITBUT, fluorescein TBUT and subjective rating with the OSDI (Table 4.4). Using a NITBUT cut-off of 10 secs (as identified from the ROC as giving the best balance between sensitivity (63%) and specificity (76%)), 7 out of the 24 (29%) with a NITBUT less than this value successfully wore contact lenses beyond 6 months, whereas of the 27 that dropped-out, 17 (63%) had a fluorescein TBUT less than 10.0 s. Fluorescein TBUT had a lower cut-off of 5.5 secs (as identified from the ROC as giving the best balance between sensitivity (56%) and specificity (82%)), 6 out of the 21 (29%) with a fluorescein TBUT less than this value successfully wore contact lenses beyond 6 months, whereas of the 27 that dropped-out, 15 (56%) had a fluorescein TBUT less than 5.5 secs. Finally, an OSDI score greater than 4.2 (as identified from the ROC as giving the best balance between sensitivity (78%) and specificity (64%)), 11 out of the 36 (31%) with an OSDI greater than this value

successfully wore contact lenses beyond 6 months, whereas of the 27 that dropped out, 25 (92%) had an OSDI greater than 4.2.

Tear Film Metrics	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NIK-BUT (s)	.430	.075	.353	.284	.576
NITBUT (s)	.304	.069	.010	.169	.439
Fluorescein TBUT (s)	.320	.071	.017	.181	.458
TMH (mm)	.475	.075	.744	.328	.623
Bulbar Hyperaemia	.527	.076	.716	.378	.677
Limbal Hyperaemia	.509	.078	.905	.356	.662
LIPCOF	.577	.075	.305	.430	.725
Osmolarity (mmol)	.489	.076	.882	.340	.638
Phenol Red (mm)	.455	.078	.552	.302	.608
Corneal Staining	.503	.076	.964	.355	.652
Conjunctival Staining	.497	.076	.964	.348	.645
LWE	.511	.076	.882	.362	.660
OSDI	.694	.069	.010	.558	.829

Table 4.4: Tear film metrics and Receiver Operating Curve discrimination between those who are successful in lens wear (n=33) and those that drop out (n=27). Figures in red show those tear metrics which showed statistical significance in their ability to discriminate between successful lens wearers and those that drop out.

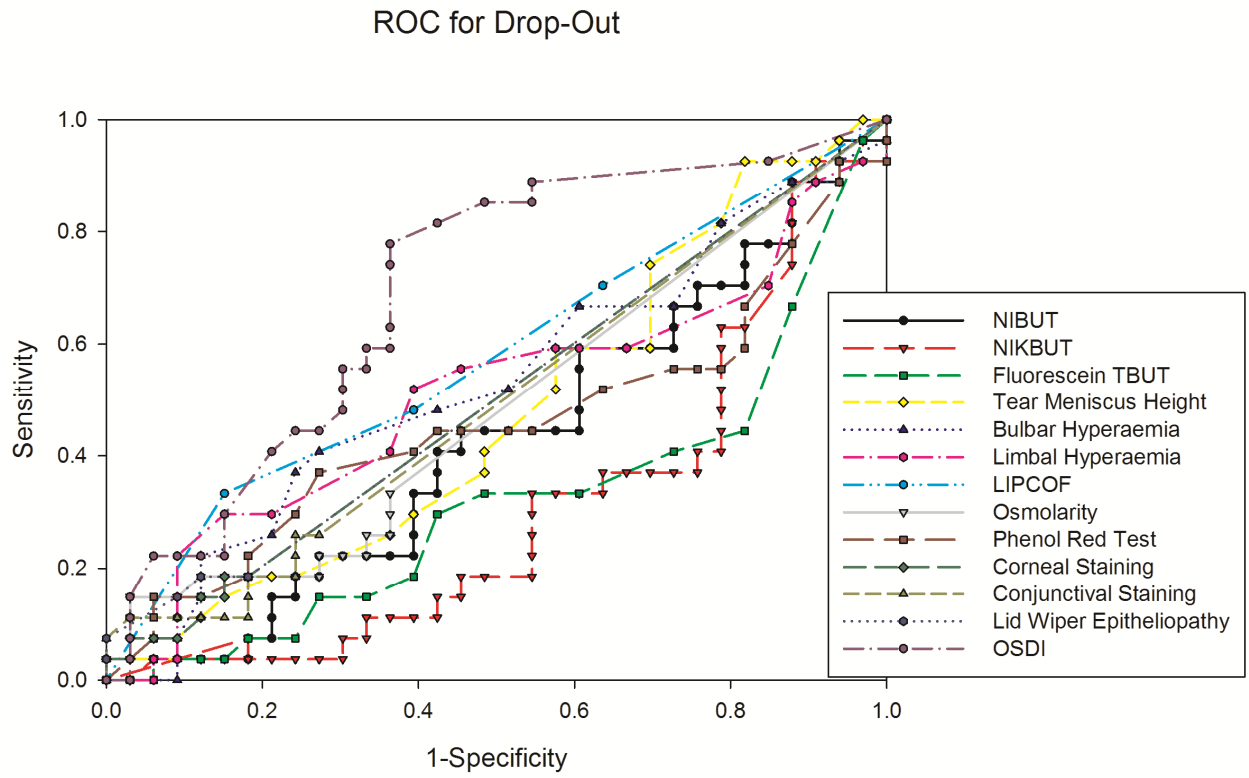

Figure 4.1: Receiver Operating Curves for each of the tear film metrics differentiating those that successfully wore contact lenses for 6 months (N=33) compared to those that dropped out (N=27).

4.4 Discussion

Discontinuation of contact lens wear can occur for a number of reasons. The most commonly cited reason is discomfort, accounting for between 43 and 72 % of drop outs (Pritchard *et* al., 1999; Schlanger 1993; Weed *et al*., 1993). Other reasons reported by lapsed lens wearers include poor vision, handling difficulties and cost (Young *et al.,* 2002).

The aim of this study was to assess the effect that six months of contact lens wear by unselected new lens wearers had on their tear metrics and ocular health and to examine the baseline characteristics of those who successfully completed 6 months wear compared with those that dropped out. The results of the study showed that NIKBUT, NITBUT with the Tearscope and fluorescein TBUT tear stability tests were all related (Table 4.2). This suggests that, rather than carrying out both an invasive and non-invasive measurement of tear film stability, one alone may suffice. Objective measures of NITBUT, such as the Keratograph, offer great potential to gain a better understanding of localised drying of the ocular surface without subjectivity, but early software versions, such as used in this study, had limitations (Best *et al.,* 2012). There was no significant difference in NIKBUT or NITBUT after 6 months of SiH contact lens wear; some previous studies with hydrogel lenses have shown similar results (Cho and Yap,1995, Chui *et al.,* 2000) while other studies have reported reduced NITBUT in hydrogel contact lens wearers (Faber *et al,* 1991; Du Toit *et al.,* 2001). There were clinically and statistically significant differences from baseline in both NITBUT (on average by 5.0 s) and fluorescein TBUT (on average by 3.2 s) between those subjects still wearing lenses after six months and those who had ceased lens wear. Receiver operating curves confirmed that this was a key metric to determine those neophyte patients likely to drop out of contact lens wear.

A tear meniscus height of less than 0.2mm can indicate a reduced tear output and has been shown to correlate with contact lens intolerance (Glasson *et al.,* 2003). Therefore the correlation of TMH with phenol red test measured tear volume was expected, despite the lack of association found by Tomlinson and colleagues, although their study had fewer and slightly younger subjects (Tomlinson *et al.,* 2001). Lid wiper epitheliopathy occurs when the cells along the upper lid margin are altered by the frictional forces which occur when the lid passes over the cornea or the front surface of a contact lens (Korb *et al.,* 2005) According to Korb and colleagues (Korb et al., 2005) 80% of symptomatic contact lens wearers will have staining of the lid wiper compared to only 13% of asymptomatic lens wearers. Lid wiper epitheliopathy was found to be associated with tear volume, but not tear meniscus height. This might suggest that the tear film thickness covering the cornea in an open eye situation is key to reducing the friction with the lid margin columnar cells, rather than the volume of the tear reservoir along the lower lid margin. However, lid wiper damage increased in the presence of a contact lens over 6 months of lens wear, whereas tear volume assessed by the phenol red test did not change, which does not support this explanation. Whilst there was a statistically significant decrease in TMH after six month of lens wear (on average by 0.02 mm) this could be considered clinically insignificant. Tear volume as assessed by the phenol red test did not change over this time period, but lid wiper damage did significantly increase, tear volume as quantified by the tear meniscus height or phenol red test did not aid in the prediction of contact lens drop-out over 6 months wear, nor did the baseline presence of lid wiper damage.

Bulbar and limbal hyperaemia, along with LIPCOF, were found to be associated prior to lens fitting. An increase in bulbar hyperaemia was found over 6 months wear, but conversely a decrease in LIPCOF occurred. Whilst statistically significant the changes found for LIPCOF of on average 0.2 to 0.3 grading scale units were not felt to be clinically significant. Possible causes could include mechanical irritation from the lens (Skotnitsky *et al.,* 2002) or solution toxicity (Tomlinson *et al.,* 2001). No significant difference in limbal hyperaemia was found despite being correlated to bulbar hyperaemia. Limbal hyperaemia can indicate corneal hypoxia and it has been shown before that eyes wearing silicone hydrogel lenses are less likely to show an increase in limbal redness (Papas *et al.,* 1997; Morgan and Brennan, 2007). None of these measures prior to lens wear predicted subsequent contact lens drop out.

A statistically significant increase was found in both corneal and conjunctival staining were found over 6 months wear, which could be attributable to a number of factors including the mechanical effects of silicone hydrogel lenses (Morgan and Efron, 2002) and lens deposition (Goldberg *et al.,* 1997). Prior studies did not find a link between dry eye symptoms and corneal staining (Nichols *et al.,* 2003; Nichols *et al.,* 2004b) and patients in this study were found to have no drop in comfort over this period. Conjunctival staining was associated with the level of symptoms as has previously been shown (Begley *et al.,* 2003; Guillon *et al.,* 2005b). Despite the lack of a significant difference between successful patients and contact lens drop outs based on the average comfort score (presumably due to the large variance between individuals in this subjective rating), the baseline OSDI was one of the best differentiators of patients likely to drop out. Interestingly, osmolarity was not found to be related to any of the other tear film metric quantified during this study, it did not

change with lens wear and did not predict contact lens drop out, despite its inclusion in the definition of dry eyes (DEWS report 2007).

It is not surprising that the regular presence of a contact lens can cause changes in both tear metrics and ocular signs such as corneal and conjunctival staining, fluorescein TBUT and LWE. These clinically significant changes were greater than might be predicted from previous studies investigating the fitting of neophytes with early silicone hydrogel contact lenses (Santadomingo-Rubido *et al.,* 2006), but indicate that contact lenses still need to be developed to achieve full biocompatibility. Care should be taken in fitting patients new to contact lenses if they have a NITBUT less than 10s or an OSDI comfort rating greater than 4.2 as they are more likely to drop-out within the first 6 months.

The cluster analysis which was carried out in chapter 3 was applied to the 60 subjects of this study with the following results (table 4.5):

Cluster	**Number in cluster**	**Number of drop-outs**	**% drop out per cluster**
1	20	10	50
2	23	11	48
3	4	1	25
5	11	4	36

Table 4.5: Percentage of drop-outs per cluster

The fact that approximately half of the subjects in the two largest clusters were still wearing contact lenses after six months and half had dropped out of lens wear suggests that clustering is not beneficial in predicting which patients will succeed with lenses and which will not. None of the other tear film metrics assessed were found to predict soft contact lens drop out. Fluorescein TBUT is strongly associated with NITBUT so its predictive abilities are largely redundant. The NITBUT and OSDI metrics are quick to obtain and can aid communication with the patient to examine other aspects related to contact lens wear success such as motivation (Thompson *et al.,* 1990, Jones *et al.,* 2009) and lens material properties (Pritchard N *et al.,* 1999; Riley *et al.,* 2006; Ramamoorthy *et al.,* 2008; Ramamoorthy *et al.,* 2010) with an aim to reduce contact lens drop-out (Pritchard *et al*.,1999; Richdale *et al*., 2007).

Chapter 5

General conclusions

Despite significant advances in contact lens materials in the past decade many patients will still experience symptoms of contact lens induced dry eye and reduced end of day comfort (Nichols and Sinnott, 2006; Richdale *et al.,* 2007). As stated previously, this is a major cause of dissatisfaction and contact lens drop out and is a significant barrier to expanding the uptake of contact lenses worldwide. Factors such as lens design, lens fit and deposit formation can impact comfort (Pritchard *et* al., 1999; Schlanger 1993; Weed *et al*., 1993) but the interaction between the lens surface and the tear film is a major factor in an individual's success or otherwise with contact lens wear. The primary aim of this thesis was to try to predict which patients may be predisposed to CLIDE prior to fitting them with lenses.

Currently available contact lenses have been shown to destabilize the tear film by thinning the lipid layer (Nichols and Sinott, 2006), reducing tear film stability and increasing tear film evaporation. The Diagnostic Methodology Subcommittee of the International Dry Eye Workshop stated it was important to develop objective analysis methods of NITBUT to help standardize tear film examination methods and improve comparability of measurements (DEWS, 2007). The Keratograph (Oculus Optikgerate GmbH, Wetzlar, German) is the first commercially available device with software ("Tear Film Scan") which permits an automated, examiner independent technique for measuring NITBUT. One of the aims of this study was to determine the validity and reliability of the measurement of corneal curvature and non-invasive tear break-up time (NITBUT) measures using this new objective tear film assessment. NITBUT as measured with the Keratograph was consistently shorter than measurements recorded with the Tearscope. The difference between the two

instruments was found to be much greater than would be expected from the subjective observer response time. This is because the Keratograph records the first incident of break-up anywhere in the tear film irrespective of how small or transient the area of break-up. Such small or transient regions of break-up would probably not be detected by an observer viewing the Tearscope mires. The correlation between the Keratograph cut off time and the Tearscope was very strong ($r = 0.88$) suggesting that the ability of an observer using the Tearscope to measure break up time is much closer to the point at which the keratograph measures sufficient ring distortion to stop measuring. Hence this value may be more clinically valuable to clinicians until the commercially available software is altered, although the relatively poor correlation with ocular symptoms compared to the Tearscope NITBUT suggests the analysis algorithms would benefit from being adjusted. When assessing corneal topography this was also found to be the case. The measurement of central corneal curvature was found to be significantly flatter when compared with a validated automated keratometer.

There are a number of dry eye tests available, but it is impractical to conduct every test on every patient. Hence it would be useful to rationalize them to see if any are of more diagnostic significance than others. Although a number of studies have investigated the correlations between dry eye tests in different populations no single study has looked comprehensively at the currently recognised clinical dry eye tests and in general, the population sizes examined have been limited. Therefore the second study (chapter 3) examined a wide range of clinical tests and a large high street practice patient cohort to allow us to better understand the independent contribution of each of the tests. The tear stability category showed non-invasive and invasive tear break-up times significantly correlated to each other, but not the other

tear film metrics. Tear volume was a less distinct category as although phenol red and TMH were significantly correlated, TMH was related to LIPCOF, LWE and bulbar hyperaemia, while the phenol red test also correlated with conjunctival staining. Conjunctival and corneal staining were most strongly correlated suggesting that it may not be necessary to conduct both tests or giving validity to their joint evaluation and insertion of fluorescein and lissamine green dyes simultaneously. Symptomology, assessed using the OSDI questionnaire, correlated more with those tests indicating possible damage to the ocular surface (including LWE, LIPCOF and conjunctival staining) than with tests of either tear volume or stability.

Dry eyes tend to be treated as a single condition with management based largely on severity of symptoms rather than signs. Although the DEWS report classified different forms of dry eye, this is based on independent theoretical mechanisms rather than the more complex clinical presentation. The ability to classify patients into a particular cluster based on their tear film metrics should allow practitioners to advise patients on the most appropriate products to manage their dry eyes. Hence chapter 3 also tried to identify whether patients can be scientifically separated into dry eye clusters, and if so whether the ability to place individuals in clusters is of any value in predicting CLIDE in neophyte contact lens wearers (chapter 4). Cluster analysis showed some statistically significant groups of patients with different sign and symptom profiles. The analysis of variation of the five way cluster analysis showed the following tear metrics to be of statistical significance between the clusters; NIKBUT, LIPCOF, phenol red, FBUT, corneal staining, OSDI and NITBUT. The largest cluster of just over one third of the cohort (n=36) demonstrated poor tear quality with both non-invasive tests. Tear volume was also low in this group and the patients reported more symptoms. In the second largest cluster, also around a third of the

cohort (n=34), the NITBUT and FBUT tests again indicated sub-optimal tear stability, but this seemed to be offset somewhat by a higher tear volume in this group. This group of patients were considerably less symptomatic and demonstrated less LIPCOF and less corneal staining. It is, maybe not surprising to find that a combination of poor tear quality and low tear secretion causes more symptoms than poor tear quality alone. Whilst poor invasive and non-invasive break up times in both groups are suggestive of poor tear quality, the patients with concomitant poor tear volume appear to be more symptomatic.

In the final experiment (chapter 4), cluster analysis was then applied to 60 neophyte contact lens wearers, approximately half of the subjects in the two largest clusters were still wearing contact lenses after six months and half had dropped out of lens wear. This suggested that clustering analysis by the method chosen is not beneficial in predicting which patients will succeed with lenses and which will not.

Early silicone-hydrogel contact lenses caused small but statistically significant changes in ocular physiology and symptomatology in new contact lens wearers over 18 months wear, but these were clinically insignificant (Santodoming-Rubido *et al.,* 2006). However, no studies have examined the effect of subsequent generations of silicone-hydrogel materials in contact lens neophytes. The final experimental chapter (chapter 4) evaluated the longitudinal changes in ocular physiology, tear film characteristics and symptomatology experienced by neophyte SiH contact lens wearers in daily wear lenses over a six month period. The study found that there were no significant differences in NIKBUT or NITBUT after 6 months of SiH contact lens wear. Lid wiper epitheliopathy (LWE) increased over 6 months of lens wear, whereas tear volume assessed by the phenol red test did not change. This was

surprising as we would expect that a reduction in tear stability or volume would lead to an increase in LWE through increased friction between the lid margin and the ocular or contact lens surface. This suggests that the increased LWE observed may result from lens factors rather than tear factors.An increase in bulbar hyperaemia was found over 6 months wear, but conversely a decrease in LIPCOF occurred and there was no change in limbal hyperaemia. Whilst statistically significant, the changes of on average 0.2 to 0.3 grading scale units were not felt to be clinically significant. A statistically significant increase in both corneal and conjunctival staining were found over 6 months wear, hence it is clear that even the latest generation of silicone hydrogels still cause a significant impact on ocular physiology and attempts to make lenses more biocompatible are still warranted.

As stated above, the primary aim of this thesis was to try to predict which patients may be predisposed to CLIDE prior to contact lens fitting. By improving our ability to identify in advance those patients at risk of developing CLIDE practitioners can provide better advice. Appropriate wearing schedules, lens materials, lens wearing modalities and possible adjunctive use of ocular lubricants or liposomal sprays may be suggested to aid comfort. As identified above, while certain tear metrics were seen to increase following six months of silicone-hydrogel contact lens wear including LWE, bulbar hyperaemia and corneal and conjunctival staining their presence at initial assessment was not found to be predictive of drop-out. There were clinically and statistically significant differences in both NITBUT (on average by 5.0 s) and fluorescein TBUT (on average by 3.2 s) between those subjects still wearing lenses after six months and those who had ceased lens wear. Receiver operating curves confirmed that this was a key metric to determine those neophyte patients likely to drop out of contact lens wear. Neither the degree of bulbar nor limbal hyperaemia

predicted subsequent contact lens drop out. The baseline OSDI was one of the best differentiators of patients likely to drop out and care should be taken in fitting patients new to contact lenses if they have a NITBUT less than 10s or an OSDI comfort rating greater than 4.2 as they are more likely to drop-out within the first 6 months. Previous studies have found that NIBUT, OSDI or a combination of both tests can be beneficial in predicting contact lens drop out (Fonn *et al*., 1999; Glasson *et al.,* 2003, Nichols and Sinnott 2006; Pult *et al*., 2009, Pult *et al*., 2011) . The results of our study reinforced these findings. Surprisingly, we found greater changes in tear metrics with contact lens wear than Santdomingo-Rubido found with wearers of a previous generation SiH lens in 2006 demonstrating that contact lens materials have still not achieved full biocompatibility.

So, have the aims of this study been achieved?

Whilst there were concerns about the sensitivity and clinical value of the NIKBUT values produced by the Keratograph the manufacturers claim to have improved on this situation by modifying the software so that a reading is now given for average NIKBUT. A study to evaluate this new software could be considered.

As it is impractical for eye care practitioners to conduct every dry eye test on every patient it is useful to rationalize them. Finding strong correlations between two tests allows practitioners to consider performing only one, rather than both. NITBUT and FBUT are correlated suggesting that only one of these tests needs to be carried out in practice to establish tear film stability. Similarly the phenol red thread and TMH were found to be significantly correlated as were conjunctival and corneal staining. This would suggest that practitioners could reduce these 6 tests down to three without compromising their diagnostic abilities. Symptomology, assessed using the

OSDI questionnaire, correlated more strongly with those tests indicating possible damage to the ocular surface (including LWE, LIPCOF and conjunctival staining) than with tests of either tear volume or stability. An OSDI questionnaire used in conjunction with a single test of tear film stability and a single test of tear volume could allow a practitioner to better advice on the most appropriate products.

Cluster analysis showed some statistically significant groups of patients with different sign and symptom profiles, in clinical practice dry eyes tend to be treated as a single condition. We succeeded in identifying 4 clusters. The largest and most symptomatic cluster demonstrated both poor tear film stability and volume. Another cluster, also with poor tear film stability, had normal tear volumes and were less symptomatic. The ability to identify clusters of dry eye patients allows practitioners to give more appropriate advice on dry eye products or the most appropriate contact lens modality or material. For example those patients in cluster 3 were symptomatic, have normal tear volume but poor tear stability and may benefit more from a liposomal spray than an artificial tear supplement. Future research will determine how useful this form of dry eye classification could be in clinical eye-care practice to inform management decisions.

Hence, this thesis has validated a more objective form of tear film assessment. It introduced the concept of cluster analysis to identify different clinical forms of dry eye. It is hoped that this may better inform clinical treatment and it demonstrated that the combination of a tear film stability metric, a tear film volume metric and a short questionnaire can adequately charactise the tear film. This may assist practitioners in identifying those patients likely to drop out of modern contact lens wear, in advance of fitting. Hence expectations can be set, lubricious lenses selected and more

frequent aftercare applied to minimize this risk, affording patients a better experience of lens wear and increasing the contact lens market.

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Appendix 1: Papers

Appendix 2: OSDI questionnaire

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

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

Subtotal score for answers 1 to 5 (A)

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

Subtotal score for answers 6 to 9 (B)

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

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

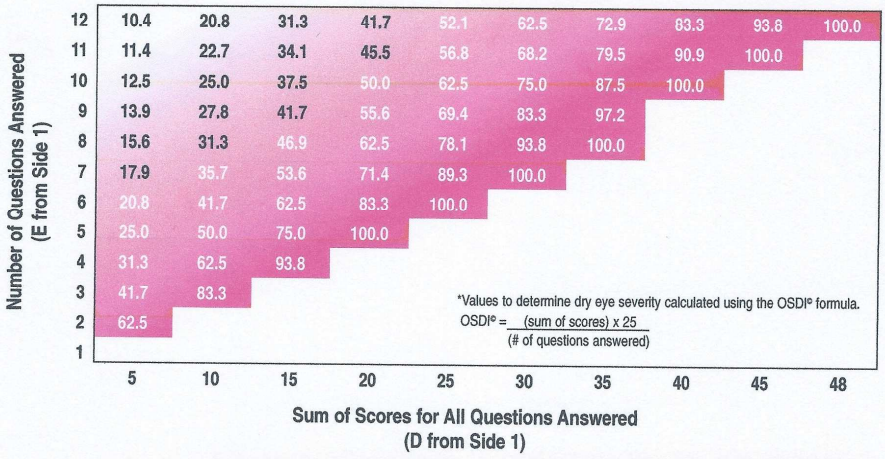
Please turn over the questionnaire to calculate the patient's final OSDI© score.

Evaluating the OSDI® Score[1]

The OSDI® is assessed on a scale of 0 to 100, with higher scores representing greater disability. The index demonstrates sensitivity and specificity in distinguishing between normal subjects and patients with dry eye disease. The OSDI® is a valid and reliable instrument for measuring dry eye disease (normal, mild to moderate, and severe) and effect on vision-related function.

Assessing Your Patient's Dry Eye Disease[1, 2]

Use your answers D and E from side 1 to compare the sum of scores for all questions answered (D) and the number of questions answered (E) with the chart below.* Find where your patient's score would fall. Match the corresponding shade of red to the key below to determine whether your patient's score indicates normal, mild, moderate, or severe dry eye disease.



Patient's Name: _____ Date: _____

How long has the patient experienced dry eye disease? _____

Eye Care Professional's Comments: _____

1. Data on file, Allergan, Inc.
2. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. *Arch Ophthalmol.* 2000;118:615-621

Appendix 3: Ethics form

Aston University
Life & Health Sciences

ETHICS FORM

All parts of the *Ethics Application* must be written concisely using terminology that would be understandable to an educated lay person on an ethics committee.

Title: **Predicting Contact Lens Induced Dry Eye**

Principal Investigator: Prof James Wolffsohn

Contact Details: j.s.w.wolffsohn@aston.ac.uk x4160

Other Staff / Students involved: Nigel Best (OD student) and Laura Best (practice Dispensing Optician)

A. PROJECT OBJECTIVES / BACKGROUND

A1. What are the primary research questions / objective?

Contact lenses can induce dry eye, particularly towards the end of the day, due to a disruption of the tear film dynamics. This is the major cause of contact lens discontinuation. The ability to predict those patients who will have a problem with contact lens induced dry eye will allow for better patient selection, counseling and contact lens choice. Therefore this study aims to determine the clinical signs prior to lens fitting that will predict the level of induced dry eye following commencement of standard contact lens wear.

A2. Where will the study take place?

Clinical Optometric practice

A3. Describe the statistical methods and/or other relevant methodological approaches to be used in the analysis of the results *(e.g. methods of masking / randomization)*

Prospective, investigator masked to future outcome

A4. List the clinical techniques to be conducted on patients as part of the study and indicate whether they fall within the scope of normal professional practice of the individual to perform them

Tear film will be assessed using the tearscope (lipid thickness and break-up time), tear meniscus height, lid wiper epitheliopathy, lissamine green and fluorescein staining, phenol red test, tearlab (using a disposable tip placed momentarily against the sclera to assess tear osmolarity), a dry eye questionnaire and comfort/wearing time diary. All these tests fall within the remit of the optometrist conducting the measurements.

See protocol – information sheet.

B. RESEARCH PARTICIPANTS

B1. How many participants will be recruited? Please provide justification (power analysis software available from http://www.psycho.uni-duesseldorf.de/abteilungen/aap/gpower3/)

60 patients will be recruited allowing at least 15 degrees of freedom if 25% develop dry eye symptoms.

B2. What restrictions will there be on participation (age, gender, language comprehension etc)?

Subjects must wish to wear contact lenses for the first time, not have significant dry eye symptoms and be deemed suitable for the study contact lenses by their optometrist.

B3. How will potential research participants in the study be (i) identified, (ii) approached and (iii) recruited? *If research participants will be recruited via advertisement then attach a copy of the advertisement in the appendix of the ethics report.*

Patients meeting the inclusion criteria assessed as part of their normal clinical eye examination will be given the information sheet and may agree to take part in the study at any time after this by contacting the practice.

B4. Will the participants be from any of the following groups? *Tick as appropriate and justify any affirmative answers.*

Children under 16:	☐
Adults with learning disabilities:	☐
Adults who are unconscious or very severely ill:	☐
Adults who have a terminal illness:	☐
Adults in emergency situations:	☐
Adults with mental illness (particularly if detained under Mental Health Legislation):	☐
Adults suffering from dementia:	☐
Prisoners:	☐
Young Offenders:	☐
Healthy volunteers:	☐
Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, students: patients	☐
Other vulnerable groups:	☐

Participants will need to be healthy patients (other than dry eyes) to enable recruitment. It will be made clear to them that choosing not to take part will not affect their clinical treatment.

B5. What is the expected total duration of participation in the study for each participant?

1 year

B6. Will the activity of the volunteer be restricted in any way either before or after the procedure (e.g. diet or ability to drive)? *If so then give details.*

None

B7. What is the potential for pain, discomfort, distress, inconvenience or changes to life-style for research participants during and after the study?

Lissamine green instillation, fluorescein instillation and phenol red testing can be slightly uncomfortable for a short period. The contact lenses could be uncomfortable to the patients during wear, in which case they can remove them.

B8. What levels of risk are involved with participation and how will they be minimized?

The ocular physiology can be compromised by contact lenses and the standard aftercare appointments will assess the health of the eye and any need for cessation of wear.

B9. What is the potential for benefit for research participants?

None

B10. If your research involves individual or group interviews/questionnaires, what topics or issues might be sensitive, embarrassing or upsetting? Is it possible that criminal or other disclosures requiring action could take place during the study?

No upsetting or disclosure questions

C. CONSENT

C1. Will a signed record of informed consent be obtained from the research participants? *If consent is not to be obtained, please explain why not.*

Yes

Participants information sheet and consent form enclosed

C2. Who will take consent and how it will be done?

The optometrist

C3. How long will the participant have to decide whether to take part in the research? *Justify your answer.*

As long as they need

C4. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The practice holds contact details on all patients

C5. Will individual research participants receive any *payments/reimbursements* or any other *incentives* or *benefits* for taking part in this research*? If so, then indicate how much and on what basis this has been decided?*

No

C6. How will the results of research be made available to research participants and communities from which they are drawn?

By publication on completion of the study

D. DATA PROTECTION

D1. Will the research involve any of the following activities? *Delete as appropriate and justify any affirmative answers.*

Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access: ☐
Electronic transfer of data by e-mail: ☐
Sharing of data with other organizations: ☐
Use of personal addresses, postcodes, faxes, emails or telephone numbers: ☐
Publication of direct quotations from respondents: ☐
Publication of data that might allow identification of individuals: ☐
Use of audio/visual recording devices: ☐

The data spreadsheet will be password protected with Microsoft encryption

D2. Will data be stored in any of the following ways? *Delete as appropriate and justify any affirmative answers.*

Manual files: ☐
Home or other computers: ☐
University computers: ☐

The data spreadsheet will be password protected with Microsoft encryption

D3. What measures have been put in place to ensure confidentiality of personal data? *Give details of whether any encryption or other anonymisation procedures will be used, and at what stage.*

The data spreadsheet will be password protected with Microsoft encryption. Patient contact details will not be recorded as the patient number can be linked to patient files (securely stored within the practice, separate to the collected data)

D4. If the data is not anonymised, where will the analysis of the data from the study take place and by whom will it be undertaken?

At the university/practice and by the investigators.

D5. Other than the study staff, who will have access to the data generated by the study?

No one

D6. Who will have control of, and act as the custodian for, the data generated by the study?

Prof J Wolffsohn

D7. For how long will data from the study be stored [minimum 5 years]? *Give details of where and how the data will be stored.*

5 years in a locked data storage room and on computer storage in encrypted passworded form

E. GENERAL ETHICAL CONSIDERATIONS

E1. What do you consider to be the main ethical issues or problems that may arise with the proposed study, and what steps will be taken to address these?

Patient's time to take part in the study, but this is voluntar. The patient-researcher relationship, but the information sheet contains a clear statement that the participant may withdraw from the study at any time without their usual clinical care being affected. Keeping a diary may be an inconvenience to the patient, but this is brief (just daily comfort and total and comfortable wearing time).

Appendix 4: Consent form (Predicting contact lens induced dry eye)

Personal Identification Number for this study: _____

CONSENT FORM

Title of Project: **Predicting Contact Lens Induced Dry Eye**

Research Venue: Clinical Optometric Practice

Name of Investigator(s): Nigel Best, Laura Best and James Wolffsohn

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

3. I agree to take part in the above study. ☐

_____	_____	_____
Name of Research Participant	Date	Signature
_____	_____	_____
Name of Person taking Consent	Date	Signature

1 copy for research participant; 1 copy for supervisor

Appendix 5: Study participant information sheet

Predicting Contact Lens Induced Dry Eye

Investigators Nigel Best, Laura Best and James Wolffsohn

Location Specsavers Opticians in Darlington

Objectives / Background

Although most people can wear contact lenses very comfortably, some people find their eyes get dry, particularly towards the end of the day. In this study we aim to see whether we can predict who will get these symptoms from assessment of the tear film and front of the eye prior to commencing lens wear. For those who get dry eye symptoms with their contact lenses, newer moisturising contact lenses will be trialled to see whether the symptoms can be overcome.

Inclusion Criteria

To take part in this study, you must be seeking to wear contact lenses for the first time and have been assessed by your optometrist for suitability to wear Ciba Vision's Air Optix lens, as standardly fitted in their practice. Your eye will have been found to be healthy, with no reported dry eye symptoms. You will be at least 18 years of age. If you are willing to take part in the study you will be asked to complete a consent form, but may leave the study at any time without giving a reason. This will not affect your normal clinical treatment.

The Measurements

The measurements that will be made at your initial appointment and subsequent aftercares:

- What symptoms you are feeling and how severe they are (using a short questionnaire)*

You will then be seated in front of a clinical instrument with your chin on a rest while the eye is examined in white light.

- How long your tear film lasts after a blink (holding your eye open as long as possible several times)
- How high the tear meniscus is along your lower eyelid
- How red your eye is
- How much disruption to the front of your eye is seen with two temporary dyes (fluorescein and lissamine green*. The dyes wash out of the eye within 10 minutes and leave no lasting sign. A blue as well as white light will be used)
- How much tears your eye produces (measured with a single-use thread hooked on to your lower eyelid which may irritate a little)*
- The concentration of your tear film (termed osmolarity: measured by placing a single-use probe momentarily against the white of your eye which may irritate a little)*

You will be asked to keep a brief diary between visits to record your eye comfort and how long you could wear the contact lenses comfortably each day

All of these tests are standard measures of dry eye and there are no known risks

Study Length

The study will run for one year and check ups will take place after 1 week, 1 month, 6 months and 1 year, as is standard practice for new patients. The additional measures denoted by a '*' will take no more than 5 minutes at each visit, with the appointments taking no longer than 30 minutes in total.

Further Information

Any further queries you may have can be addressed by one of the investigators at the study location.

Appendix 6: Consent form (Dry eye indicators)

Personal Identification Number for this study: _____

CONSENT FORM

Title of Project: **Assessing dry eye indicators**

Research Venue: Clinical Optometric Practice

Name of Investigator(s): Nigel Best, Laura Best and James Wolffsohn

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my legal rights being affected. ☐

3. I agree to take part in the above study. ☐

_____	_____	_____
Name of Research Participant	Date	Signature
_____	_____	_____
Name of Person taking Consent	Date	Signature

1 copy for research participant; 1 copy for supervisor

Appendix 7: Ethical approval

Aston University
Life & Health Sciences

Response from AOREC

25th March 2010

Project title: ***Predicting contact lens induced dry eye***

Reference Number: Best OD
Researchers: Nigel Best, Laura Best and Prof James Wolffsohn

I am pleased to inform you that the Audiology / Optometry Research Ethics Committee has approved the above named project.

The details of the investigation will be placed on file. You should notify The Committee of any difficulties experienced by the volunteer subjects, and any significant changes which may be planned for this project in the future.

Yours sincerely

Chair AOREC

Appendix 8: Chapter 2 data

Participant number	Tearscope	NIBUT (K)	NIBUT (K) Repeat
1	7.3	3.84	3.2
2	12.6	3.82	1.3
3	9.9	1.55	1.86
4	16.4	1.25	3.64
5	9.2	2.05	4.74
6	11.6	1.76	1.6
7	11.1	2.43	2.83
8	29	3.31	11.94
9	27	3.51	2.22
10	30	4.06	11.38
11	29	9.94	7.1
12	9.1	2.79	2.83
13	9.5	8.57	2.8
14	16	2.92	19.7
15	9.8	3.92	5.03
16	30	4.73	4.01
17	5	0.77	0.36
18	12.1	3.22	2.88
19	24	3.24	6.42
20	8.6	0.36	2.43
21	7.9	0.55	2.55
22	17.5	9.1	5.1
23	18	4.24	7.98
24	9.4	1.48	3.15
25	12.1	6.3	4.9
26	11.6	3.44	0.36
27	10.1	1.51	5.6
28	24.4	3.25	6.46
29	30.3	10.99	5.49
30	10.4	4.41	3.56
31	8.2	4.5	1.12
32	30.3	9.6	9.9
33	18.2	5.33	2.77
34	20.7	6.37	2.39
35	10.3	3.03	2.34
36	11.6	9.43	8.61
37	30.4	8.34	12.25
38	6	1.89	3.04
39	15	1	1
40	30	29	27
41	21.1	12.51	12.53
42	18	3.66	5.48
43	20	2.25	21.4
44	15	3.51	5.6
45	11	2	4
46	15	1.24	1.31
47	19	6	7
48	9	2	6

49	16	3	3
50	11	4	14.61
51	14	4	3
52	30.3	0.59	12.64
53	30.8	1.71	24
54	27.5	22.24	20.75
55	17.4	5.93	7.41
56	18.1	12.85	5.63
57	13.6	5.312	3.8
58	10.2	2.8	1.64
59	30.42	7.1	24
60	30.37	2.81	12.25
61	16.77	0.69	22.34
62	15.6	2.8	1.7
63	13.1	2	1.7
64	30.5	1.1	11.9
65	30.4	1.1	11.9
66	9.56	1.9	2.8
67	13.1	10.2	3.8
68	17.1	5.2	3.1
69	8.2	3.3	0.6
70	13	3.47	1.23
71	17.5	5.8	3.06
72	9.7	5.6	6.9
73	11.1	2.71	3.73
74	10.7	4.32	3.45
75	15.5	5.46	2.6
76	7.3	2.49	2.15
77	10.2	1.12	0.25
78	13.2	2.51	8.57
79	14.9	5.08	3.06
80	16.4	3.25	10.7
81	13.2	0.36	2.1
82	30.6	11.9	24
83	30.3	1.47	0.56
84	13.1	3.26	0.78
85	30.8	2.02	5.2
86	14	1.3	0.69
87	16.7	3.96	2.29
88	12.4	9.63	8.08
89	16.6	2.85	2.15
90	14.2	5.26	10.26
91	17.3	5.31	4.72
92	17.8	2.42	0.36
93	18.7	1.45	3.18
94	30.1	3.36	24.2
95	17.8	9.35	2.52
96	10.4	12.37	4.45
97	13.8	5.01	3.59
98	20.1	5.78	6.21
99	20.8	2.35	0.72
100	17.2	5.31	4.72

Appendix 9: Chapter 3 data

Participant number	NIBUT (K)	T.M.H	Bulb Hyp	LIPCOF	Phenol Red	FBUT	Corneal Stain	Conjunctival Stain	LWE	NIBUT (T)	OSDI
1	3.84	0.15	2.5	0	5	3	0.3	0.2	2	7.3	18.75
2	3.82	0.55	2.8	0	25	8	0	0	0	12.6	9.1
3	1.86	0.19	1.8	0	9	7	1.9	0.8	0	9.9	4.2
4	1.25	0.25	2.7	0	24	7	0	0.4	2	16.4	14.58
5	2.05	0.3	2.2	0	13	6	0	2.3	0	9.2	18.18
6	1.76	0.3	2.3	0	9	24	0	1.9	0	11.6	12.5
7	2.83	0.32	2.6	2	24	16	0	0	0	11.1	2.08
8	3.31	0.3	2.7	2	15	13	0	0	0	29	2.67
9	3.51	0.3	2.4	2	14	4	0	1.6	0	9.1	16.67
10	11.38	0.3	2.6	0	17	8	0	0	0	29	2.67
11	9.94	0.25	2.3	0	22	7	1.3	0	0	29	8.33
12	2.79	0.25	2.4	1	6	5	0	0	0	9.1	31.25
13	3.14	0.35	2.5	3	15	6	0	0	0	9.5	14.58
14	19.7	0.15	2.2	3	2	3	0	0	0	16	10.42
15	5.03	0.2	2.8	3	0	4	0	3.3	0	9.8	10.17
16	4.01	0.35	2.6	1	19	21	0	0	0	30	4.17
17	0.36	0.25	2.6	3	11	7	0	2.2	0	5	10.42
18	3.22	0.42	2.9	0	24	4	1.5	0	0	10.3	0
19	6.42	0.23	2.1	0	8	30	0	2.4	0	24	2.08
20	2.43	0.37	2.6	1	27	4	2.1	0	0	8.67	18.18
21	2.25	0.12	2.3	1	8	4	0	1.5	0	7.9	0
22	9.1	0.27	3	1	8	10	0	0	0	9.1	12.5
23	7.98	0.26	1.6	0	26	6	0	0	0	18	33.33
24	3.15	0.24	3.5	1	23	4	0	0	0	9.4	22.73
25	4.9	0.28	2.8	3	19	4	1	0	0	8.9	6.25
26	3.44	0.27	2.5	2	14	7	0	0	1	9.1	11.37
27	5.6	0.21	2.1	1	22	4	0	0	0	5.6	6.25
28	6.46	0.2	2	1	17	21	0	0	0	24.4	14.58
29	5.49	0.21	1.5	0	9	22	0	0	0	30.3	0

30	4.41	0.35	2.1	0	30	14	0	0	0	8.9	2.27
31	2.04	0.32	3.1	3	10	5	0	3.4	2	5	20.83
32	9.6	0.35	2.9	0	15	17	0	0	0	30.6	0
33	5.33	0.18	2.2	2	22	4	0.8	2.5	0	18.27	2.08
34	2.39	0.27	2.8	1	10	5	1.2	0	0	14.59	9.09
35	2.34	0.21	2.9	3	20	4	0	0	0	9.74	0
36	8.61	0.25	2.4	2	8	9	0	0	0	9.43	10.42
37	4.16	0.15	2	0	5	10	0	0	1.5	6.3	18.75
38	1.62	0.82	3.2	0	25	7	0.3	0.3	0	10.2	9.1
39	4.83	0.41	2	0	7	5	2.2	2.4	0	5.2	4.2
40	4.17	0.2	2.8	0	18	8	0	0	1.5	12.5	14.58
41	2.67	0.25	2	0	8	8	0	2.6	0	11.3	10.42
42	4.7	0.27	2.1	0	15	26	0	2.4	0	24	12.5
43	3.19	0.37	2.9	2	17	14	0	0	0	11.5	2.08
44	7.13	0.3	2.4	1	9	18	0	0	0	29	2.67
45	8.86	0.35	2.2	3	5	5	0	2.3	1	29	16.67
46	11.69	0.5	2.7	0	20	12	0	0	0	14.7	2.67
47	10.5	0.25	2.7	0	25	12	0	0	1.5	29	8.33
48	2.83	0.26	1.7	1	9	6	0	0	1.5	10.5	31.25
49	3.62	0.35	2.1	3	7	5	0	2.2	0	8.8	14.58
50	19.7	0.25	2.6	3	4	5	0	1.6	0	16	10.42
51	2.54	0.2	2.1	2	6	3	1.2	2.8	0	15.1	10.17
52	8.41	0.35	2.5	1	20	20	0	0	0	30	4.17
53	11.2	0.19	3.1	3	9	12	0	3.2	0	13.6	10.42
54	2.16	0.33	2.6	0	15	10	1	0	0	8	0
55	10.3	0.15	2.3	0	1	31	0	2.6	0	24	2.08
56	5.63	0.21	2.2	0	22	10	0.4	0	0	18.19	4.16
57	3.8	0.2	3.3	3	8	5	0	0	0	13.56	16.67
58	1.64	0.19	2.4	1	16	5	0	0	0	10.21	2.08
59	11.67	0.32	3.6	3	25	14	1.9	2.4	0	20.7	52.08
60	7.81	0.2	2.6	3	30	9	0	0	0	14	2.08
61	8.34	0.2	1.5	0	17	13	1.1	0	0	30.4	2.08
62	1.19	0.23	2	3	20	10	0	0	0	15	0
63	27	0.21	2.3	0	22	15	0.3	0.2	0	30	10.42

64	12.53	0.24	2.6	1	18	2	0	0	0	20.8	16.67
65	3.66	0.21	2.7	1	12	5	0.5	2.8	2	18	20.83
66	2.25	0.28	0.4	1	14	6	1	2.2	0	20	0
67	4.7	0.21	2.6	3	12	2	0.2	2.2	1.5	15	33.33
68	4.47	0.12	2.7	3	13	6	2.2	2.5	2.5	11	31.25
69	1.24	0.33	2.7	3	21	6	0	0	1.5	5	20.83
70	6.31	0.28	2.8	3	22	9	1	0	0	19	0
71	2.96	0.2	2.8	3	20	2	0.4	1.4	2	9	22.73
72	3.51	0.24	1.3	0	21	7	0	0	2.5	16	10.42
73	4.36	0.25	2.8	3	26	7	0	0.5	0	11	20.83
74	4.87	0.17	1.7	3	22	4	0	0	0	14	2.08
75	3.04	0.24	1.7	3	8	3	0	0	0	5.6	18.75
76	4.79	0.3	2.4	3	15	4	0	0	0	9	20.83
77	1.9	0.19	3.3	3	9	12	0	3.2	0	13.6	10.42
78	2.17	0.25	2.2	0	13	6	0	2.3	0	9.2	18.18
79	2.44	0.5	2.7	0	17	8	0	0	0	29	0
80	2.51	0.25	2.4	2	21	6	0	0	2	14.91	4.16
81	7.7	0.17	2.1	2	9	8	1.2	0	1.5	13.5	4.17
82	17.01	0.18	1.6	1	20	9	0	0	0	17	2.08
83	2.16	0.26	3.8	2	20	9	0	1.5	0	10.8	18.75
84	4.4	0.23	3.2	1	14	15	0	0	0	18.8	0
85	14.81	0.4	3.6	3	30	12	0	0	0	14.9	2.08
86	13.9	0.2	2.6	3	30	12	0	0	0	25.1	2.08
87	4.38	0.31	2.4	0	20	13	0	0	2	9.81	
88	20.75	0.3	2.6	2	9	14	0	1.8	1.5	22.2	14.58
89	7.41	0.2	2.8	2	9	22	0	2.2	0	19.17	14.58
90	0.36	0.37	2.6	1	27	4	2.1	0	0	8.7	8.33
91	7.28	0.19	2.2	3	15	16	0	0	0	21.3	27.27
92	1.32	0.58	2.2	0	30	12	0	0	0	8.67	2.08
93	10.21	0.19	2.4	0	11	10	0	0	0	14.5	14.58
94	3.69	0.12	3.2	3	21	4	0	2.5	2.5	11.27	20.83
95	3.69	0.24	2.6	2	21	5	0	0	0	9.35	3.65
96	11.19	0.2	2.1	0	12	15	0	0	0	27.7	0
97	8.3	0.28	2.3	0	20	8	0	0	0	10.1	17.18

98	12.91	0.2	1.6	1	5	5	0	0	0	18.64	14.58
99	2.59	0.27	2	1	18	6	0	0	0	9.25	2.08
100	6.61	0.1	2.9	3	15	10	0	0	0	30.4	2.08

Appendix 10: Chapter 4 data

Participant number	NIBUT (K)	T.M.H	Bulb Hyp	Limb Hyp	LIPCOF	Osmolarity	Phenol Red	FBUT	Corn Stain	Conj Stain	LWE	OSDI	NIBUT(T)
1	3.84	0.15	2.5	2	0	329	5	3	0.3	0.2	2	18.75	7.3
2	3.82	0.55	2.8	2.3	0	311	25	8	0	0	0	9.1	12.6
3	3.31	0.3	2.7	2	2	329	15	13	0	0	0	2.67	29
4	1.76	0.3	2.3	2	0	319	9	24	0	1.9	0	12.5	11.6
5	2.83	0.32	2.6	2.3	2	327	24	16	0	0	0	2.08	11.1
6	3.22	0.42	2.9	2.6	0	315	24	4	1.5	0	0	0	10.3
7	0.77	0.25	2.6	2.3	3	316	11	7	0	2.2	0	10.42	5
8	6.42	0.23	2.1	2.7	0	316	8	30	0	2.4	0	2.08	24
9	2.05	0.3	2.2	1.8	0	318	13	6	0	2.3	0	18.18	16.3
10	4.06	0.3	2.6	2.6	0		17	8	0	0	0	2.67	29
11	4.73	0.35	2.6	2.4	1	312	19	21	0	0	0	4.17	30
12	9.94	0.23	2.3	2.5	0	353	22	7	1.3	0	0	8.33	29
13	11.19	0.2	2.1	2	0	307	12	15	0	0	0	0	27.7
14	4.38	0.31	2.4	2.6	0		20	13	0	0	2	20.83	9.81
15	11.67	0.32	3.6	3.2	3		25	14	1.9	2.4	0	52.08	20.7
16	0.56	0.12	2.3	2	1		8	4	0	1.5	0	0	7.9
17	3.44	0.27	2.5	2.4	2		14	7	0	0	1	11.37	9.1
18	6.46	0.22	2	1.5	1		17	21	0	0	0	14.58	24.4
19	6.9	0.35	2.9	2.8	0		15	17	0	0	0	0	30.3
20	5.33	0.18	2.2	2.7	2		22	4	0.8	2.5	0	2.08	18.3
21	6.61	0.1	2.9	2.1	3		15	10	0	0	0	2.08	30.4
22	2.59	0.27	2	1.6	1		18	6	0	0	0	2.08	9.25
23	3.44	0.27	2.5	2	2		14	7	0	0	1	2.08	9.1
24	1.64	0.19	2.4	2.6	1		16	5	0	0	0	2.08	6.7
25	12.91	0.2	1.6	1.5	1		5	5	0	0	0	14.58	18.64

26	2.51	0.25	2.4	2.2	2		21	6	0	0	2	4.16	14.9
27	8.3	0.28	2.3	2.1	0		20	8	0	0	0	17.18	10.1
28	7.7	0.17	2.1	2.6	2		9	8	1.2	0	1.5	4.17	13.5
29	17.01	0.18	1.6	1.4	1		20	9	0	0	0	2.08	17
30	2.16	0.25	3.8	3.5	2		20	9	0	1.5	0	4.16	10.8
31	14.81	0.4	3.6	3.4	3		30	12	0	0	0	2.08	14.9
32	4.4	0.23	3.2	2.8	1		14	15	0	0	0	0	18.8
33	13.9	0.2	2.6	2.3	3		30	12	0	0	0	2.08	25.1
Drop-Outs within 6 months of Baseline													
34	1.86	0.19	1.8	0.6	0	309	9	7	1.8	0.8	0	4.2	9.9
35	1.25	0.25	2.7	2.5	0	303	24	7	0	0.4	2	14.58	16.4
36	3.51	0.3	2.4	1.8	2	302	14	4	0	1.6	0	16.67	9.1
37	2.79	0.25	2.4	1.8	1	330	6	5	0	0	0	31.25	9.1
38	3.14	0.35	2.5	1.5	3	327	15	5	0	0	0	14.58	9.5
39	2.92	0.15	2.2	2.3	3	335	2	3	0	0	10.4	10.41	14.6
40	5.03	0.2	2.8	3	3	352	0	4	0	3.3	0	10.17	9.8
41	20.75	0.3	3.2	2.6	2	313	9	14	0	1.8	1.5	14.58	22.2
42	0.36	0.37	2.6	2.8	1	356	27	4	2.1	0	0	8.22	8.67
43	9.1	0.27	3	2	1		8	10	0	0	0	12.5	9.1
44	7.98	0.26	1.6	1.8	0		26	6	0	0	0	33.33	18
45	1.91	0.24	3.5	3.1	1		23	4	0	0	0	22.73	9.4
46	4.9	0.28	2.8	3.1	3		19	4	1	0	0	6.25	8.9
47	5.6	0.21	2.1	2.6	1		22	4	0	0	0	6.25	5.6
48	5.49	0.21	1.5	1.2	0		9	22	0	0	0	0	30.3
49	4.41	0.35	2.1	2.5	0		30	14	0	0	0	2.27	8.9
50	2.04	0.32	3.1	2.4	3		10	5	0	3.4	2	20.83	5
51	2.39	0.27	2.8	2.5	1		10	5	1.2	0	0	9.09	14.59

52	5.63	0.21	2.2	2.6	0		22	10	0.4	0	0	4.16	7.79
53	2.34	0.21	2.9	3.3	3		20	4	0	0	0	0	9.74
54	8.61	0.25	2.4	2	2		8	9	0	0	0	10.42	9.43
55	3.8	0.2	3.3	3	3		8	5	0	0	0	16.67	13.56
56	1.32	0.58	2.2	2.8	0		30	12	0	0	0	2.08	8.67
57	10.21	0.19	2.4	1.8	0		11	10	0	0	0	4.17	14.5
58	3.69	0.12	3.2	3	3		21	4	0	2.5	2.5	20.83	11.27
59	7.28	0.19	2.2	1.6	3		15	16	0	0	0	27.27	20.44
60	3.69	0.24	2.6	2	2		21	5	0	0	0	6.25	9.35