Schirmer Tear Test 2 and Tear Break-Up Time values in a South African young black adult population

by

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DECLARATION

I, Naimah Ebrahim Khan, hereby declare that the dissertation submitted for the degree Master in Optometry to the University of KwaZulu-Natal has not been submitted before for consideration for a degree at this University or any other University previously.

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NAIMAH EBRAHIM KHAN

DEDICATIONS

This is dedicated to my daughter Aaminah.

You may be little but you are my teacher, my inspiration, my ray of sunshine.

ACKNOWLEDGEMENTS

I would like to thank Allah (God Almighty).

My deepest appreciation to my husband, my parents and the rest of my family for their support and encouragement.

Professor Oduntan for his supervision and academic guidance.

My friends and colleagues at the University of KwaZulu-Natal, Optometry Department for the encouragement and guidance.

'The ink of the scholar is more sacred than the blood of a martyr' and 'Seek knowledge from the cradle to the grave' (Prophet Muhammad (peace be upon him))

'Knowledge revives the dead hearts and drives them out of darkness into the light; and knowledge is the light of the inner eyes that cures ones blindness and restores ones inner sight' (Mu'adh bin Jabal)

ABSTRACT

Aim: The aim of this study was to establish normal values for Schirmer tear test (version 2) and tear break up time (TBUT) in a South African young adult Black population.

Method: Following ethical approval by the biomedical research and ethics committee, KwaZulu-Natal, participants were recruited from the city of Durban in South Africa via personal invitations, poster advertisements and University of KwaZulu-Natal optometry clinic clients. McMonnies questionnaire for dry eye diagnosis was administered and those who failed were excluded from the main study. Two hundred (100 males and 100 females) participants who met the inclusion criteria were included in the study. Following a slit lamp examination of the eye, the Schirmer test was administered and the following day, the TBUT was measured. A re-test version of the two procedures were conducted one week after, at about the same time of the day for each subject.

Results: The participants were aged 18-30 years, mean = 20.77 ± 2.29 years. The mean Schirmer test values for all participants (N = 200; 400 eyes) was 15.96 ± 6.86mm. The values for the males and females (200 eyes each) were 16.34 ± 6.93mm and 15.58 ± 6.81mm respectively. The mean TBUT (400 eyes) was 7.18 ± 1.89 secs. The mean values for the males and females (200 eyes each) were 6.90 ± 1.88 secs and 7.32 ± 1.67 secs respectively. A strong positive correlation ($r = 0.895$) and ($r = 0.914$) respectively was found between the right and left eyes in the two tests.

Conclusion: Generally, the mean values found in this study for the Schirmer test are similar to those that have been reported in the literature. However, values for TBUT differ from the values that have been previously reported, being higher in some instances and lower in others. These findings have implications for dry eye diagnosis and also contact lens practice in South Africa.

Key words: Schirmer tear test 2, Tear break up time, Dry eye, McMonnies questionnaire

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CHAPTER 1. INTRODUCTION

1.1. OUTLINE OF THE REPORT

The study will be presented with an introduction (chapter 1), literature review (chapter 2), methodology (chapter 3), results (chapter 4) and the discussion and conclusion (chapter 5). Thereafter, the references used in the study will be listed followed by an attachment of the appendices.

1.2. INTRODUCTION

In South Africa, ophthalmic patients often present at optometry clinics complaining of the sensation of dry and itchy eyes, which is sometimes accompanied by hyperaemia of the bulbar and palpebral conjunctiva. The majority of these patients are often diagnosed as having dry eye conditions, which is often the cause of the constant eye discomfort that they experience. They may be denied wearing, or forced to discontinue wearing contact lenses, which may affect their social and/or recreational activities, depending on their prescription. In South Africa, contact lens wear amongst young adults (18-30 years) is gaining popularity as a choice of vision correction.

Dry eyes are a result of either the inability to produce adequate tears or the poor quality of the tear layers and it occurs in people of all ages in South Africa, Africa and the world. Clinically, the Schirmer Tear Test 2 is often used to assess the produced tear volume and the Tear Break-Up Time values are used to assess tear quality. These two tests were performed among a population of young black adults in the city of Durban, KwaZulu-Natal to determine normal values for these tests in a young South African population. These values may be useful in the diagnosis and management of dry eyes in this age group in this part of the country.

1.3. BACKGROUND

The outer portion of the eye consists of a number of structures, each of which has a specific function. The ocular surface, tear film, lacrimal glands, and eyelids act as a functional unit to preserve the quality of the refractive surface of the eye; to resist injury and to protect the eye against changing bodily and environmental conditions (Rolando and Zierhut, 2001). The tear film plays a vital role in nourishing, lubricating and protecting the ocular surface (Tiffany, 2008).

Dry eye is often a consequence of tear film anomaly. There are three distinct layers of the tear film: an outer lipid layer, a watery aqueous layer in the middle and a slimy mucous layer which lies in apposition to the cornea. A deficiency in any one of these layers could result in a patient experiencing discomfort and exhibiting signs of dry eye. Furthermore, tears go through four processes: production by the lacrimal gland, distribution by blinking, evaporation from the ocular surface and drainage through the naso-lacrimal duct. Abnormalities in any one of these steps can also lead to a dry eye (Tsubota, 1998).

To identify patients at risk for dry eye, practitioners sometimes make use of dry eye questionnaires, with the McMonnies Dry Eye Questionnaire being considered a gold standard for examining dry eye symptoms (Erickson *et al* 2002). The questionnaire is used to screen patients for the possibility of dry eye disease so that the index of suspicion of the practitioner is raised for those at risk, and further testing would therefore be performed. This is a self-administered questionnaire format with 14 questions that are weighted differently in scoring (McMonnies and Ho, 1987). A score of over 20 is indicative of dry eye, between 10 and 20 is suggestive of borderline dry eye disease (O'Toole, 2006), and below 10 suggests no dry eye symptoms.

There are many tear function tests that are currently utilized by eye care practitioners worldwide to test tear integrity of patients and assist in diagnosing dry eye. These tests include Schirmer test, Tear break-up time (TBUT), the

Phenol red thread test, Lacrimal equilibration time, Jones test, Tear thinning time, Lipid layer thickness test, tear osmolarity and Tear meniscus height. The Health Professions Council of South Africa (HPCSA) has recommended that practitioners should perform at least two of the tear function tests before diagnosing a patient as having a dry eye (Moodley, 2008). In South Africa, the two commonly performed tests are the Schirmer test and TBUT.

Overseas normative tear test values are used in the evaluation of tears for Africans including South Africans. However, there has been limited research to suggest that these values are appropriate for these patients both internationally and in South Africa. It is therefore, considered necessary to establish normative values for the commonly conducted tear tests in a South African population. The Schirmer and Tear break-up time tests were selected for investigation in this study, with the McMonnies Dry Eye questionnaire being used to determine the presence or absence of dry eye.

The Schirmer test is used to assess and estimate tear secretion (Ozdemir and Temizdemir, 2010), and can be performed with or without a local anaesthetic. The presence of the anaesthetic eliminates reflex tearing and is indicative of the basal secretion of tears (Schirmer 2). If the test is performed without the anaesthetic (Schirmer 1), the results yielded would be indicative of both reflex and basal tears. Schirmer 2 was selected for the current study. The procedure for this test includes: a local anaesthetic is administered and a filter paper strip (Schirmer strip) is placed into the inferior cul-de-sac for five minutes. Thereafter, the strip is removed and the wet length of the strip is measured with a millimeter ruler. Schirmer values of less than 10mm in five minutes are considered suspect for dry eye (Caffery and Paugh, 2005).

The volume of tears is not the only method of assessing normality of tears. The technique of assessing tear stability using fluorescein installation is called Tear Break-up time (TBUT). The technique has been widely used in the clinical

diagnosis of dry eye and in screening potential contact lens wearers (Cho and Brown, 1993). The test is performed by placing a drop of fluorescein into the eye while the patient keeps their eyes open. The ocular surface is viewed with a broad beam and a cobalt blue filter. The time taken from the last blink until the appearance of the first dry spot is taken as the reading. Traditionally, the normal break-up time ranges from 15 to 45 seconds, with a break-up time of less than 10 seconds being considered abnormal (Kanski, 2003).

There has been an increased awareness throughout the world that the traditionally used normal values for these tear tests may not be applicable universally. The results of a number of studies indicate disagreement with the traditional normal values (Sukul et al, 1983; Chopra et al, 1985; Maugdil et al, 1989; Cho and Brown, 1993; Cho and Yap, 1993a; Al-Abdulmunem, 1997; Briggs, 1998; Amaechi and Osunwoke, 2004; Fermon et al, 2010; Ozdemir and Temizdemir, 2010).

Some of the reasons cited for the differences in normal values are environmental or racial factors. Cho and Brown (1993) reported that the TBUT in Caucasians residing for more than a year in Hong Kong was higher than that in Hong Kong Chinese. Ozdemir and Temizdemir (2010) have emphasized that normal values differ with age, race and sex of the patient. In this study, the McMonnies questionnaire, Schirmer 2 and Tear break-up time were used to evaluate the tears in a young African population of both sexes without dry eyes.

1.4. PROBLEM STATEMENT

While overseas normative tear test values are used for South Africans, there has been limited research to suggest that these values are appropriate for these patients. This could lead to misdiagnosis of dry eye among South Africans.

1.5. HYPOTHESIS/RESEARCH QUESTION

H_0 (1): Normal values for the Schirmer 2 tear test will not be different from that reported in the literature.

H_A (1): Normal values for the Schirmer 2 tear test will be different from that reported in the literature.

H_0 (2): Normal values for the Tear break-up time test will not be different from that reported in the literature.

H_A (2): Normal values for the Tear break-up time test will be different from that reported in the literature.

1.6. AIM AND OBJECTIVES

The aim of the study was to establish normal values for the Schirmer 2 tear test and Tear Break-Up time test in a South African young Black adult population.

The study objectives were to:

1. screen a young black adult population sample for dry eye using the McMonnies dry eye questionnaire.
2. assess the rate of tear flow / basal tear secretion rate using the Schirmer test 2 in the population sample without dry eyes.
3. assess the stability of the tear film using the Tear break-up method in the population sample without dry eyes.
4. estimate the range and mean of normal Schirmer test 2 in a young adult South African population sample.
5. estimate the range and mean of normal TBUT in a young adult South African population sample.
6. establish gender differences in Schirmer test 2 values in the sampled population.
7. establish gender differences in TBUT values in the sampled population.

1.7. TYPE OF STUDY AND METHOD

This is a quantitative clinical study. A convenient sampling method was employed to select participants whose tear quantity and quality were evaluated with Schirmer and TBUT respectively.

1.8. SIGNIFICANCE OF THE STUDY

This study is of significance in establishing clinically normal values for the Schirmers 2 tear test and Tear break-up time for the young Black adult South African population in KwaZulu-Natal. This will help eye care practitioners in the diagnosis and management of patients presenting with tear related problems. Proper and timely diagnosis of dry eyes will assist to improve the patient's quality of life.

CHAPTER 2. LITERATURE REVIEW

2.1. INTRODUCTION

This chapter discusses tears, dry eye syndrome, questionnaires, tear tests and treatment for dry eyes.

2.2. TEARS

Tears coat the anterior surface of the eye and provide lubrication, act as a transport mechanism for oxygen, carbon dioxide and nutrients for the eye. Tears are produced by different structures of the eye and consist of three layers which are discussed below.

2.2.1. Tear structure, composition and biochemistry

2.2.1.1. Tear Structure

The tear film of the human eye consists of three layers: Mucous, aqueous and lipid, each of which has separate functions (Kanski, 2003). These are shown in Figure 2.1. The three layers are derived from the bulbar conjunctiva, where the goblet cells produce the mucous secretion; the lacrimal gland and the accessory lacrimal glands of Krause and Wolfring that contribute the lacrimal (aqueous layer); and the meibomian glands, situated at the tarsus, as well as the accessory glands of Zeiss and Moll, which produce the sebaceous (lipid) layer (Mandell, 1988).

The mucous material is deposited onto the corneal surface by the action of the lids and the tarsal conjunctiva during a blink (Lemp *et al*, 1970; Mandell, 1988). The importance of the mucous component of the tears has been highlighted in many studies, and has been found to play a role in wetting the corneal surface (Iwata *et al* 1969; Lemp and Dohlman 1970; Lemp *et al* 1971; Mandell, 1988). A

deficiency in this layer may result in a hyposecretive and evaporative state (Kanski, 2003).

The aqueous layer supplies atmospheric oxygen to the avascular corneal epithelium and also provides an antibacterial function due to the presence of tear proteins. This layer is 6.5 to 7.5 µm thick and serves to wash away debris and noxious stimuli from the eye. A deficiency in this layer may result in a hyposecretive dry eye (Kanski, 2003).

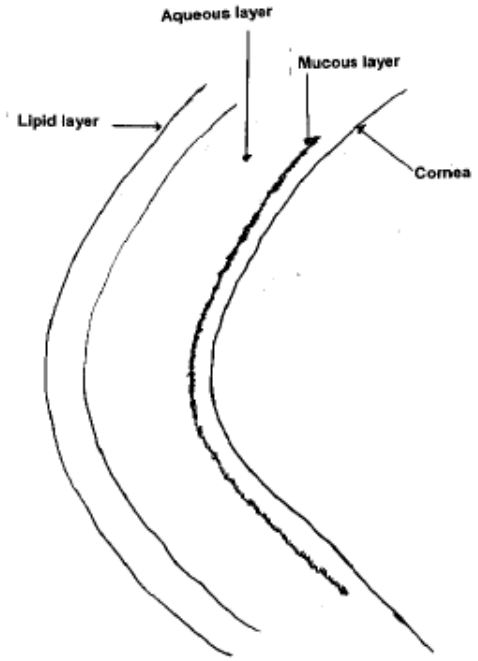

Figure 2.1. A schematic representation of the cornea and tear layers

The oily lipid layer forms a protective film over the cornea and reduces tear evaporation to approximately 10 percent of what it would be without this layer (Mishima and Maurice, 1961; Records, 1979). Functions of the lipid layer include providing a smooth optical surface for the cornea, enhancing the stability of the tearfilm, enhancing spread of the tear film, preventing spillover of tears from the lid margin, preventing contamination of the tear film by sebum and sealing the apposed lid margins during sleep. The chief function is to retard water evaporation from the surface of the open eye (Foulks, 2007). The lipid layer

lowers the surface tension of the tear film and draws water into the tear film, thereby increasing the thickness of the aqueous layer. This layer also lubricates the eyelids as they pass over the surface of the globe. A dysfunction of this layer may result in an evaporative dry eye (Kanski, 2003).

2.2.1.2. Tear composition and biochemistry

Tears contain proteins (mucins, enzymes, glycoproteins and immunoglobulins), water, organic solutes, electrolytes and lipids. The lipid layer contains several classes of lipids, examples of which are wax esters, triglycerides, free fatty acids and polar lipids (Gillan, 2010). The aqueous layer contains proteins, water and electrolytes (Dartt, 2004). The mucous layer contains mucin types that are secreted or membrane-associated (Ramamoorthy and Nichols, 2008).

2.2.2. TEAR DYNAMICS AND DISTRIBUTION

Tear dynamics can be determined by evaluating secretion, blinking, evaporation and drainage (Tsubota, 1998). Tears are produced by the lacrimal gland, and are distributed over the ocular surface by blinking. Thereafter some of the tears evaporate while the rest are drained through the punctum into the nasal cavity. The tear pathway is shown in Figure 2.2.

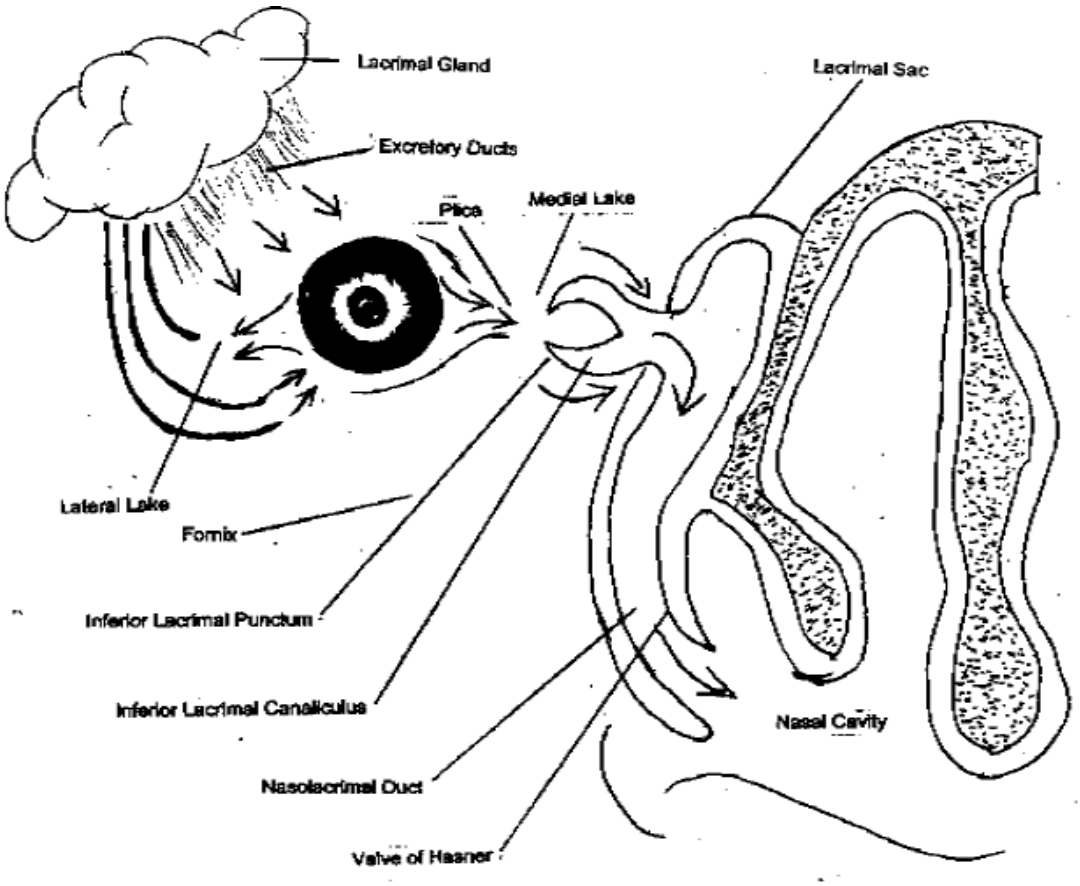

Figure 2.2. A schematic diagram of the tear pathway

Tear distribution occurs via blinking, which occurs from temporal to nasal. Blinking causes tears to be spread across the ocular surface and assists movement of tears toward the puncta for drainage. Blinking also assists in the release of the lipid component from the meibomian gland (Driver and Lemp, 1996). Blinking abnormalities causes improper tear distribution which can lead to ocular surface abnormalities. The normal rate for blinking has been generally accepted as 12-15 blinks per minute (www.iacle.org).

A psychiatric point of view is that blinking is affected by ones state of mind, for example, it is commonly thought that an agitated state of mind induces a higher blink frequency. The principal determining factors of blink rate are ocular surface reflexes and environmental factors. Blinking can also be affected by visual tasks,

for example, visual display terminals (VDT's). Kojima *et al* (2011) reported that patients using VDT's had a lower tear meniscus volume with significant dry eye and visual symptoms. Anyone concentrating on something for an extended period of time can have a reduced blink rate and experience ocular fatigue. Decreased blink rate is also a major factor in dry eyes. Incomplete blinking (lagophthalmos) can occur and results in a portion of the cornea always being dry (Tsubota, 1998).

During blinking, the lower lid hardly moves. The upper lid closes via the action of the orbicularis oculi (innervated by the facial nerve) and opens via the action of the levator palpebrae superioris, which receives innervation by the oculomotor nerve (the third cranial nerve). The levator palpebrae superioris arises from the underside of the lesser wing of the sphenoid above and in front of the optic foramen (Warwick, 1976). The orbicularis consists of a palpebral and an orbital portion. The palpebral portion is the central part of the muscle which is confined to the lids. It consists of pale muscle fibres and may be divided into pre-tarsal and pre-septal strata. The junction of the two lies at the upper and lower lid furrows. The palpebral portion is used in closing the eye without effort. An example of this would be involuntary closure. Reflex closure also occurs when there is any danger or if there is a loud noise. The orbital portion has a curved origin from the medial side of the orbit. The origin is the muscular or short tendinous fibres and is not continuous. From the origin, the peripheral fibres sweep across the orbital margin in a series of concentric loops and the more central fibres form nearly complete rings. The orbital portion is used to close the eyes tightly. The skin of the forehead, temple and cheek is drawn toward the medial side of the orbit when this region of the muscle is in action (Warwick, 1976).

2.2.3. TEAR EVAPORATION AND DRAINAGE

The evaporation rate is influenced by ambient conditions, hormonal regulation, blink rate, area of palpebral aperture, tear film compartments and tear film lipid

layer (Foulks, 2007). The evaporation rate is also determined by the status of the lipid layer and the protein constituents of the tear film (primarily lipocalin), the mucin coating of the epithelial cells, and the aqueous component of lacrimal secretions (Goto *et al*, 2003). Wojtowicz and McCulley (2009) recommended that evaporometry measurements should be taken during the afternoon rather than the morning as there was variability in the readings in the morning. For the effective drainage of tears, gravity, siphonage, capillary attraction and muscular activity must work effectively to conduct tears down the nasolacrimal duct. Blockage of the punctum will prevent adequate drainage of tears. The presence of a number of peptides and molecules within the tear fluid that are responsible and essential for immune defense mechanisms and outflow properties of tears have been found (Paulsen and Brauer, 1993). These assist in the drainage of tears.

2.2.4. TEAR FUNCTIONS

Tears maintain a smooth surface for light refraction and lubrication of the eyelids, cornea and conjunctiva. The lubrication alleviates mechanical damage during blinking. Tears supply the cornea with nutrients by transporting oxygen and other nutrients to the avascular cornea and regulating the electrolyte composition and pH. White blood cells have access to the cornea and conjunctiva via the tears. Foreign body removal is also aided by tears. The tear film protects the ocular surface by responding to stresses which include dessication, noxious chemicals, bacterial, viral and parasitic infection (Ohashi *et al*, 2006). Tear proteins such as immunoglobulin A (IgA), lysozyme and lactoferrin inhibit colonization and growth of bacteria (McClellan and Fracs, 1997).

2.3. DRY EYE SYNDROME

Dry eye syndrome is a condition that occurs when there is an anomaly in the tear pathway. This will be further discussed in terms of the hormonal regulation of tear secretion, neuronal regulation of tear secretion, the classification of the

major causes of dry eye, the prevalence and incidence of dry eye and the factors influencing dry eye.

2.3.1. Hormonal regulation of tear secretion

Homeostasis of the tear film involves delicate hormonal and neuronal regulatory mechanisms (Baudouin, 2001). Androgens (sex hormones) modulate the physiology, anatomy and immune system of the lacrimal gland (Sullivan *et al*, 1996). Hormones such as follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, progesterone and estrogens also influence normal and pathological lacrimal function (Oprea *et al*, 2004). Meibomian gland acini also express both androgen and estrogen receptors suggesting that the meibomian glands, like the sebaceous glands and lacrimal glands are hormonally regulated (Rocha *et al*, 2000; Esmaeli *et al*, 2000).

Females have been identified as a higher risk for dry eye. Suzuki *et al* (2008) discussed that the sex associated difference is probably due to the effects of endogenous or exogenous estrogens on the meibomian gland. Suzuki *et al* (2008) conducted an evaluation of post-menopausal women and demonstrated that women using estrogen replacement therapy have a higher prevalence of severe dry eye symptoms and clinically diagnosed dry eye syndrome as compared to women who never used the treatment. Similarly, Mathers *et al* (1998) also found a relationship between hormone levels and tear production in pre and postmenopausal women. Postmenopausal women displayed higher estrogen levels and decreased tear function.

2.3.2. Neuronal regulation of tear secretion

The cornea is very richly innervated and thus nervous signals are important for trophic regulation and corneal protection. The main and accessory lacrimal glands, mucous cells, and meibomian glands have an abundant nerve supply (Baudouin, 2001). The nerve supply comes mainly from the parasympathetic system but the sympathetic nerves and sensory fibres from the trigeminal nerve

(calcitonin gene-related peptide (CGRP) and substance P) also play a role. The lacrimal gland is densely innervated with parasympathetic nerves containing acetylcholine and vasoactive intestinal peptide (VIP) and some sympathetic (norepinephrine) and sensory (CGRP and substance P) nerves. Dartt *et al* (1996) discussed that VIP is present in nerves that are parasympathetic. Vasoactive Intestinal Peptide surrounds conjunctival goblet cells and stimulates secretion. These nerves appear to be the efferent arm of the sensory reflex pathway that stimulates goblet cell secretion. Other neurotransmitters like met-enkephalin, leu-enkephalin and sigma receptors also play regulatory, stimulatory or inhibitory roles in lacrimal secretion (Baudouin, 2001). A dysfunction or abnormality in any of these mechanisms can result in an anomaly in lacrimal regulation and can result in dry eye.

2.3.3. Classification of the major causes of dry eye

Dry eye can be divided into two subgroups, tear deficient and evaporative dry eye (Kaercher and Bron, 2008). A deficiency in the lipid layer of the tear film is aetiological in about 80% of the patients suffering from dry eye, which results in excessive evaporation (Dausch *et al*, 2006). The tear film is exposed to variations of relative humidity in different environmental conditions and similar to any other aqueous solution exposed to air of less than hundred per cent humidity, it evaporates (McCulley *et al*, 2006). The effects of relative humidity are seen in different situations where the humidity conditions are low or extremely low, such as deserts and pressurized cabins of commercial airplanes (McCarty and McCarty, 2000).

Dry eye conditions can also be classified into those with adequate aqueous tear production and those with aqueous tear deficiency. Adequate aqueous dry eye patients suffer from meibomian gland dysfunction that can result in lipid tear deficiency. Aqueous tear deficiency may be subclassified into non-Sjogren's and Sjogrens syndrome. Patients with non-Sjogrens aqueous tear deficiency have less severe symptoms and ocular surface disease than those with Sjogrens

syndrome. In Sjogrens syndrome, immune-mediated destruction of the lacrimal gland results in severe aqueous tear deficiency. Aqueous tear deficiencies lead to an ocular surface disease termed keratoconjunctivitis sicca (KCS). Keratoconjunctivitis sicca results from abnormal terminal differentiation of the ocular surface epithelia and is associated with marked reduction in mucin production by these cells (Pflugfelder, 1996).

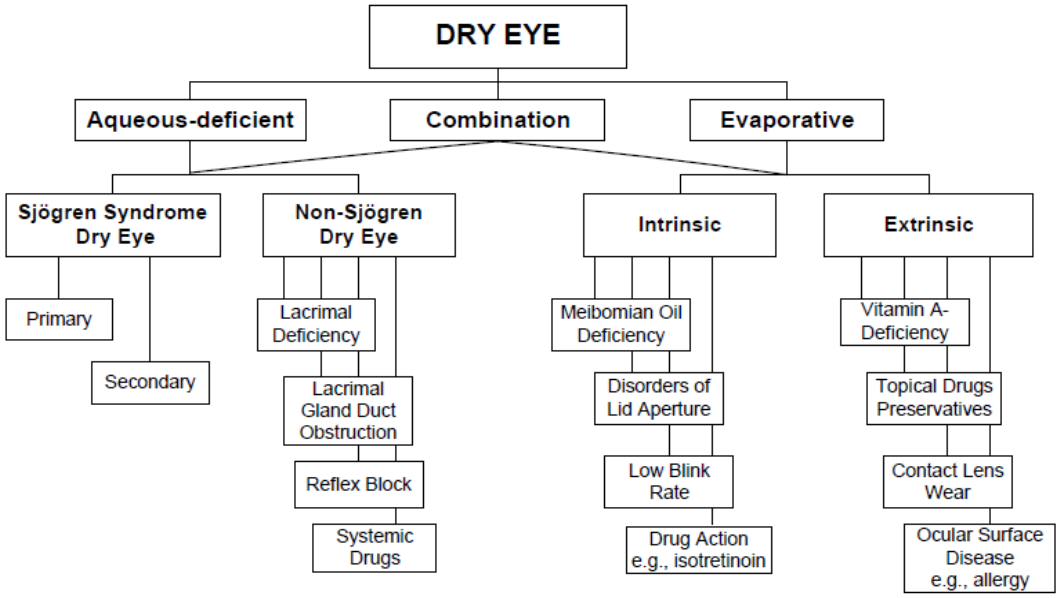

Figure 2.3. Classification and major etiological causes of dry eye (Reproduced with permission from American Academy of Ophthalmology. Cornea/external disease panel, 2011)

Human meibomian glands are embedded in the tarsal plate with individual glands present in a single row along the lower and upper lid. Each meibomian gland has multiple acini connected by a long central duct which runs throughout the length of the gland (McCulley and Shine, 2004). Meibomian gland dysfunction is associated with inflammation, obstruction or abnormal secretion of the meibomian glands. It results in an altered or reduced lipid excretion that leads to disruption of the tear film. This causes irritation to the cornea, conjunctiva and lids (Driver and Lemp, 1996).

2.3.4. Prevalence and Incidence

Gillan (2009) used The Ocular Surface Disease Index to ascertain the prevalence of dry eye symptoms in a research population based in Johannesburg, South Africa. The results of the study yielded a prevalence of 64%. This is a relatively high value compared to that reported by other studies (Lemp, 2008; Nichols *et al*, 2004) where the prevalence varied between 0.39% and 33.7%.

Dry eye syndrome in elderly Tibetans at high altitude was investigated by Lu *et al* (2008). A total of 1840 participants were tested and 52.4% of the population was symptomatic. A statistically significant correlation between dry eye symptoms and signs was present. Guo *et al* (2010) investigated dry eye symptoms of elderly Mongolians at high altitude. A total of 1816 participants were tested and 50.1% were symptomatic. A statistically significant correlation between dry eye symptoms and signs was present.

The Beijing eye study (Jie *et al*, 2009) was conducted in 2001 and consisted of 4439 participants. A random sample of 1957 of the participants was used to assess dry eye symptoms. The subjective symptoms of dry eye were positive in 21% of the participants. A population based study of dry eye symptoms in Indonesia yielded a prevalence of 27.5% (Lee *et al*, 2002). In contrast to other studies, dry eye symptoms were more prevalent in males. Brewitt and Sistani (2001) have stated that one in four patients consulting an ophthalmologist in Germany complains of the symptoms of dry eye.

A hospital-based population in India was studied for dry eye and a prevalence of 18.4% was found. Dry eye was higher in females, more common in rural residents and highest among farmers/labourers (Sahai and Malik, 2005). Dry eye disease leading to a clinical diagnosis or severe symptoms was prevalent in Japanese private high school students (Uchino *et al*, 2008). It was found that the prevalence of dry eye (24.4%) was higher in female high school students

compared to males (21%). Dry eye disease was also more prevalent in female (48%) video display terminal users compared to the 26.9% reported in males (Uchino *et al*, 2009).

The American Optometric Association has stated that dry eye has been recognized as a common and often chronic problem (Eldridge, 2012). A survey was conducted and the results showed that nearly half (48%) of all adults in the United States experience one or more dry eye symptoms regularly, with 52% being women. In the age group of 55 and over, 30% of men and 19% of women reported experiencing dry eye symptoms for more than ten years. Bukhari *et al* (2009) found the prevalence of dry eye in a normal population sample of 251 Saudi Arabian subjects in Jeddah to be 93.2% based on a dry eye symptoms risk factors questionnaire and diagnostic tests (TBUT, Fluorescein corneal staining and Schirmer's test).

2.3.5. Factors influencing dry eye syndrome

Many factors are considered to influence dry eye symptoms and disease, some of which are, the diurnal variation in tear volume, contact lens wear, age, systemic diseases, gender, diet, water intake and environmental factors such as air conditioners. These are detailed in Table 2.1 and some will be discussed in further detail.

Table 2.1. Some risk factors for dry eye

Level of Evidence		
Mostly consistent*	**Suggestive†**	**Unclear‡**
• Older age	• Asian ethnicity	• Cigarette smoking
• Female gender	• Medications	• Hispanic ethnicity
• Postmenopausal estrogen therapy	Tricyclic antidepressants	• Medications
• Low dietary intake of omega-3 fatty acids	Selective serotonin reuptake inhibitors	Anticholinergics
• Medications	Diuretics	Anxiolytics
Antihistamines	Beta-blockers	Antipsychotics
• Connective tissue disease	• Diabetes mellitus	• Alcohol use
• LASIK and refractive excimer laser surgery	• HIV/HTLV1 infection	• Menopause
• Radiation therapy	• Systemic chemotherapy	• Botulinum toxin injection
• Hematopoietic stem cell transplantation	• Large-incision ECCE and penetrating keratoplasty	• Acne
• Vitamin A deficiency	• Isotretinoin	• Gout
• Hepatitis C infection	• Low-humidity environments	• Oral contraceptives
• Androgen deficiency	• Sarcoidosis	• Pregnancy
	• Ovarian dysfunction	

ECCE = extracapsular cataract extraction; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus

* Mostly consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data.

† Suggestive evidence implies the existence of either: 1) inconclusive information from peer-reviewed publication or 2) inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal.

‡ Unclear evidence implies either directly conflicting information in peer-reviewed publications or inconclusive information but with some basis for a biological rationale.

Reproduced with permission from Smith JA (Chair). Epidemiology Subcommittee of the International Dry Eye Workshop. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007). Ocul Surf 2007;5:99.

2.3.5.1. Tear volume

Evaporation is lowest on waking and within two hours it rises to a constant value for the rest of the day. An explanation for this pattern may be low tear production during sleep and the presence of a thick tear film lipid layer on waking (Tomlinson and Cedarstaff, 1992). A diurnal reduction in tear volume may be one of the reasons responsible for the common increase in 'end of day' ocular dryness symptoms reported by many patients in clinical practice (Srinivasen *et al*, 2007).

2.3.5.2. Contact lens wear and dry eye

Dry eye symptoms during contact lens wear could lead to a reduction in wearing time or discontinuation of use (Nichols *et al*, 2004). Uchino *et al* (2009) reported

that contact lens wear was associated with a higher prevalence of severe dry eye. Corneal staining in contact lens wearers continues to be a frequent but sometimes not well understood phenomenon. Contact lens factors (water content, material, wearing time, deposition) seem to be more associated with corneal staining instead of contact lens care solutions or other ocular surface and tear film, demographic or medical factors (Nichols and Sinnott, 2011).

2.3.5.3. Dry eye in systemic diseases

Dry eye has been associated with systemic diseases such as diabetes. Dry eye and the use of artificial tears in diabetics over the age of 50 were significantly higher when compared with non-diabetics (Kaiserman *et al*, 2005). Idu and Oghre (2010) also found a greater prevalence of dry eye signs and symptoms in non-insulin dependent diabetes mellitus (NIDDM) patients. It was postulated that parasympathetic innervation alteration in NIDDM could lead to reduced nervous supply in the lacrimal glands and thus decrease aqueous tear production (Idu and Oghre, 2010). Reflex tear secretion that is congruent with corneal irritation is highly dependent on the sensitivity of the cornea. Diabetic patients generally present with reduced sensitivity and thus reflex tear secretion could be decreased. Diabetics also suffer from squamous cell metaplasia and goblet cell loss. Goblet cells of the conjunctiva secrete the mucin portion of tears which contribute to tear film stability therefore it can be concluded that goblet cell loss in diabetics affects the tear film stability.

2.3.5.4. Gender and dry eye

Females have generally been recognized as having greater dry eye symptoms, but Lee *et al* (2002) reported the prevalence of dry eye was 1.4 times higher in males than females. The findings of Sahai and Malik (2005) contradicted this notion as dry eye prevalence was higher in females than males in their study. Uchino *et al* (2009) reported results that concurred with Sahai and Malik (2005). A higher prevalence was reported in female high school students (24.4%) compared to 21% in males. Also among video display terminal users Uchino *et*

al (2009), reported dry eye disease was more prevalent in females (48%) as compared to males (26.9%). Ozdemir and Temizdemir (2010) found no significant difference in dry eye symptoms between the sexes. Patel and Farrell (1989) also reported no significant differences in tear film stability between males and females.

2.3.5.5. Dry eye in urban versus rural areas

Dry eye syndrome was more commonly reported in urban areas than in the rural region, possibly due to higher levels of air pollution in the city (Jie *et al*, 2009). Moen *et al* (2011) studied the tearfilms of residents and workers in an area (in Norway) after an explosive accident in an attempt to see if air pollution affects tear film stability. The area was polluted for two years until the authorities could remove all the waste. The tear films of residents that were not exposed to the area were also evaluated. The authors found that air pollution does indeed affect tear film stability and overall ocular health and comfort.

However, in India dry eye was marginally more prevalent in rural residents compared to urban residents (Sahai and Malik, 2005). According to the authors, a rationalization for this could be that the rural residents in India are mostly labourers/farm workers who work outdoors and in direct sunlight for most of the day.

2.3.5.6. Refractive error

In the Beijing eye study, undercorrection of a refractive error was a significant factor associated with dry eye symptoms (Jie *et al*, 2009). The study was a population based study in China which was carried out in four communities and included four thousand four hundred and thirty nine participants. Sahai and Malik (2005) found that there was a higher prevalence of dry eye in those people with uncorrected refractive errors (25.3%) as compared to those with corrected refractive errors (15.6%) in their study on the prevalence and attributable risk factors in a hospital-based population in India. Nichols *et al* (2005) also reported

that the prevalence of dry eye was higher in those with refractive error as compared to emmetropes. The study had eight hundred and ninety three participants and included contact lens wearers, spectacle wearers and emmetropes. Dry eye was reported most by contact lens wearers (52.3%) and spectacle wearers (23.9%) as compared to emmetropes (7.1%).

2.3.5.7. Age versus dry eye

The prevalence of dry eye increases with age (Lu *et al*, 2008), increased sunlight and ambient temperature (Lee *et al*, 2002). Ozdemir and Temizdemir (2010) also investigated dry eye with age and found that the production rate of tears decreases as age increased. A significant linear reduction in precorneal tear film stability occurs between the ages of 8 and 80 years (Patel and Farrell, 1989). The findings of Wang *et al* (2005) were in agreement with Patel and Farrell (1989) as they also discussed that results of the Schirmer test showed that the rate of tear secretion decreased with advancing age. Fluorophotometry also revealed that the tear turnover rate decreased with age.

2.3.5.7. Dry eye in psychiatric disorders

Some authors have commented that there is a significant link between depression or anxiety disorders and dry eye disease. Patients with psychiatric disorders may have dry eye symptoms including dryness, burning and itching. Patients with dry eye disease may have a greater likelihood of having depression and psychosis than those without dry eye disease (Wang *et al*, 2010). Patients who are being treated with anti-depressants for depression, OCD (obsessive compulsive disorder) and anxiety are seen frequently in practice and dry eye disease has a significant impact on the quality of life of these patients (Eldridge, 2012).

Wen *et al* (2012) stated that the use of antidepressants should be considered in the differential diagnosis of dry eye disease. They studied dry eye disease in patients with depressive and anxiety disorders in Shanghai. Of the 472 included

in the study, 37% were diagnosed with depression, 36% had generalized anxiety disorder, 13% had both depression and generalized anxiety disorder, 12% had obsessive compulsive disorder and 2% had a panic disorder. Dry eye disease was present in 60% of the study sample. Patients with dry eye disease were found to be older, had a longer duration of the psychiatric disease and were on anti-anxiety or anti-depressant medication.

Galor *et al* (2011) are in agreement with these findings. The prevalence and associated risk factors of dry eye disease in a veteran population in the United States was studied. The use of systemic medication including anti-depressant medication, anti-anxiety medication and anti-benign prostatic hyperplasia medications were all associated with an increased risk of dry eye syndrome. Sixteen thousand eight hundred and sixty two patients had dry eye. Galor *et al* (2011) stated that several medical conditions were found to increase the risk of dry eye disease such as those for post-traumatic stress disorder, depression, thyroid disease and sleep apnea.

In an elderly population in Korea, 657 subjects were evaluated for dry eye disease and depression (Kim *et al*, 2011). Depression was associated with dry eye disease symptoms in subjects with normal or mildly reduced tear production. Kim and colleagues are of the opinion that the discordance between symptoms and signs of dry eye disease in certain patients may be due to depression.

2.3.5.8. Migraine headaches

A link between headaches/migraines and dry eye have been suspected by researchers. The prevalence of headache in Sjogrens syndrome was discussed by Gokcay *et al* (2008). Migraine headaches and dry eye syndrome are both life-disabling diseases (Koktekir *et al*, 2012). Koktekir and colleagues had 66 participants in their study which consisted of a control group and those diagnosed with migraines. These migraine sufferers were further divided into those with an aura, without an aura and basilar migraine. TBUT and Schirmer 2

values scores were significantly reduced in the group of participants suffering from migraines. An increased frequency of dry eye disease was found to occur in patients with migraine. This suggests that migraine headaches are related to dry eye disease.

2.4. DIAGNOSIS OF DRY EYE

The diagnosis of dry eye requires a battery of interviews and tests to be performed ie. Dry eye questionnaires and clinical testing. These include symptom assessment, contact lens and medical history, slit-lamp biomicroscopic evaluation of the eyelids, evaluation of the meibomian glands, assessment of tear film quality, tear meniscus height, assessment of blink quality, fluorescein tear break-up time (TBUT), fluorescein and rose Bengal staining of the cornea and conjunctiva, phenol red thread test and the Schirmer test (Nichols *et al*, 2004).

2.4.1. Screening for dry eye

Questionnaires have been an integral tool in the dry eye diagnosis for many years, many of which have also been used as screening tools. Questionnaires based on symptoms have been used to screen populations for undiagnosed cases as well as prevalence. Dry eye symptom questionnaires are also useful tools in drug trials and in assessing the response to dry eye therapy. Simpson *et al* (2008) assessed dry eye symptoms using four questionnaires and found that the results were highly correlated. Some commonly used questionnaires include: The McMonnies questionnaire, the Dry Eye Syndrome questionnaire (DES), the Contact Lens Dry Eye Questionnaire (CLDEQ), the Ocular Surface Disease Index (OSDI) and the Schaumberg questionnaire. Although the McMonnies questionnaire was the only one used in this study to screen for dry eye at the start, the others will be reviewed to highlight their various strengths.

2.1.1.1. The McMonnies Questionnaire

The McMonnies dry eye questionnaire is considered a 'gold standard' for examining dry eye symptoms in disease conditions which is why it was selected for use in the research (Erickson *et al*, 2002). It is among the earliest and most widely used screening instruments for dry eye syndromes with a sensitivity ranging between 87% and 98% and a specificity of between 87% and 97% (Nichols *et al*, 2004b). The questionnaire helps detect the presence of dry eye disease and those at risk of developing dry eye disease. It has 14 questions focusing on risk factors for dry eye. Some of the questions include age, gender, contact lens history, dry eye symptoms, previous dry eye treatments, secondary symptoms (associated with environmental stimuli), medical conditions associated with dry eye syndrome, dryness of mucous membranes and medication use (Nichols *et al*, 2004b).

There has been uncertainty about whether the McMonnies questionnaire can be used to grade disease severity. Gothwal *et al* (2010) evaluated the McMonnies questionnaire and its use and found that it is an acceptable screening tool but that it does not grade disease severity. It has been found to perform better in predicting contact lens induced dry eye than the ocular comfort index (Michel *et al*, 2009).

Nichols *et al* (2004b) found that the McMonnies questionnaire demonstrates fair reliability and validity as a patient-reported instrument for use in patient care and clinical studies of patients with dry eye disease. Erickson *et al* (2002) share these sentiments as they have stated that the McMonnies dry eye questionnaire is a statistically reliable instrument and practitioners can feel confident that the questionnaire provides a consistent and repeatable measurement.

2.4.1.2. The Dry Eye Syndrome (DES) Questionnaire

The DES questionnaire was developed to assess ocular surface symptoms in mild to moderate dry eye. The questionnaire includes categorical scales to

measure the prevalence, frequency, diurnal intensity and intrusiveness of common ocular surface symptoms like discomfort, dryness, visual changes, soreness and irritation, grittiness and scratchiness, burning and stinging, foreign body sensation, light sensitivity and itching. Questions on age, gender, affected daily activities, computer use, use of systemic and ocular medications, allergies, self-assessment and previous diagnosis of dry eye are also included (Begley *et al*, 2002). The authors stated that the measurement of symptom frequency and diurnal intensity by the dry eye syndrome questionnaire provides a sensitive tool that may be useful in clinical trials for dry eye.

2.4.1.3. The Contact Lens Dry Eye Questionnaire

The CLDEQ is a self-administered survey developed to examine the distribution of dry eye symptoms among contact lens wearers. The questionnaire focuses on ocular surface symptoms rather than presumed risk factors for dry eye syndrome. It consists of 36 questions specific to symptoms of contact lens related dry eye. There are nine symptom subscales: discomfort, dryness, visual changes, soreness and irritation, grittiness and scratchiness, foreign body sensation, burning, photophobia, and itching. Each subscale probes the frequency of the symptom, which is followed by three questions concerning the intensity of the symptom at different times of the day (Nichols *et al*, 2002). The strength of this questionnaire is that it is accurate and better able to discriminate contact lens related dry eye than the McMonnies questionnaire (Nichols *et al*, 2002). However, as the study did not focus on people wearing contact lenses, it was not used for this research.

2.4.1.4. Ocular Surface Disease Index (OSDI)

The OSDI is a 12 item screening questionnaire for dry eye. Three subscales sequentially probe for symptoms of ocular irritation, the impact of vision-related functioning and environmental triggers of dry eye syndrome. The questionnaire is criticized because the step in difficulty between each category is not constant and the difficulty of all questions is not necessarily comparable (Michel *et al*,

2009). In this questionnaire there has been an attempt to segregate subjective symptoms based on the severity of dry eye (Narayanan *et al*, 2005). Pult *et al* (2009) have found that the ocular surface disease index can assist in the prediction of dry eye. The strength of this questionnaire is that it probes for three different aspects.

2.4.1.5. Schaumberg Questionnaire

The Schaumberg questionnaire was developed and validated by Schaumberg in 2001. Questions that are probed in the questionnaire are: have you ever been diagnosed by a clinician as having dry eye syndrome? ; How often do your eyes feel dry (not wet enough) and how often do your eyes feel irritated? Uchino *et al* (2009) used the Schaumberg questionnaire successfully in an epidemiologic study in Japan to identify dry eye disease. Gulati *et al* (2006) discussed that the questionnaire had a sensitivity of 77% and specificity of 83%.

2.5. CLINICAL DIAGNOSIS OF DRY EYE

A number of tests can be used to diagnose dry eye, but the two commonly used tear tests are the Schirmer test and Tear break-up time which were used in this study.

2.5.1. The Schirmer tear test

The clinical diagnosis of dry eye is confirmed by a suitable test of tear production. The technique commonly used is the Schirmer test, being considered one of the most useful in detecting the severest, most tear deficient dry eye (Kallarackal *et al*, 2002). It was first described by Schirmer in 1903 and is still the method most commonly used clinically to evaluate aqueous tear production (Schirmer, 1903; Kashkouli *et al*, 2010). The Schirmer procedure was modified by De Roetth in 1953 when he changed the paper to Whatman standard No.41 filter paper. In 1961 standardized Schirmer test strips were introduced for the first time by Halberg and Behrens (Halberg and Behrens, 1961). Shapiro and Merin (1979)

used a 5cm litmus paper strip to determine the values of Schirmer 1 in a normal population.

Traditionally, the procedure for the Schirmer test involves placing a Schirmer test strip hooked onto the inferior tarsus while the patient blinks normally. After five minutes, the strip is removed and the wet length measured with a millimeter rule. The test can be performed without the administration of a topical anaesthetic (Schirmer 1), where both the basal and reflex secretion of the tears is measured. Alternatively, Schirmer 2 can be performed by the instillation of a local anaesthetic before insertion of the Schirmer strip and thus only the basal secretion rate will be tested. A wet portion of the strip less than 5mm is considered abnormally low (Tsubota, 1998).

Several attempts have been made by researchers to reduce the testing time for the Schirmer test. Kashkouli *et al* (2010) investigated reducing the test time to one minute instead of the traditionally used five minutes for Schirmer 1. A significant correlation between the one minute and five minute test time was found. The researchers stated that this method was advantageous as it was both faster and more comfortable for the patient. Karampatakis *et al* (2010) discussed similar results when investigating reducing the test time to two minutes instead of the traditionally used five minutes. Furthermore, it was stated that all the study participants preferred the shorter duration citing the unpleasant test procedure as their reason. Bawazeer and Hodge (2003) investigated performing a one-minute Schirmer 2 test. An acceptable correlation between the results for the five minute and one minute test was discussed. While the study recommended that reducing the test time is clinically acceptable, the five minute testing time is still used.

There has been discussion regarding the location of the Schirmer strip on the lid margin, but it has been established that there was no significant differences in relation to whether the paper is placed at the medial or lateral site of the lower lid

margin (Jones, 1972; Loran *et al*, 1987). Jordan and Baum (1980) stated that lid margin and eyelash stimulation was found to increase the tear turnover rate greater than 300% despite topical anaesthesia in healthy study participants. There is speculation that this finding affects the Schirmer value since the Schirmer strip is placed on the lid margin over a portion of the eyelashes. The eyelid margin should be blotted to remove any tears before placing the Schirmer strip. This prevents a false high value due to tears already being present on the eyelid.

There has been much discussion whether a closed or open eye state should be maintained during the test. Nelson (1982) and Pandher *et al* (1985) did not place any emphasis on this issue. Other authors (Doughman 1973; Shapiro and Merin 1979; Clinch *et al* 1983) suggest that the patient should continue to blink normally throughout the procedure. Also, Loran *et al* (1987) did not find any differences in the test results when the eyes were open or closed. However, Serruya *et al* (2009) found a statistical difference in the results when the eye was kept open and when it was closed. In agreement with these authors, Serin *et al* (2007) suggested that conducting the Schirmers test with closed eyes produces less variable results and more repeatability. Kashkouli *et al* (2010) are in agreement that the closed eye state is advantageous in maintaining more stable and uniform test conditions as it eliminates the influence of external factors such as temperature, evaporation and humidity.

Several disadvantages of the Schirmer test have been reported. These include low reproducibility, sensitivity and specificity, frequent discomfort, difficulty of performing the test in children, potential injury to the conjunctiva and cornea, lack of a definite site of paper placement in the conjunctival sac, uneven absorption of tears by the paper strip and lack of control over reflex lacrimation (Cho and Yap, 1993a). Oduntan and Oni (1995) reported that the Schirmer test is not repeatable and is unreliable. They further stated that the Schirmer test may be reliable in patients with dry eye syndrome but not in patients with normal or near

normal tear production, therefore when using the Schirmer test for clinical diagnosis of dry eye, caution should be exercised.

Yokoi *et al* (2000) investigated tear meniscus and the Schirmer test. It has been discussed that the capillarity of the Schirmer strip with its rigid mesh-like structure is stable and the absorptive capacity predictable. The baseline meniscus curvature influences the wetting length. As meniscus volume decreases in dry eye, the suction effect of the meniscus increasingly opposes entry of fluid onto the Schirmer strip. It was concluded that this may explain why the Schirmer tear test is useful in detecting the severest, most tear deficient dry eye.

Age and gender have been reported to influence Schirmer test values. Ozdemir and Temizdemir (2010) reported decreasing Schirmer test results with increasing age in a Turkish population. A possible reason cited for this is the decrease in tear production with increasing age. The reasons behind the decrease in tear production could be the reduction in sex hormone levels after menopause in women and the decrease in androgen levels in men. Ozdemir and Temizdemir (2010) found no statistical difference in the Schirmer test between the genders when investigating a normal Turkish population. Karampatakis *et al* (2010); Shapiro and Merin (1979) and Fermon *et al* (2010) found no significant difference in the results between genders.

There have been several studies on tear evaluation using the Schirmer test. The authors and dates, objectives of the previous studies; number of subjects and genders are shown in Table 2.2.

Table 2.2. Previous studies on Schirmer tear test and their findings in chronological order

Authors and date	Objective of the study	Subjects, number and gender	Range, Mean / ± (mm)	Comments
Shapiro and Merin (1979)	Standardise Schirmer and TBUT, compare each to the other and determine if influenced by sex, climate and hereditary and environmental influences.	440 Israelis	33.1 ± 33.2 (Lower limit 5mm in 5 minutes)	
Maugdil *et al* (1989)	Designed to estimate Schirmer test and BUT in an Indian population and living conditions.	110 (62 male; 48 female) Indians	All: 27.9 ± 7.89 Male: 25.21 ± 5.11 Female: 33.27 ± 10.50	
Oduntan and Oni (1995)	Mean and repeatability of the value obtained by the Schirmer test in a normal Arab population.	23 Saudi Arabian males	10.6±6.3	
Serin *et al* (2007)	Compare the repeatability of the Schirmer test administered with the eyes open with the repeatability of Schirmer test administered with the eyes closed.	14 (3 male; 11 female) Turkish	Closed Eyes (Right eyes): 21.12±7.36 Closed Eyes (Left eyes): 22.57±8.49 Open Eyes (Right eyes): 23.12±7.25 Open Eyes (Left eyes): 25.17±7.53	
Serruya *et al* (2009)	To analyse the difference between measurements of Schirmer test 1 and 2 with open and closed eyes.	30 (12 male; 18 female) Brazilians	Closed eyes: 10.30±11.55 Open eyes: 18.85±17.88	
Fermon *et al* (2010)	To standardize the Schirmer test 1 and TBUT in a group of healthy people from Mexico.	747 (381 male; 366 female) Mexicans	All: 8.64±1.76 Male: 8.71 Female: 8.59	
Ozdemir and Temizdemir (2010)	Investigate age and gender related changes in the results of Schirmer and TBUT in a normal population.	140 (70 male; 70 female) Turkish	Decade 2: male 8-28 ; female 9-35 Decade 3: male 10-34; female 7-33 Decade 4: male 9-30; female 6-32 Decade 5: male 4-35; female 6-24 Decade 6: male 4-22; female 4-24	Participants were placed in age brackets according to decade.

			Decade 7: male 3-20; female 5-24 Decade 8: male 5-20; female 4-21	
Karampatakis *et al* (2010)	Compare the 2 and 5 minute Schirmer test in healthy individuals.	162 (81 male; 81 female) Greeks	2 min (Right eyes): 12.71±2.47 2 min (Left eyes): 12.62±2.09 5 min (Right eyes): 16.74±3.59 5 min (Left eyes): 16.831±3.38	
Kashkouli *et al* (2010)	Assess the results of 1 minute and 5 minute Schirmer test when eyes are open and closed in normal subjects and patients with dry eye disease.	34 (15 male; 19 female) Iranians	Closed eyes (1 minute): 9.88±8.2 Closed eyes (5 minutes): 26.76±16.07 Open eyes (1 minute): 13.44±7.8 Open eyes (5 minutes): 32.73±14.9	

2.5.2. Tear Break-up time

The Tear break-up time (TBUT) is used mainly to assess the stability of tears (Kallarackal *et al*, 2002). Tear stability describes the effectiveness of the cohesive forces present between the three layers of the tear film. When one or more of the layers break up, the tear film will be unstable. TBUT is the time interval between a complete blink and the first appearance of a dry spot in the precorneal tear film after the installation of fluorescein viewed with a cobalt blue filter (Cho and Brown, 1993; Savini *et al*, 2008). Traditionally, three readings are taken and the results averaged. This technique has gained world-wide popularity as it is simple and convenient to perform (Cho and Brown, 1993). There have, however, been some reservations from researchers. Mengher *et al* (1985) discussed that the instillation of fluorescein reduced the tear film stability.

Although researchers have highlighted some shortcomings of TBUT, it is widely used for both clinical and research purposes but has been criticized of inaccuracy and non-reproducibility (Vanley *et al*, 1977). The large ranges of normal values, the lack of a standardized procedure for the application of fluorescein to the tear film and the poor association with subjective symptoms have reinforced these views (Nichols *et al*, 2004; Lin *et al*, 2005). Even though there is a wide range of values amongst individuals, there is a general agreement that a TBUT shorter than 10 seconds reflects tear film instability and a TBUT shorter than 5 seconds is a marker indicative of dry eye.

Shimazaki (1995) and Moore *et al* (2009) have suggested that three measurements should be taken in succession for each eye and an average value of ≤10 seconds and 7 seconds can be taken as an indication of dry eye. Lemp and Hamill (1973) took 5 measurements and suggested that 10 sec be used as the lower limit for normal values. Norn (1969) suggested that 30 sec be used as the normal value.

These results that were considered normal have been questioned by many researchers. Maugdil *et al* (1989) reported a mean TBUT in Indians of 13.8 ± 4.79 sec indicating that the range of values was 8-31 sec. Chopra *et al* (1985) also reported TBUT in Indians, the overall mean being 7.81 ± 6.63 sec and the range 1.67-40.33 sec. The mean TBUT in males was 8.90 sec and 6.98 sec in females respectively. Sukul *et al* (1983) discussed results where males had a mean of 11.42 sec and a range of 3.5-17 sec. Females had a range of 5.5-14 sec with a mean of 9.42 sec in the right eye and 8.93 sec in the left eye.

Briggs (1998) reported a mean TBUT in Saudi Arabian subjects of 18 ± 7 sec having a range of 5-39 sec. Al-Abdulmunem (1997) reported higher values in Saudi males, the mean being 29.83 ± 11.98 sec. Amaechi and Osunwoke (2004) found a TBUT of 15.2 ± 3.1 sec for the young adult population of Nigeria. Shapiro and Merin (1979) noted normal values for TBUT as 13.2 ± 8.9 sec with a lower limit value of 10 sec.

Fermon *et al* (2010) reported that the average TBUT in Mexicans was 7.6 sec, the range being 6.19-9.01 sec. The mean value for females was 7.59 sec and 7.63 sec in males. Cho and Brown (1993) reported a mean TBUT of 8 sec in Hong Kong Chinese and a mean of 14.9 sec for Caucasians living in Hong Kong. Cho and Yap (1993b) reported similar results, with a mean TBUT of 7.8 ± 2.4 sec in Hong Kong Chinese and a mode of 7 sec. Cho and Yap (1993b) also researched TBUT in Singapore Chinese and reported a mean TBUT of 6.5 ± 4.0 sec and a mode of 5 sec. Lee and Kee (1988) reported a mean TBUT of 13.38 ± 5.31 sec and Lemp et al (1971) stated that the normal TBUT range is between 15-25 sec. Lemp and Hamill (1973) stated values between 15-34 sec to be considered as normal and 10 seconds to be used as the lower limit for normal values.

Cho *et al* (1998) studied the effects of successive measurements on TBUT values, the effect of fluorescein re-application on TBUT values and the effect of increasing palpebral aperture size on TBUT values. A significant difference between the values of the successive measurements was found (TBUT1: 3.2 sec, TBUT2: 3.8 sec and TBUT3: 4.5 sec). The re-application of fluorescein did not yield a significant difference in the values. Increasing the palpebral aperture size showed an increasing trend in TBUT values (3.6 sec with a wide palpebral aperture as compared to 3 sec with the normal palpebral aperture).

Tear Break-Up Time has generally been performed using fluorescein as the dye. Norn (1969) used three different dye solutions: 0.125% fluorescein with sodium chloride (without preservative) pH=7.26; a Fluorescein-Novesin mixture (pH=6.65-6.37) containing 0.125% fluorescein, 0.3% novesin and 0.0025% phenylmercuric nitrate as preservative; and a fluorescein-rose Bengal mixture (pH=7.70) containing 50 mg fluorescein sodium, 50 mg rose Bengal, 45 mg sodium chloride, distilled water to 5g with 0.001% phenyl mercuric nitrate added. 0.01ml of the solution was instilled into the inferior conjunctival fornix.

Various methods of staining the tearfilm have been discussed in the literature. Instilling a sodium fluorescein solution into the inferior conjunctival fornix from a needle mounted tube; using a slightly moistened fluorescein strip; a fluorescein solution prepared with saline and sodium hydroxide delivered with catheter and syringe; and sodium fluorescein instilled with a laboratory pipette (Cho and Brown, 1993). Lee and Kee (1988) used a glass rod dipped in 2% fluorescein solution and applied this on the inferior temporal bulbar conjunctiva.

The method of observation of the fluorescein has been debated. A 1-2mm wide beam to scan the cornea has been the most popular method employed. Some researchers preferred to use an additional yellow barrier filter. A diffuse beam has also been used. A horizontal slit instead of a vertical slit may also be

employed. Lemp *et al* (1971) held the patients lids apart but did not exert any pressure on the globe when observing the TBUT.

Al-Abdulmunem (1999) investigated the relation between TBUT and spontaneous blink rate. A strong and significant correlation was found. It was stated that blink rate could be easily affected by visual task difficulty, mental activity, attention and corneal sensitivity but it cannot be denied that there exists a relationship between TBUT and blink rate.

Norn (1969) discussed that there were no differences in the TBUT from 10-70 years but after age 70, there seemed to be a reduction in tear film stability. Cho and Yap (1993) found that TBUT decreases with age in both Hong-Kong Chinese and Singapore-Chinese. Ozdemir and Temizdemir (2010) found similar results in a normal population in Turkey. Briggs (1998) also reported that TBUT values decreased with increasing age in a normal Saudi population. However, Chopra *et al* (1985) found no significant difference in TBUT values with increasing age in an Indian population.

Norn (1969) reported a decrease in the TBUT of females when compared to males. Sukul *et al* (1983) discussed a significant difference between the sexes when investigating TBUT in a normal Indian population. Cho and Yap (1993) reported a difference between the sexes in Singapore-Chinese but no difference between the sexes in Hong-Kong Chinese. Kee and Lee (1988) did not find a difference between the sexes. Briggs (1998) did not find a difference between males and females in a normal Saudi population. Similarly, Chopra *et al* (1985) did not report a difference in the results between the genders in an Indian population nor did Ozdemir and Temizdemir (2010) find a difference in gender when investigating a Turkish population.

Genis *et al* (2011) conducted an evaluation of the knowledge and use of tear film evaluation tests by Spanish practitioners. Their results yielded that the TBUT was the test of first preference of optometrists and ophthalmologists. Danjo (1997) reported that the diagnostic usefulness of Schirmers test was inferior to that of TBUT. It was further concluded by Danjo (1997) that in the investigation of dry eye, both Schirmer's test and TBUT should be performed to detect tear abnormalities.

There have been several studies on tear evaluation using the Tear Break-up time test. The authors and dates, objectives of the previous studies; number of subjects and genders are shown in Table 2.3.

Table 2.3. Previous studies and their findings on Tear Break-up Time in chronological order

Authors and date	Objective of the study	Subjects, number and gender	Range, Mean / ± (mm)	Comments
Norn (1969)	Studying how long the fluorescein-stained precorneal film is intact from the termination of blinking to the occurrence of holes in the film (wetting time).	64 (30 male;34 female)	30 sec	
Lemp *et al* (1971)	Determine whether or not there was any correlation between breakup time of the precorneal tearfilm, aqueous tear production and conjunctival mucous production.	9	15-25 sec	
Lemp and Hamill (1973)	Designed to furnish quantitative data on factors affecting the measurement of BUT, its reproducibility and its relationship to age, sex, corneal sensation and palpebral fissure width. By furnishing in normal eyes, it's easier to define a methodology for performing an estimate of BUT and to provide a series of values for normal eyes, which will permit interpretation of this test.	50 (17 male; 33 female)	15-34 sec. Lower limit 10 sec	
Shapiro and Merin (1979)	Standardise Schirmer and TBUT, compare each to the other and determine if influenced by sex, climate and hereditary and environmental influences.	440 Israelis	13.2 ± 8.9 sec. Lower limit 10 sec	
Sukul *et al* (1983)	Study tear film break up time in normal Indian subjects so that it may be of future help in the study of dry eye syndrome.	101 (65 male; 36 female) Indians	Male (Right eyes): 11.42 (3.5-17) Male (Left eyes): 8.87 (3.55-19) Female (Right eyes): 9.42 (5.5-14) Female (Left eyes): 8.93 (5.5-14)	
Chopra *et al* (1985)	Designed to find out the average tear film break up time in normal Indian subjects and its relationship to age, sex, palpebral fissure width and blink rate. The study was also aimed at determining the effect, if any, of contact lenses on tear film break up time.	100 Indians	All: 7.81±6.63 Male: 8.90 Female: 6.98	
Lee and Kee (1988)	Investigate the significance and interpretation standard by analyzing the distribution and reproducibility of the break up time in normal and dry eye patients.	30 Koreans (15 male;15 female)	13.38 ± 5.31	
Maugdil *et al* (1989)	Designed to estimate break up time and Schirmer test in the Indian population and living conditions.	110 (62 male; 48 female) Indians	13.8±4.79	
Cho and Yap (1993)	Investigate the effect of age and gender on the TBUT values of two groups of Chinese, Hong Kong Chinese and Singapore Chinese using the FBM (full beam method) of observation.	92 Hong Kong Chinese; 76 Singapore Chinese	H-K Chinese: 7.8±2.4 Singapore Chinese: 6.5±4	

Cho and Brown (1993)	Summarise the differences and conclusions of various investigators.	17 Caucasians. 68 Hong Kong Chinese (47 male; 21 female)	Hong Kong Chinese: 8 Caucasians: 14.9	Two observation methods were used: Scanning or full beam
Cho and Yap (1995)		21 Hong Kong Chinese	4	
Al Abdulmunem (1997)	Designed to establish normal values of BUT for normal male subjects living in Saudi Arabia.	143 Saudi Arabian males	29.83±11.98	
Briggs (1998)	Establish normal TBUT values in a comprehensive Saudi population sample and to determine the effect of age and gender within the sample.	220 (140 male; 80 female) Saudi Arabians	All: 18±7	
Cho *et al* (1998)	1. There is any difference in the TBUT values made in succession (each TBUT value being the average of two closest of three TBUT measurements); 2. Re-application of fluorescein affect TBUT values; 3. Opening the eyes as wide as possible during TBUT measurements (to increase palpebral aperture size) affects the TBUT values.	45 (27 male; 18 female)	TBUT 1: 3.2 TBUT 2: 3.8 TBUT 3: 4.5	3 successive readings of TBUT taken.
Abelson (2000)		100 Americans	7.1	5µl fluorescein inserted with a micropipette
Amaechi and Osunwoke (2004)	Comparison of NIBUT and TBUT in the Nigerian population, The aim of the study is to establish normal NIBUT and TBUT values.	45 Nigerians	15.2±3.1	
Ozdemir and Temizdemir (2010)	Investigate age and gender related changes in the results of Schirmer and TBUT in a normal population.	140 (70 male;70 female) Turkish	Decade 2: male 36-52 sec; female 25-49 Decade 3: male 26-50; female 20-46 Decade 4: male 17-40; female 28-42 Decade 5: male 14-33; female 17-38 Decade 6: male 11-28; female 12-38 Decade 7: male 11-29; female 11-26 Decade 8: male 9-18; female 11-23	Participants were placed in age brackets according to decade.
Fermon *et al* (2010)	To standardize the Schirmer test 1 and TBUT in a group of healthy people from Mexico.	747 (381 male;366 female) Mexicans	All: 7.60±1.41 Male: 7.63 Female: 7.59	

2.5.3. Other tests of tears

Other tests are the Phenol red thread test, lacrimal equilibration time, Jones test, Tear thinning time, Lipid Layer thickness test and tear meniscus height are also used for tear evaluation. However, the Schirmer test and Tear break-up time test are the most popular tests. The other tests were included to give a background on the different methods that can be employed to evaluate tears.

2.5.3.1. The Phenol red thread test

The Phenol red thread test has been identified as a potential alternative test for tear flow evaluation that utilizes similar test principles as the Schirmer test but instead of a strip it makes use of a cotton thread impregnated with phenol red dye (Caffery and Paugh, 2005). Phenol red is pH sensitive and changes from yellow to red when wetted by tears. The time interval for this test (15 seconds) is shorter when compared to the Schirmer's test. After 15 seconds, the length of the colour change on the thread length of the thread wetted by the tears is measured in millimeters. Wetting lengths should be between 9mm and 20mm. Patients with dry eyes have wetting values of less than 9mm. The Phenol red thread test causes less irritation on the ocular surface than Schirmer tear test (Caffery and Paugh, 2005). Cho and Kwong (1996) recommended that more than one measurement should be taken on different days before using the results for diagnosis or management of the patient.

Tomlinson *et al* (2001) are of the opinion that the Phenol red thread test does not measure tear volume of the eye or residual tears in the lower conjunctiva. They stated that it measures the uptake of a small amount of fluid from the eye and stimulates a low degree of reflex tearing. Further, it was concluded that although the Phenol red thread test is more comfortable for the patient than Schirmer test, it may not be as valid a measurement of reflex tear facility.

Reliability and repeatability of the tests used in dry eye testing is an integral and vital component in dry eye evaluations. Cho and Chan (2003) investigated inter-examiner differences in the measurement of the Phenol red thread test. A significant difference was found between examiners. It was therefore advised that caution be exercised when using the results for diagnosis as the repeatability of the test was borderline.

Patel *et al* (1998) stated that the phenol red thread test can assist in differentiating between aqueous deficient and non-aqueous deficient dry eye. Doughty *et al* (2007) discussed that the phenol red thread test data could be affected if performed with either open or closed eyes. It was advised that practitioners clearly state whether the open or closed eye state was utilized during testing.

Sakamoto *et al* (1993) investigated the Phenol red thread test in the United States and Japan. A significant difference in the values between both countries was found. This emphasizes the need for establishing norms in different countries for all the dry eye tests.

2.5.3.2. Lacrimal Equilibration Time

Lacrimal Equilibration Time (LET) is a method employed in the testing of the precorneal tear film stability. Baseline visual acuity is stressed with the installation of a predetermined ophthalmic preparation (methyl cellulose) and the time taken to recover normal visual acuity is measured. The normal values reported are ≤ five minutes.

2.5.3.3. Jones Test

The Jones test allows one to assess the patency of the lacrimal drainage system from the punctum to the inferior meatus of the nose. The procedure of the test involves the insertion of fluorescein to the inferior cul de sac of one eye. After 3-

5 minutes have elapsed the patient is asked to blow their nose onto tissue paper and the paper is then viewed with a cobalt blue filter. If fluorescein is present, it is indicative of an intact drainage system. An alternative to this method is to wipe along the mucosa of the inferior meatus of the nose with a sterile cotton bud instead of the patient blowing their nose.

2.5.3.4. Some Non-invasive techniques

A number of non-invasive techniques have been developed to evaluate tears and they will each be briefly described to indicate their strengths and the reasons why they were not used in the study. The following nine tests will be described: Tear thinning time, lipid layer thickness, Tear meniscus height, Interferometry, High speed videokeratoscopy, Wavefront sensing, Thermography, Tear Stability Analysis system, Meibometry, Tear Film Osmolarity and Tear film fluorophotometry/ Fluorescein clearance.

a. Tear Thinning Time

Tear thinning time test is a test of tear integrity, and commonly referred to as NIBUT or non-invasive break up time. It is the time interval in seconds between the blink and the first observable distortion of the reflected mire from a keratometer. Some practitioners view this method to investigate the tear film stability as more accurate due to its non-invasive nature. However, Cho and Douthwaite (1995) have reported that NIBUT values seem to be significantly higher than those of TBUT. The limitation of this test is that only a small area of the pre-ocular surface is tested.

b. Lipid layer thickness

The Lipid layer thickness test tests the external lipid layer of the tear film. The lipid layer is viewed with a slit lamp biomicroscope. Deficiencies in this layer could enhance tear evaporation and thus create a risk for dry eye. The test is

limited by the experience of the observer. Yokoi *et al* (1996) have used interferometry to develop a classification of interference patterns for the lipid layer. The classification is very similar to the grading scale used when performing the traditional lipid layer thickness test. Isreb *et al* (2003) studied the correlation between the lipid layer thickness test and TBUT and Schirmer 2. Isreb and colleagues (2003) concluded that the measurement of the lipid layer thickness is a reliable test for the diagnosis of dry eye. The limitation of this test is that it is based on the skill of the examiner.

c. Tear meniscus height

Tear meniscus height/tear prism height is a tear production test used to evaluate the volume of tears by the height of the tear meniscus at the lower lid margin and the surface of the eye. It has been discussed that this may provide insight into the overall tear volume. A normal value for tear meniscus height is 0.22 mm (Edrington and Schornack, 2005). A lower cut off limit for normal would be ≤0.1mm, while ≥0.25mm would indicate reflex tearing and/or sub-optimal drainage (Doughty *et al*, 2002). A variation of this test is to instill fluorescein onto the ocular area and to view the tear meniscus with a cobalt blue filter.

For the study of tear kinetics at the ocular surface, a video-meniscometer was developed. The device comprises of a rotatable projection system with a target composed of a series of black and white stripes. The target is introduced co-axially using a half silvered mirror. The meniscometer performs real-time recording of meniscus behavior and transfers this to a computer where image analysis software is used to calculate the radius of curvature of the meniscus (Yokoi and Komuro, 2004).

Optical coherence tomography (OCT) can also be used to measure tear meniscus dynamics (Wang *et al*, 2006). Optical Coherence Tomography is a

non-invasive method that allows real time tear dynamics to be assessed. Wang *et al* (2008) used OCT to measure both the upper and lower tear menisci. The authors discussed that the relationships between tear meniscus results and clinical tests such as tear break up time and the Schirmer test could provide further information about the tear system for a better understanding. Yuan *et al* (2010) showed that dry eye patients have reduced tear meniscus dynamics during normal blinking and smaller increases of meniscus volume during delayed blinking.

d. Interferometry, High speed videokeratoscopy, Wavefront sensing

Tearfilm thickness can also be measured using interferometry based on wavelength-dependent fringes (WDF). The optical path difference from the reflection at the surface of the tearfilm, and at the interface of tearfilm and cornea, causes an interference wave which indicates the precorneal tearfilm thickness. An interference thin-film thickness measurement device based on wavelength-dependent fringes needs to be used (Hosaka *et al*, 2011).

Szczensa *et al* (2007) described lateral shearing interferometry as being a suitable method of assessing the tearfilm on the cornea. A lateral shearing interferometer (LSI) was used to analyse the interference fringes obtained from the tearfilm using the fast Fourier transform (FFT) technique. This method is based on evaluating the degree of fringe disturbance by calculating the second momentum of Fourier spectra on the interferogram. This test provides an alternative non-invasive method of measuring the precorneal tear volume.

Szczesna *et al* (2011) used three non-invasive techniques to measure tear film surface quality: dynamic-area high speed videokeratoscopy (HSV), wavefront sensing (DWS) and lateral shearing interferometry (LSI). Measurements were performed in both natural blinking conditions and suppressed blinking

conditions. Szczesna and colleagues (2011) reported that these non-invasive techniques can be used for predicting dry eye.

e. Thermography

Thermography is a non-invasive method of measuring the surface temperature of an object. Non-contact measurement, which provides the examiner with a colour-coded image of the temperature of the eye, is usually referred to as ocular thermography (Morgan *et al*, 1996). The cornea is warmest over the limbus and coolest at the center. In dry eyes, the mean ocular surface temperature is higher than for normal eyes. Conjunctival hyperaemia associated with dry eyes could be a reason for the higher temperature. Nakamori *et al* (1997) stated that ocular temperature is higher in dry eye patients because they blink at a higher frequency.

The rate of cooling of the tearfilm over the center is higher in dry eyes than in normal eyes. The larger difference in initial temperature in dry eyes between the eye and the atmosphere was understood to be the main reason for this, but the rate of evaporation of the tearfilm could also be a cause (Craig *et al*, 2000). Kamao and associates (2011) agreed with these findings as their results showed that the temperature at the center of the cornea decreased in dry eye patients. Morgan *et al* (1996) also agreed that dry eyes cool at a greater rate than normal eyes. They have speculated that there could be two reasons for this, the first one being that the ocular surface temperature of patients with dry eyes is greater and follows Newton's law of cooling. (Newton's law of cooling indicates that the rate of heat flow between the two bodies is proportional to the difference in temperature between the two bodies). The second reason could be the greater rate of tear evaporation.

An ocular surface thermographer can be used to measure the surface temperature of the eye. One of the features that allow the ocular surface

thermographer to obtain reliable results with consistency is that readings are taken in a similar manner to that of a standard autorefractor or keratometer with an auto alignment function which enables data to be collected quickly, objectively and noninvasively. Kamao *et al* (2011) have advised that the ocular surface thermographer can be used as a noninvasive method for dry eye screening.

f. Tear Stability Analysis system

Tear film stability can also be analysed using the Tear stability analysis system (TSAS). Images of ring mires are projected onto the cornea for a period of time and these images are captured and analysed. Gumus *et al* (2010) evaluated tear stability in 45 patients using the TSAS system (RT-7000 auto refractor-keratometer). Images of ring mires are projected onto the cornea every second for six seconds and these images were captured and analysed. Gumus *et al* (2010) concluded that the TSAS is a useful non-invasive instrument for evaluating tear stability and classifying dysfunctional tear syndrome.

g. Meibometry

Meibometry is a quantitative method to assess the meibomian lipid reservoir. A laser diode is used to take a lipid sample using a loop of translucent plastic tape. The tape is mounted on an ultrasonagraphy probe holder and applied to the lower lid margin for three seconds. The tape is then air dried for three minutes and the remaining oil on the paper is then read in the laser meibometer (Yokoi and Komuro, 2004).

h. Tear Film Osmolarity

A single biophysical measurement that captures the balance of inputs and outputs from the tear film dynamics is tear osmolarity (Tomlinson *et al*, 2006). An increase in tear osmolarity is a hallmark of dry eye disease. The benefit of

measuring tear osmolarity in the diagnosis of dry eye disease has been undermined by the difficulties of its measurement. The measurement of tear osmolarity has been limited to laboratories. One of the first methods for measurement of tear osmolarity was through observation of the change in the freezing point of tear samples. Ogasawara *et al* (1996) utilized electrical conductivity of tear samples to determine osmolarity.

A new technology called the Tearlab osmolarity system enables the clinician to collect and measure the osmolarity in a 50nL sample (Sullivan *et al*, 2010). Tear sampling is performed in five or six seconds and the calculation of tear osmolarity is performed in less than twenty seconds.

Tomlinson *et al* (1996) found that the accuracy of tear osmolarity was superior to Schirmer, lactoplate and Rose Bengal staining. Lemp *et al* (2011) shared these sentiments as they stated that tear osmolarity is the best single metric both to diagnose and classify dry eye disease. They have recommended that values of more than 308mOsms/L be used as the threshold for the most sensitive detection of dry eye subjects. It has been stated that 296.5±9.8 mOsm/L be used as the normal value for tear osmolarity and 305 mOsm/L as the cut off value for dry eye (Versura *et al,* 2010). Versura and colleagues (2010) have also concluded that tear osmolarity shows good performance in dry eye diagnosis and assists to grade the severity of the dry eye.

i. Tear film fluorophotometry/ Fluorescein clearance

Tear turnover can be determined by the measurement of fluorescein disappearance via fluorophotometry or other fluorescein clearance tests. Tear turnover is the percentage decrease of fluorescein concentration in tears per unit of time (Senchyna and Wax, 2008).

2.6. THE ROLE OF SYMPTOMS IN THE DIAGNOSIS OF DRY EYE

A clinician often relies on symptoms to arrive at a diagnosis and treatment plan without any sign of visible tissue damage. Accurate measurement of symptoms should be included as part of the diagnostic assessment and management of dry eye patients in order to determine their response to treatment (Begley *et al*, 2002).

Clinically, dry eye can be divided into three stages. In the first stage, the patient has symptoms but no signs are present. In the second stage, the symptoms of stage one, along with reversible signs such as small erosions and ulcers in the corneal epithelium, mucous secretion, and hyperaemia of the nasal and temporal bulbar conjunctiva are present, and the third stage has the symptoms and signs of the first and second stages, along with irreversible signs, such as corneal leucomas and ulcerations, which leads to sight threatening corneal complications (Rahman *et al*, 2007).

Rahman *et al* (2007) studied the validity of symptoms as a screening tool for dry eye. A strong correlation between symptoms and clinical tests were found. It was concluded that symptom assessment is an important tool for dry eye diagnosis. Symptom assessment plays a large role in the diagnosis of dry eye (Nichols *et al*, 2004).

2.7. MANAGEMENT AND TREATMENT OF DRY EYE

Early diagnosis and timely treatment can ameliorate patients' symptoms and avoid complications such as secondary microbial infections and corneal ulceration. A number of treatments are available to manage dry eye, of which three will be reviewed, artificial tears, anti-inflammatories and punctal occlusion.

2.7.1. Artificial Tears

The most widely used treatment for dry eye is tear replacement by artificial tears. Artificial tear supplements can either be preserved or unpreserved. The goal of using tear substitutes is to increase humidity at the ocular surface and to improve lubrication (Calonge, 2001). Some tear supplements have been formulated to attempt to mimic tear composition by containing lipid, aqueous and mucin. These cannot provide the same benefits as natural tears, as natural tears are very complex in biochemistry make-up and composition. The viscosity of tear replacements influences the duration of action, with longer lasting, higher viscosity formulas temporarily disturbing vision after instillation. This disturbance in vision prevents them from being used during the waking hours. Diabetics suffer from dry eyes, and the use of artificial tears in diabetics over the age of 50 was significantly higher when compared with that in non-diabetics (Kaiserman, 2005).

Albietz and Bruce (2001) concluded that preserved topical tear replacements increased expression of conjunctival inflammatory markers and reduced goblet cell density in patients with dry eye syndrome. In addition, it was shown that treatment with non-preserved re-wetting agents did not decrease the levels of inflammatory markers, nor did it increase the goblet cell density in dry eye syndrome.

There are reports that 48% of patients in the United States that use over-the-counter drops stated that their eye care professional or pharmacist influenced their decision in their choice of dry eye management. Sixty three per cent stated that the drops were only somewhat or not at all successful in managing their dry eye symptoms (Eldridge, 2012).

2.7.2. Anti-inflammatory Pharmacologic agents

Inflammation often plays a key role in propagating and sustaining dry eye, resulting in the development of a new line of successful anti-inflammatory treatments. Anti-inflammatory pharmacologic agents have shown great success in patients with moderate to severe dry eye when compared with alternative treatment modalities (McCabe and Narayanan, 2009).

2.7.3. Punctal occlusion

Punctal plugs block naso-lacrimal drainage to increase moisture at the ocular surface. The two main types of plugs are temporary (collagen) plugs or longer lasting silicone plugs. Punctal occlusion decreases tear production and ocular sensation in normal patients. This in turn may alter the ocular surface-lacrimal gland interactive feedback mechanism (Yen et al, 2001). It was also discussed that in normal subjects, an auto-regulatory mechanism to return tear production, tear clearance and ocular surface sensation to pre-occlusion levels occurs 14-17 days after punctal occlusion.

2.8. MOTIVATION FOR THE PRESENT STUDY AND METHODS USED

Contact lens use is becoming more common in Africa, particularly among young adults. Tear characteristics evaluated by Schirmer and TBUT are often used as an inclusion and exclusion criteria for contact lens wear. Normal values of Schirmers 2 and TBUT have been reported in the literature for many countries such as India, Mexico, Turkey, Saudi Arabia and China. Only one study could be found reporting on an African population, this being in Nigeria (Amaechi and Osunwoke, 1994). No previous study could be found reporting on normal values for these procedures in a South African population. The typical climatic conditions in Africa, with variations from country to country may be expected to influence the tear profiles of those residing on the continent. It was therefore of interest to investigate normal values for tear tests in the South African population.

The McMonnies dry eye questionnaire was selected to exclude any participants exhibiting dry eye symptoms or signs. As discussed previously, the McMonnies questionnaire is among the earliest and most widely used screening instruments for dry eye syndromes with a sensitivity ranging between 87% and 98%, and specificity between 87% and 97% (Nichols *et al*, 2004). The McMonnies survey helps detect the presence of dry eye disease and those at risk of developing dry eye disease.

Schirmer 2 and TBUT have long been established to be among the most favored tests of practitioners (Korb, 2000; Genis *et al*, 2011; Koktekir *et al*, 2012; Bukhari *et al*, 2009; Kayikcioglu *et al*, 1999; Nichols *et al*, 2004; Cho and Yap, 1995; Kallarackal *et al*, 2002; Isreb *et al*, 2003).

It has been suggested that a battery of tests should be used in the diagnosis of dry eye disease (Korb, 2000; Genis *et al*, 2011). In the current research, the Schirmer 2 tear test and the Tear Break Up time test was selected based on certain factors, the first one being that each test examines a different aspect of the tearfilm. Schirmers 2 assesses the basal secretion rate of the tearfilm i.e. how much/the volume of tears that are actually being produced. Tear Break-Up Time, however, does not assess the actual volume of tears although one can argue that the volume of tears present in the eye does play a miniscule role in the TBUT value. Tear Break-Up Time assesses the stability/integrity of the tearfilm i.e. how strong the cohesive forces in the tearfilm are and how long they can be held together. It has also been suggested that TBUT assesses the quality of the tearfilm.

Both of these factors are very important when assessing the tearfilm. A patient may have an acceptable Schirmers score (implying that an adequate volume of tears is being produced) but a very low TBUT score (implying that the tear quality and stability is impaired). In this case, it could mean that the patient needs to

consider changing their diet to include foods that contain more omega 3 fatty acids (American academy of ophthalmology cornea/external disease panel, 2011), as this will improve the quality of the tears and the lipid layer. Other ways that the practitioner can advise this patient is to pay careful attention to their environment. Central heating, car windscreen demisting, air travel, dry climates, air pollution (cigarette smoke) or even a hair dryer could exacerbate the symptoms and cause discomfort (Vibhute *et al*, 2010; American academy of ophthalmology cornea/external disease panel, 2011).

Another scenario is a patient that has a low Schirmer score but an acceptable TBUT. The implication is that the patient has good tear quality but is not producing enough tears. There could be many reasons for this: the patient may be on chronic medication of which the side effect is decreased tear production examples of which are diuretics, antihistamines, anticholinergics, antidepressants and systemic retinoids (American academy of ophthalmology cornea/disease panel, 2011). The patient may also have a dysfunction of the lacrimal gland for example in diseases such as sarcoidosis, Vitamin A deficiency, trachoma, trauma, chronic contact lens wear, diabetes or even just aging. The patient may have Sjogrens syndrome. These patients present with dry eyes, dry mouth and connective tissue diseases such as arthritis sometimes also accompanies these symptoms. The most common mode of treating this type of condition is via artificial tear substitutes or punctal plugs.

A patient may also present with a normal Schirmer and TBUT value. In this case, the most common culprit for all the dry eye symptoms would be poor blinking habits. The normal blink rate is 12-15 blinks per minute (IACLE. www.iacle.org). A patient that has a low blink rate may also keep the eyes open wider than normal. This generally occurs when spending a long time looking at the computer, TV, microscope or when concentrating on a task such as reading. The treatment protocol for this type of problem would be to encourage proper

blink habits and increase the patient's awareness of the importance of blinking correctly even while performing visual tasks that demand concentration. Lid surfacing anomalies such as proptosis, ectropion, entropion, nocturnal lagophthalmos, Bell's palsy, a pterygium or pinguecula could also be labeled as causes for this condition. If any of these are the causative factors then the practitioner will need to manage and treat these underlying factors first before addressing dry eye.

CHAPTER 3. METHODOLOGY

3.1. INTRODUCTION

This chapter outlines the study population, how the study sample was selected, the inclusion and exclusion criteria, the research tools and methods, and how the data was managed and analysed. The ethical considerations consist of patients consent and confidentiality, and institutional approval.

3.2. RESEARCH DESIGN

This was an explorative clinical study to establish normative values for the Schirmer 2 tear test and Tear Break Up Time test for a South African young Black adult population sample.

3.3. STUDY POPULATION

The study population was Black students and staff at the Durban campuses of the University of KwaZulu-Natal. The participants were recruited in October 2010 to March 2011 using three different methods: poster advertisements; personal invitations; and clinical referrals of patients attending the University of KwaZulu-Natal eye clinic (Westville Campus). Students from KwaZulu-Natal and the rest of the country attend UKZN, as well as a few from other countries.

3.4. STUDY SAMPLE

Potential participants were recruited between October 2010 and March 2011 and were checked against the inclusion and exclusion criteria. They were all required to have their eyes screened to exclude those with any conditions that they were not aware of which fell under the exclusion criteria. To achieve a 95% confidence, the statistician advised a minimum sample size of 100 participants.

However, in anticipation of some volunteers not meeting the inclusion criteria and not passing the McMonnies test, it was decided to secure the participation of 220 participants.

The study sample required was therefore 200 Black South African young adults aged 18-30 years to be selected from the UKZN student and staff population. The sample would consist of 100 (50%) males and 100 (50%) females. Students who volunteered to participate were screened and then included in the study if the inclusion criteria were met.

3.5. INCLUSION AND EXCLUSION CRITERIA

Participants were selected who met the following inclusion criteria:

- Males and females from the ages of 18 – 30.
- Free from any active ocular or adnexal disease or any systemic disease that compromise tear test values.
- Have lived in any part of South Africa for a period not less than 10 years in total.
- Women not pregnant and not in their menstrual period.
- Considered free from dry eye using the McMonnies questionnaire.

The following exclusion criteria were used:

- did not meet any of the inclusion criteria
- wearing contact lenses
- taking oral or topical antibiotics, prescribed eye medication, oral or topical contraceptives, steroids, diuretics, angio-tensin converting enzyme inhibitors, antihistamines or decongestants, sleeping pills, isotretinoin, opiate based pain relievers (such as morphine) and beta blockers or any other medication known to cause dry eye
- women who were pregnant or in their menstrual periods

3.6. DATA COLLECTION TOOLS AND VARIABLES

The instruments and materials used in the study to gather data were standard optometric equipment and included the following: a slit lamp biomicroscope, Fluorescein strips, a local anaesthetic (Novesein), Schirmer test strips and a stop watch. McMonnies dry eye questionnaire. Forms were prepared to record the results of each test (Appendix 1).

For those participants who met the inclusion criteria and successfully completed the McMonnies test, the following information was obtained:

3.6.1. Demographic details: (age and gender)

3.6.2. Schirmer 2 test: Tear quantity was measured and will be discussed in the results section according to the following:

1. Descriptive results
2. Comparative (Correlation) results
3. Bland and Altman results
4. Schirmer 2 and age

3.6.3 Tear break up test: Tear quality was measured and will be discussed in the results section according to the following:

1. Descriptive results
2. Comparative (Correlation) results
3. Bland Altman results
4. Schirmer 2 and age

3.7. DATA COLLECTION PROCESS

The study was conducted from October 2010 to March 2011. Participants were required to undergo two pre-tear test procedures: the McMonnies questionnaire and a slit lamp test. Thereafter the Schirmer 2 tear test was performed and the

Tear break up time test was performed on the following day. Participants were required to return the following week for a re-test of the Schirmer 2 tear test and the Tear break up time test on two consecutive days. The two tear tests (Schirmer 2 tear test and Tear break up time test) were used for analysis in this study.

3.7.1. Pre-tear tests procedures

The participants were asked to complete the McMonnies questionnaire which probed for the subjective symptoms of dry eyes (Appendix II). Additional questions regarding aspects of demography, eye care history and medication being taken were also asked. A slit lamp examination was performed to rule out any obvious ocular or systemic disease.

3.7.2. Tear Tests

The Schirmer 2 test was administered on the same day to obtain an indication of the basal secretion rate of tears. The subjects were requested to come the following day to take the Tear break up time assessment using a slit lamp. The participants then returned a week later and the Schirmer 2 test and tear break up time tests were performed again on two consecutive days. The results from both days were averaged, and compared to establish or determine the repeatability quality of the tests. The time of day that the tests were performed was kept constant. Minimal airflow was present and the temperature, humidity and lux levels were monitored as the tests took place in the Optometry clinic.

3.7.2.1. Tear tests procedure

The Schirmer test and Tear break up tests were performed by the same person on all occasions to ensure consistency. The conditions were standardized by always using the same clinic for the tests and ensuring that the air-conditioner was switched off. As discussed with a statistician, a pilot study was performed to validate the procedure and the questionnaire.

a. Schirmer test

The participant was seated comfortably in a dimly lit room and the test procedure was explained to them. A single drop of topical anaesthetic (Novesin 0.4% -Novartis, expiry date June 2013) was applied into the lower cul-de-sac of both eyes, and the punctum was occluded with tissue paper and the patient's finger. After one minute, the excess moisture was blotted away with tissue paper. A Schirmer strip (Haag-Streit, UK, expiry date June 2013) was notched and thereafter removed from the plastic in a sterile manner. The patient was instructed to direct his/her gaze superiorly and the Schirmer strip was placed on the patient's lower lid margin at the lateral one-third portion with the longer end of the strip hanging over the lid margin. The patient was allowed to blink normally. The strip remained in place for five minutes, after which it was removed and the end of the wet area was marked off and measured from the notch on the strip using a millimeter ruler (Mandell, 1988). All the markings were done by the researcher to ensure consistency.

b. Tear break-up test

The test procedure was explained to the participant after which they were comfortably seated at the slit lamp biomicroscope. The cobalt blue filter was switched on and the beam width adjusted to diffuse with low-medium magnification. A drop of sterile saline was placed on a fluorescein strip (Haag-Streit International AG) and the participant was instructed to direct his or her gaze superiorly. The fluorescein strip was used to touch the inferior bulbar conjunctiva such that adequate fluorescein was transferred on to the ocular surface (approximately 0.05ml). Care was taken to ensure that no laceration occurred due to the tip of the fluorescein strip. The patient was instructed to blink several times and then to stare straight ahead without blinking. The purpose of the initial blinking was to ensure that the fluorescein mixed well with the tears. The slit lamp biomicroscope was adjusted to view the cornea.

When fluorescein was viewed through a cobalt blue filter it gave the appearance of bright green fluorescence. The time taken with a stop watch between the last blink and the appearance of the first dry spot on the cornea was taken as the measurement. A dry spot was determined when a black area appeared in the green fluorescence on the cornea. The test was repeated two more times and the results of all three tests averaged to obtain the reading. The results were recorded in seconds (Moore *et al* 2009).

3.8. DATA MANAGEMENT (STORAGE AND ACCESS)

Data was first captured onto the record forms from where it was captured into the computer and analysed using the Statistical Package of Social Sciences (SPSS) version 19. All the hard copy forms were stored into a locked room in the Optometry Department on Campus as will be kept for five years, after which they will be shredded. Once entered into SPSS, only the researcher had access to the password protected computer, where it was stored. At no stage were any of the participants' names or personal details given to anyone or used in the analysis. Each participant was given a unique ID in the database and the data was only analysed anonymously. Once the data had been checked, it was provided to the statistician for analysis.

3.9. DATA ANALYSIS

The data was analysed in three categories: the demographic data, the results of the Schirmer 2 test and the Tear Break-Up time test. Data was analyzed in SPSS and included descriptive statistics to arrive at the range, mean and standard deviation of the data. Bland and Altman statistics and correlation statistics were used to compare the right and left eyes for both tests.

Reliability and validity of the data was maintained. Reliability was maintained by taking more than one reading for both tests and all tests being performed by one

researcher. This was further emphasized by the procedures being repeated over two consecutive weeks.

3.10. ETHICAL CONSIDERATIONS

Approval to conduct this study was obtained from the Research and Ethics committees, Faculty of Health Sciences, University of KwaZulu-Natal. The procedures that were investigated were within the scope of optometric practice in South Africa. Participants were fairly selected, with each person being informed of the procedures and signing written consent to participate. Confidentiality of the data was maintained and none of the participants were identified in the results. Each subject was informed that participation was voluntary and he or she was free to withdraw from the study if he or she so wished. The study was self-funded.

Significance of the study

Information obtained from the results of the study will be beneficial to the eye care practitioners (optometrists and ophthalmologists), in South Africa to identify those patients at risk for dry eyes and thus ensure that, if indicated the appropriate treatment or referral will be initiated.

CHAPTER 4. RESULTS

4.1. INTRODUCTION

This chapter will present the results of this study in the following order: demographic details, the results of the McMonnies screening test, the results of the Schirmer 2 test and finally the Tear break up time test.

4.2. DEMOGRAPHIC DETAILS

The population sample consisted of 200 participants, 100 males and 100 females, resulting in 400 eyes being examined. The ages of the participants ranged from 18 to 30 years, with a mean of 20.77 years and standard deviation (SD) of 2.29 and mode of 20 years. The ages of the females ranged from 18 to 30, with a mean of 20.25 and mode of 19 years. The ages of the males ranged from 18 to 30 with a mean of 21.18 and mode of 20 years. The number of male and female participants in each age group is shown in Figure 4.1. Most of the participants were in the 18-21 age group and the number of females was higher in the 18-21 age group but lower in the other groups.

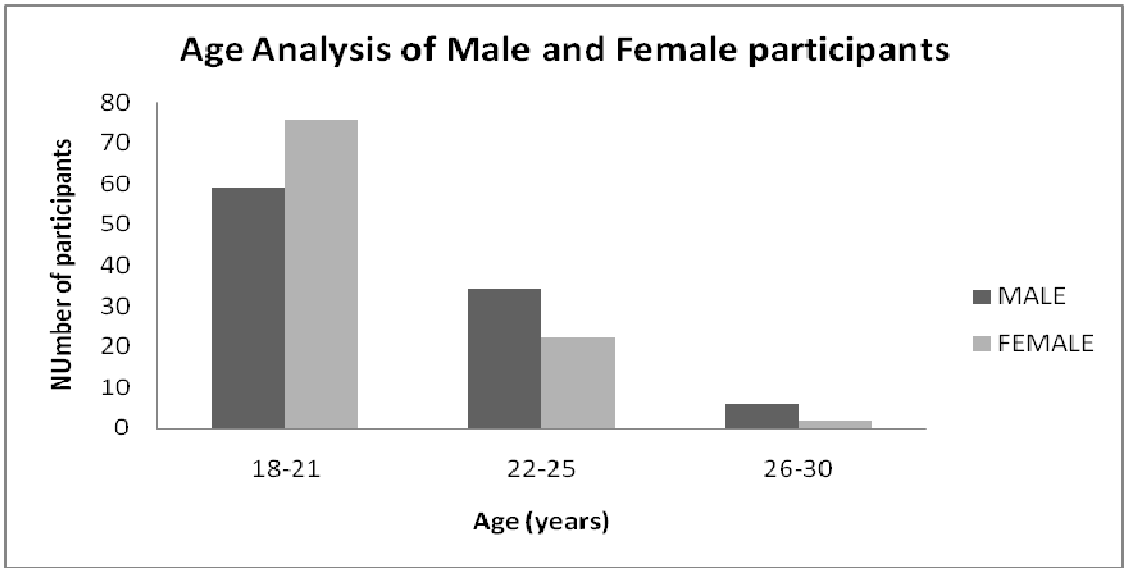

Figure 4.1: Age groups of the male and female participants. The number of subjects varied from one age group to another. The 18-21 age group being highest and 26-30 lowest. The number of females was higher in the 18-21 age group but lower in other groups.

4.3. McMONNIES SCREENING

A total of a 112 male subjects were recruited for the study, 12 of whom were excluded from the test, which resulted in 89.29% of the recruited males being included in the study. The included and excluded male subjects are illustrated in Figure 4.2. One hundred and five female subjects were recruited and 5% were excluded due to failing McMonnies. Ninety five percent of the recruited females were included in the study. The included and excluded female subjects are illustrated in Figure 4.3.

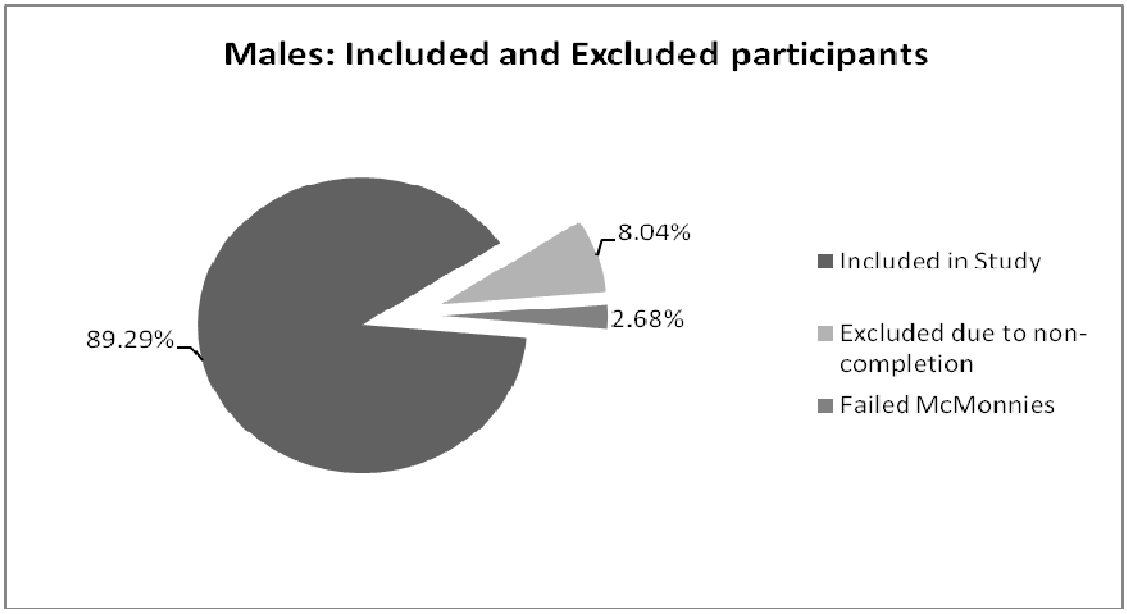

Figure 4.2: Included and excluded male participants

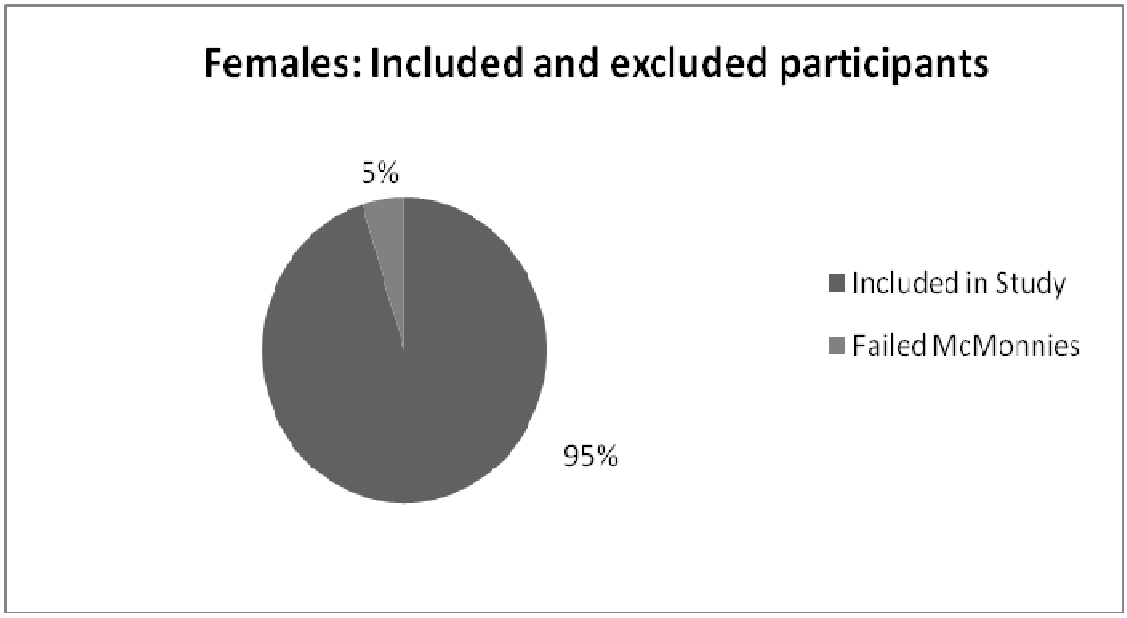

Figure 4.3: Included and excluded female particpants

4.4. TEAR QUANTITY ASSESSMENT: SCHIRMER 2 TEST

The analysis of the data from this test consisted of four components

4.4.1 Descriptive Results

4.4.2 Comparative (Correlation) Results

4.4.3 Bland and Altman Results

4.4.4 Schirmer 2 and age

4.4.1. Descriptive Results

Both eyes were tested with the Schirmer strips and the Schirmer tear test values ranged from 1.50mm to 35.50mm for the right eyes, and 1.25mm to 35.00mm for the left eye. The ranges, means and standard deviation are shown in Table 4.1. The Schirmer tear test 2 values for the males varied from 1.50mm to 30.00mm for the right eyes, and 1.25mm to 30.00mm for the left eye. The ranges, means and standard deviation are shown in Table 4.1. The Schirmer tear test 2 values in females ranged from 2.00mm to 35.50mm for the right eyes, and 2.50mm to 35.00mm for the left eye. The ranges, means and standard deviation are shown in Table 4.1.

Table 4.1. Descriptive details showing the number of eyes, the range, means and standard deviation of the Schirmer 2 values for all the participants.

Eyes	N	Range	Mean	Std. Deviation
All participants				
Right Eye	200	1.50 – 35.50	15.83	7.02
Left eye	200	1.25 – 35.00	16.09	7.09
Both Eyes	400	1..25 – 35.50	15.96	6.86
Males				
Right Eye	100	1.50 – 30.00	16.21	7.28
Left eye	100	1.25 – 30.00	16.48	7.16
Both Eyes	200	1.25 – 30.00	16.34	6.93
Females				
Right Eye	100	2.00 – 35.50	15.46	6.76
Left eye	100	2.50 – 35.00	15.70	7.03
Both Eyes	200	2.00 – 35.50	15.58	6.81

4.4.2. Comparative (Correlation) Results

There was a strong linear correlation between the right and left eyes in the total sample population (r = 0.895), with strong linear correlation between the right and left eyes (r = 0.845) in the males, and a stronger one in females (r = 0.951).

The distribution of the male and female Schirmer 2 values is shown in Figure 4.4. The 10-15 mm range showed the highest number of subjects in both the males and females.

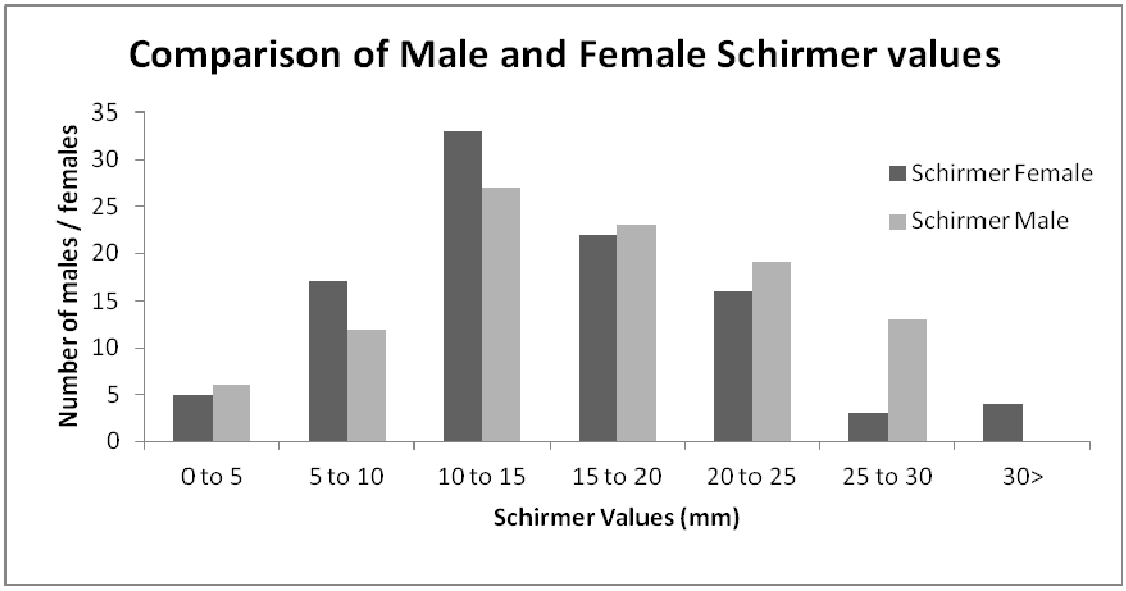

Figure 4.4. Comparison of male and female Schirmer 2 values. The 10-15 mm range showed the most amount of subjects in both the males and females.

4.4.3. Bland and Altman Results

A Bland Altman plot of the right and left eyes for all the participants is shown below in Figure 4.5. The mean difference between the right eye and the left eye was calculated at 0.256mm. This indicates that there is consistency in the Schirmer 2 tear test measurements between the right and left eye. The outliers and strays in the sample are also depicted in the graph. This will have an overall "upward skewing" effect on the results and thus shows a false high. These participants may have results that do not confirm to the majority due to an anomaly in the testing procedure.

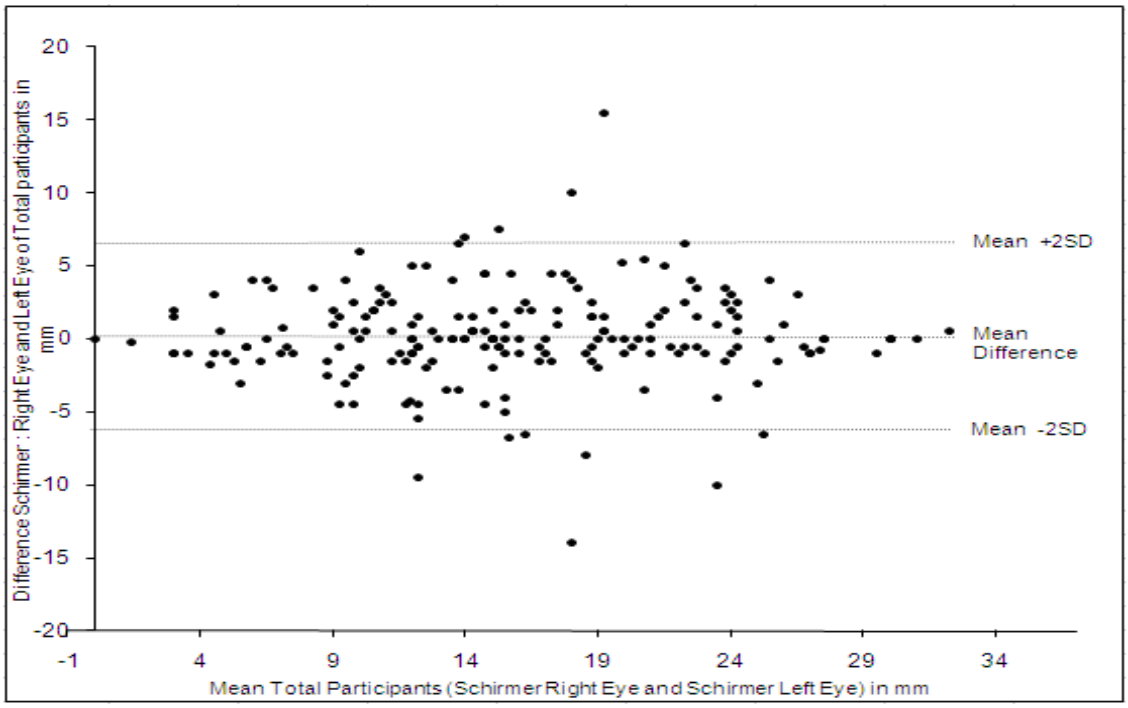

Figure 4.5. Bland and Altman plots for all the participants showing no difference between the right and left eyes.

Figures 4.6. and 4.7. show the Bland and Altman plot for the males and females respectively. The mean difference between the right eye and the left eye was calculated at 0.2675mm for males and 0.245 for females. There is little difference present between males and females.

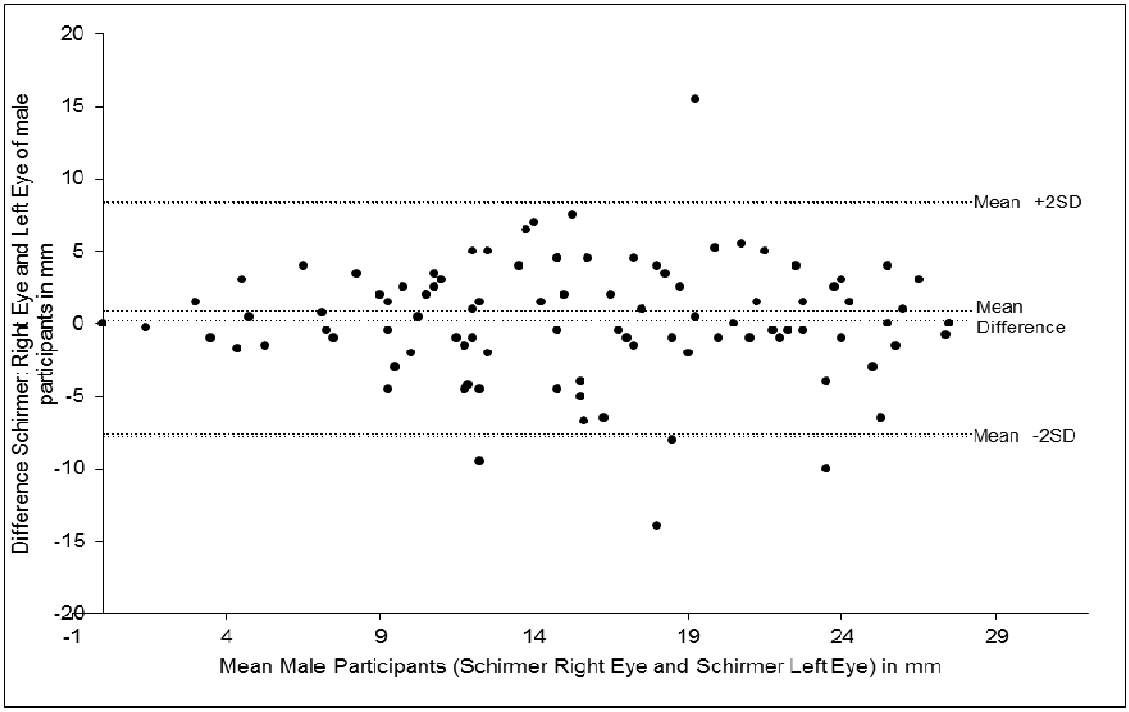

Figure 4.6. Bland and Altman plot for male participants

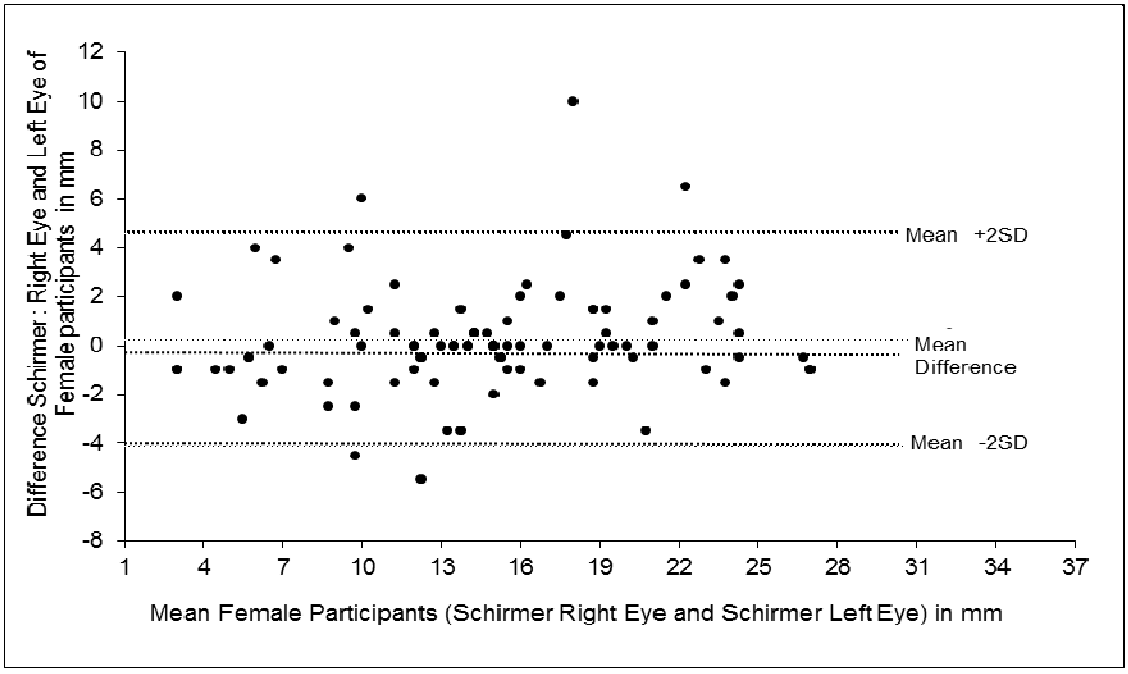

Figure 4.7. Bland and Altman plot for female participants

4.4.4. Schirmer 2 and age

Figures 4.8, 4.9 and 4.10 show the relationship between the Schirmer 2 test and age in all the participants, the male participants and the females respectively. All the graphs indicate a Schirmer values decrease with advancing age.

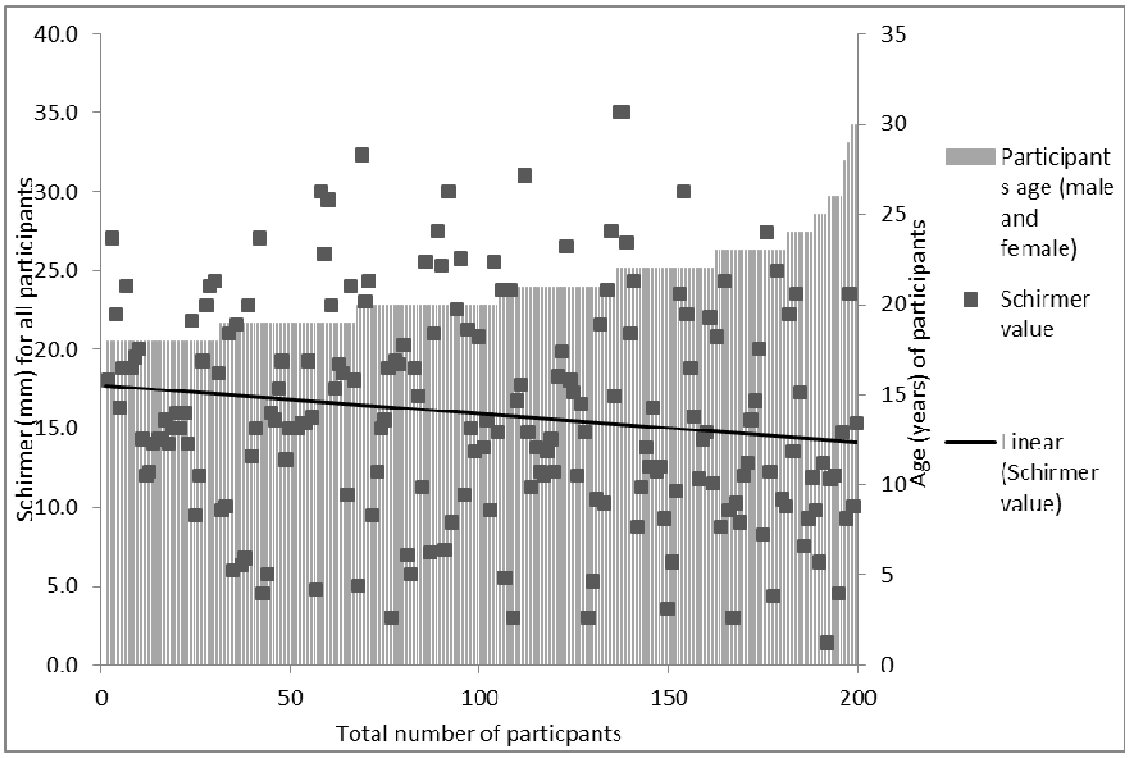

Figure 4.8. The relationship between Schirmer 2 and age of all participants. The Schirmer value increases as age increases.

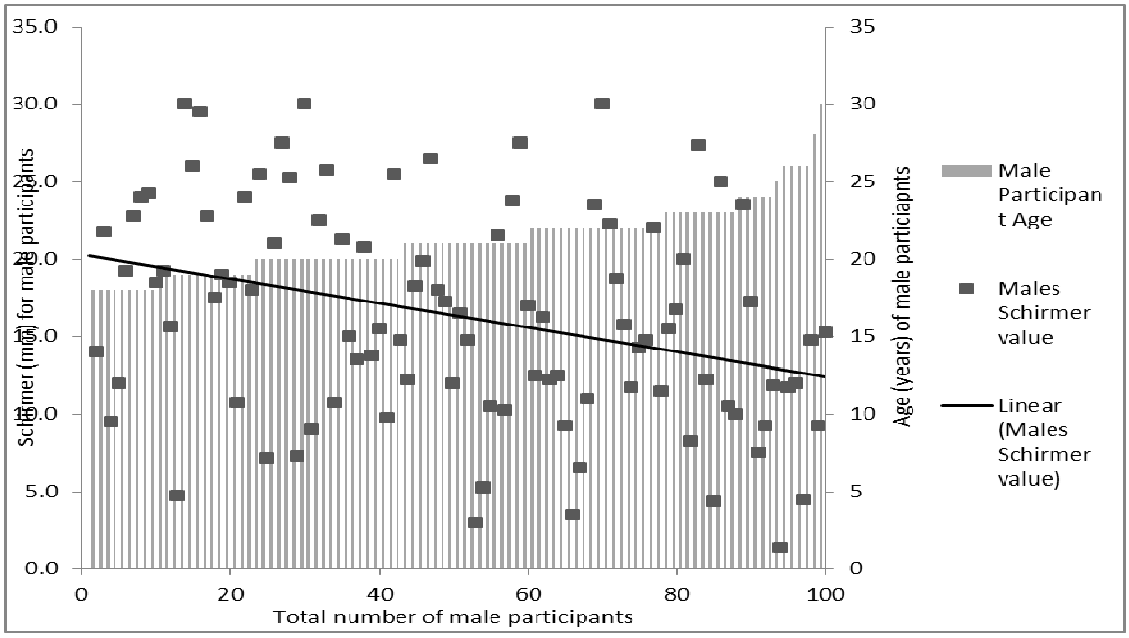

Figure 4.9. The relationship between Schirmer 2 and age in male participants

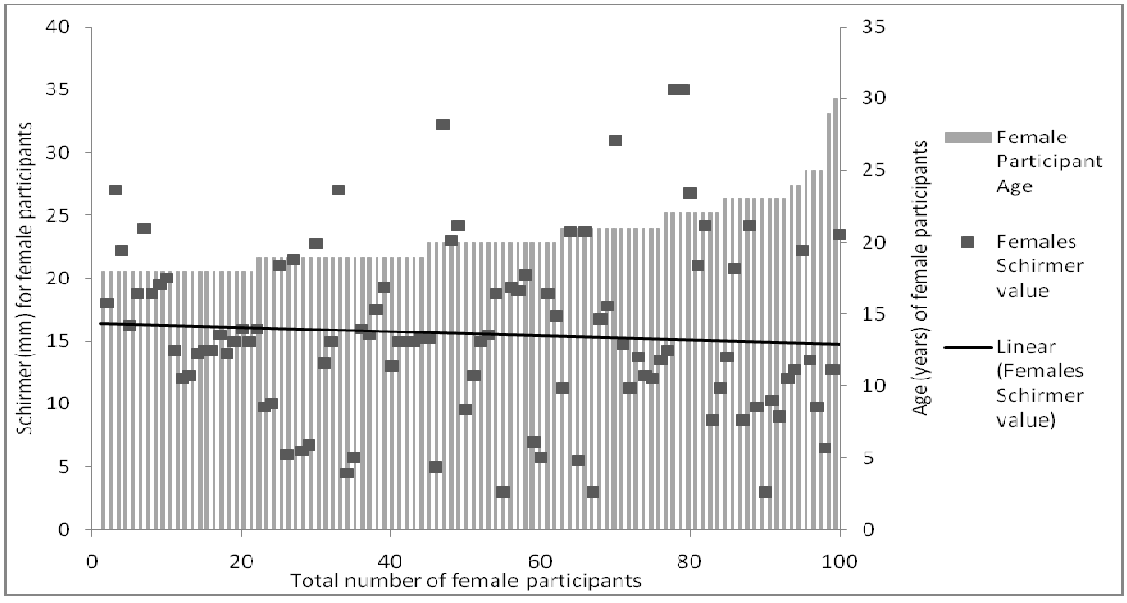

Figure 4.10. The relationship between Schirmer 2 and age in female participants

4.5. TEAR QUALITY ASSESSMENT: TEAR BREAK UP TIME

The analysis for this data consisted of three components

4.5.1. Descriptive Results

4.5.2. Comparative (Correlation) Results

4.5.3. Bland and Altman Results

4.5.1. Descriptive Results

The Tear break up test values for all the participants varies from 3.33 seconds to 13.42 seconds for the right eyes, and 3.50 seconds to 12.25 seconds for the left eyes. The ranges, means and standard deviations are shown in Table 4.2. The Tear break up test values for males varies from 3.84 seconds to 13.42 seconds for the right eyes, and 3.50 seconds to 12.17 seconds for the left eyes. The ranges, means and standard deviations are shown in Table 4.2. The Tear break up test values for females varies from 3.33 seconds to 12.75 seconds for the right eyes, and 3.50 seconds to 12.25 seconds for the left eyes. The ranges, means and standard deviations are shown in Table 4.2.

Table 4.2. Descriptive details showing the number of eyes, the range, means and standard deviation of the Tear Break up time values for all the participants.

Eyes	N	Range	Mean	Std. Deviation
All participants				
Right Eye	200	3.33 – 13.42	7.18	1.89
Left eye	200	3.50 – 12.25	7.03	1.77
Both Eyes	400	3.33 – 13.42	7.11	1.79
Males				
Right Eye	200	3.84 – 13.42	7.01	1.98
Left eye	200	3.50 – 12.17	6.78	1.87
Both Eyes	400	3.50 – 13.42	6.90	1.88
Females				
Right Eye	200	3.33 – 12.75	7.36	1.78
Left eye	200	3.50 – 12.25	7.27	1.64
Both Eyes	400	3.33 – 12.75	7.32	1.67

4.5.2. Comparative (Correlation) Results

There was a strong linear correlation between the right and left eyes in the total sample population (r = 0.914), with a strong linear correlation in the males of an r value of 0.913, and an r value of 0.915 in the females. A comparison of the values for the males and females TBUT are shown in Figure 4.11. The majority of the participants had a tear break up time in the range of 6-8 seconds. Fewer males had a Tear break-up time between 9 and 11 secs.

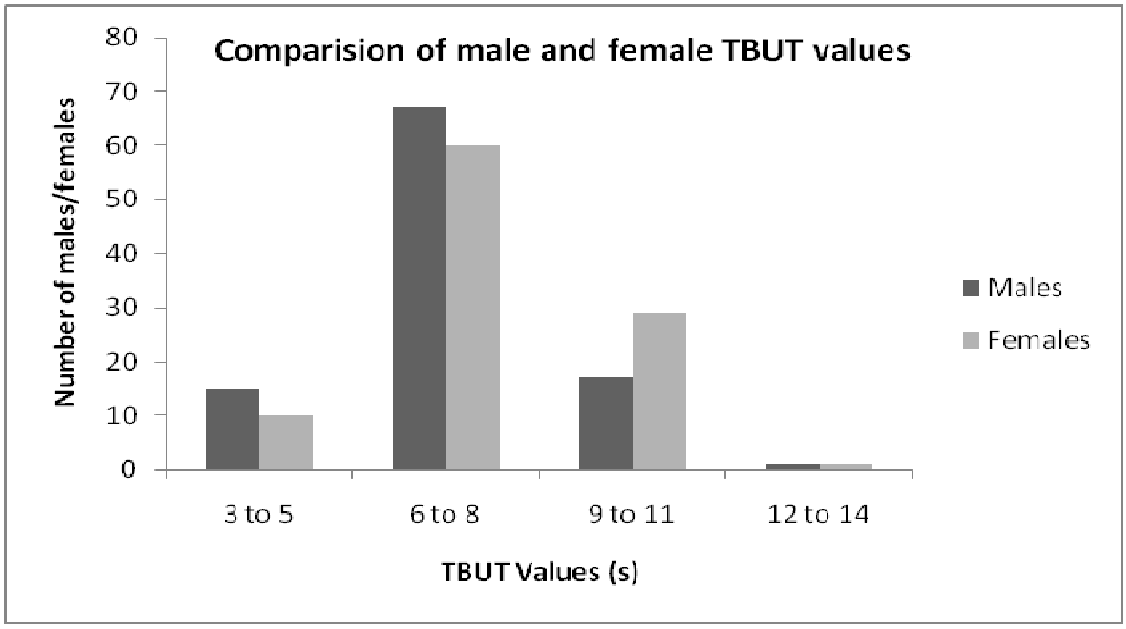

Figure 4.11. Distribution of male and female Tear Break up time results. The majority of the participants had a tear break up time in the range of 6-8 seconds. Fewer males had a Tear break up time between 9 and 11 sec.

4.5.3. Bland and Altman Plots

A Bland Altman plot of the right eye and the left eye for the total sample participants is shown as Figure 4.12 below. The mean difference between the right eye and the left eye was calculated at 0.157 seconds. This indicates that there is consistency in the tear break up time between the right and left eyes. The outliers and strays in the sample are also depicted in the graph. This will have an overall "upward skewing" effect on the results and thus shows a false high. These participants may have results that do not confirm to the majority due to an anomaly in the testing procedure.

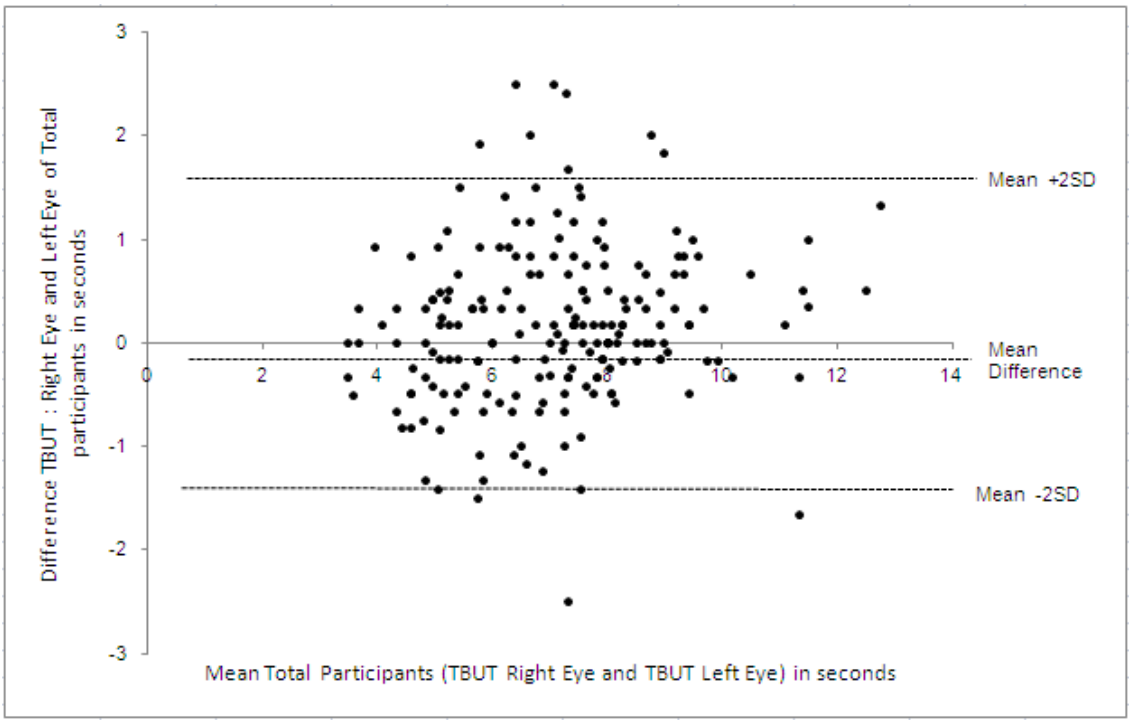

Figure 4.12. Bland and Altman for all the participants showing that TBUT between the right and left eyes are similar.

Figure 4.13. and 4.14. show the Bland and Altman plot for males and females respectively. The mean difference for males was 0.2250 and for females was 0.0902.

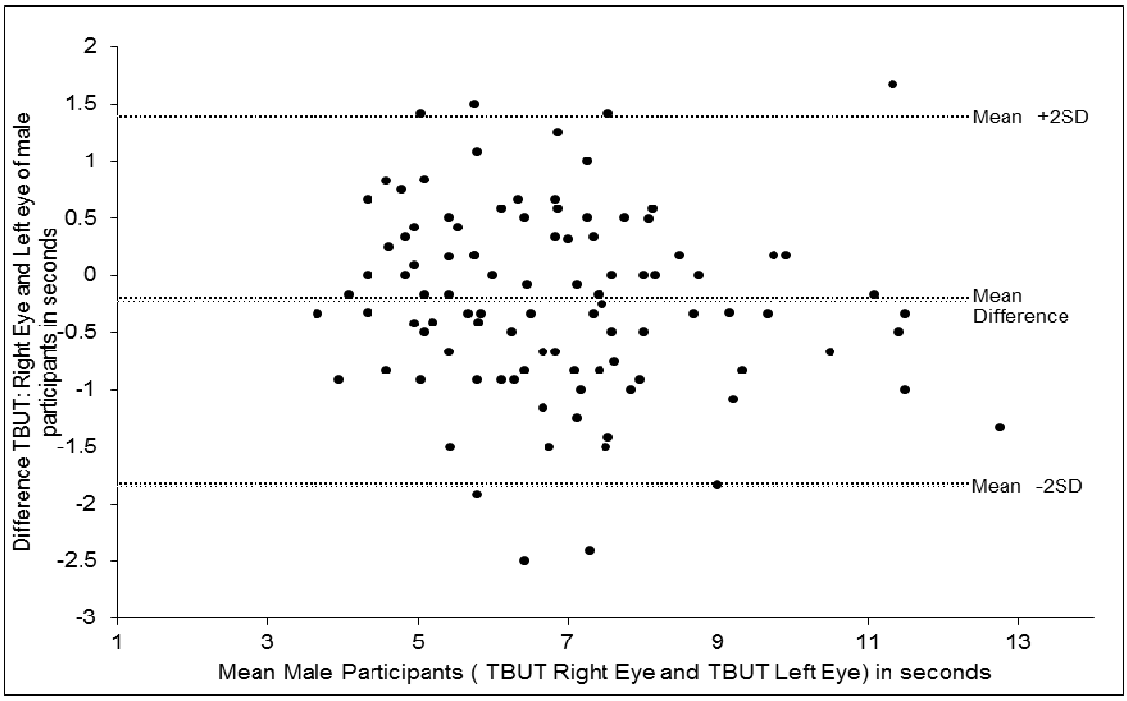

Figure 4.13. Bland and Altman plot for the male participants

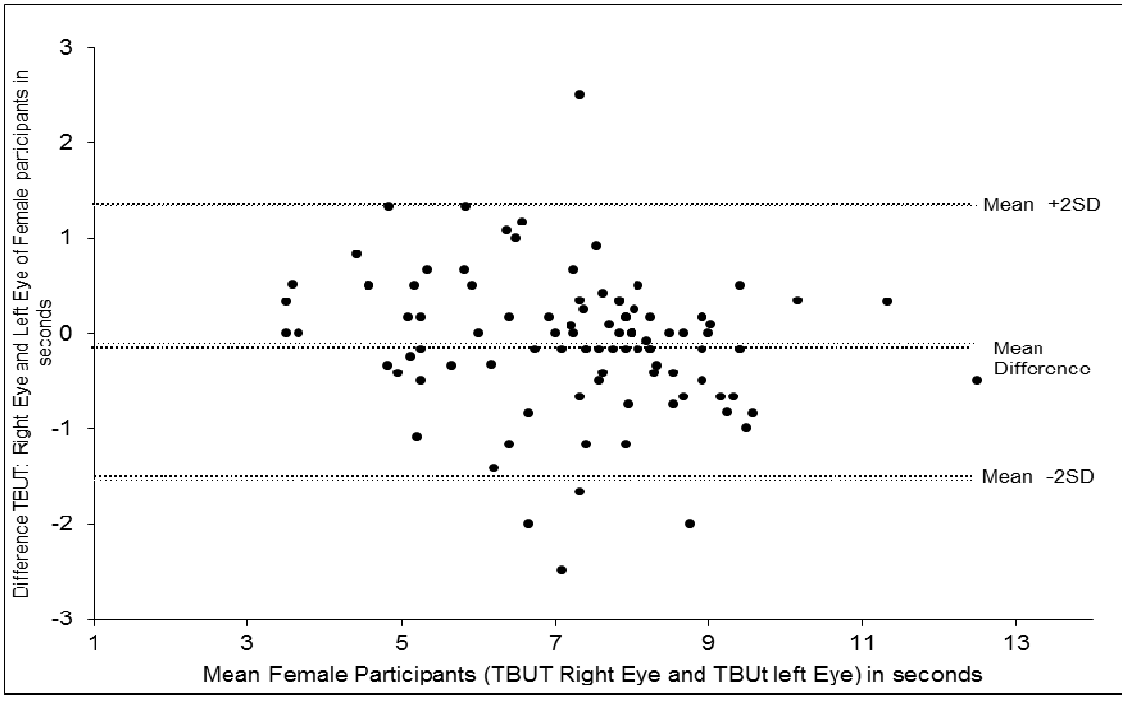

Figure 4.14. Bland and Altman plot for female participants

4.5.4. Tear break up time and age

The relationship between TBUT and age are shown in Figures 4.15, 4.16 and 4.17. The trend shows that TBUT decreases with increasing age in all the participants, in the males and in the females.

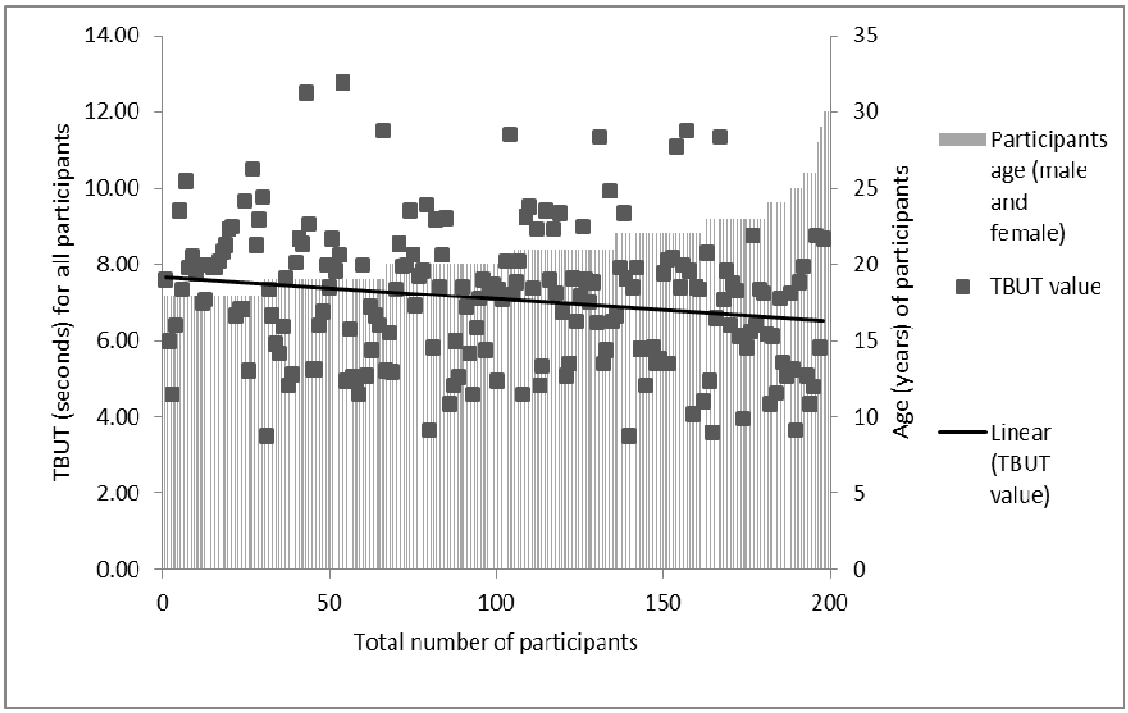

Figure 4.15. The relationship between Tear break up time and age of all the participants. TBUT slightly increased with increasing age.

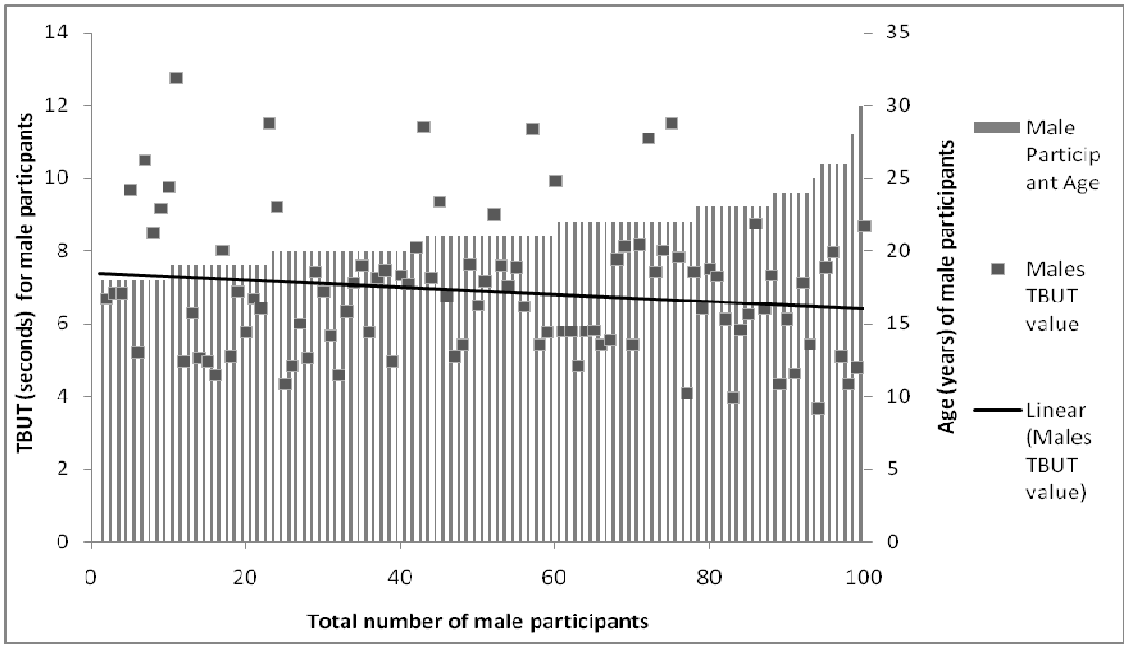

Figure 4.16. The relationship between Tear break up time and age of the male participants

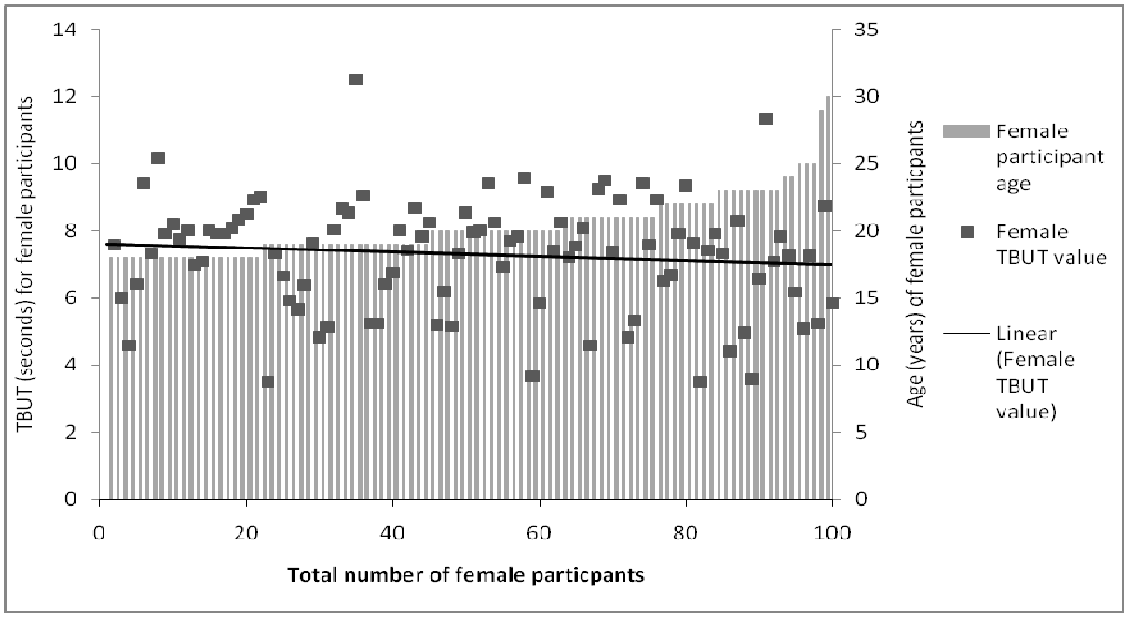

Figure 4.17. The relationship between Tear break up time and age of the female participants

4.6. McMONNIES, SCHIRMER 2 and TBUT

The trend analysis between McMonnies, Schirmer 2 and Tear break up time are shown in Figure 4.18. It can be seen that an inverse relationship exists between McMonnies and TBUT and Schirmer. As the McMonnies score increases, the Schirmer score increases and TBUT score decreases.

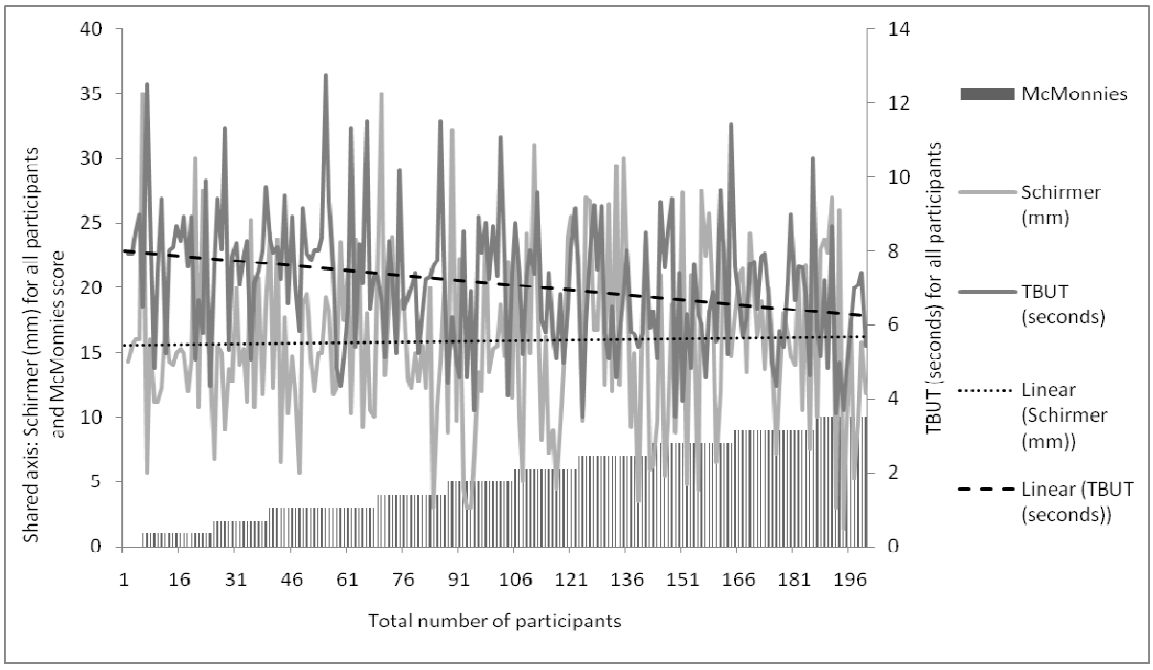

Figure 4.18. Trend analysis for McMonnies, Schirmer 2 and TBUT. Schirmer 2 values increased and TBUT values decreased with McMonnies scores.

CHAPTER 5. DISCUSSION AND CONCLUSION

5.1. INTRODUCTION

In this chapter, the findings of the study compared to local and international research findings, its limitations, recommendations and what contribution this study may make to the field of eye care are discussed. The discussions will focus on the demographic details, the results of the McMonnies test, Schirmer 2 test and tear break up time.

Using contact lenses has not only become a fashion statement, but has become the preferred way to correct eye problems among young adults in South Africa. A number of factors such as a lack of funds, a lack of time and resources to commit to contact lens wear, the care regime, immaturity or even lack of parental approval, may prevent the patient from venturing into contact lens use at an early age. Dry eyes among users have been reported and are one of the reasons that people stop using them.

5.2. DEMOGRAPHIC DETAILS

The demographic details will consist of sample size, age and gender.

5.2.1. Sample size

A total of 200 participants (400 eyes) were used in this study, this being higher than advised by the statistician, and higher than some previous studies that reported on norms for both the Schirmer tear test and tear break up time (Maugdil *et al*, 1989; Ozdemir and Temizdemir, 2010) (Lemp and Hamill, 1973; Norn, 1969; Sukul *et al*, 1983; Chopra *et al*, 1985; Lee and Kee, 1988; Al-Abdulmunem, 1997; Briggs, 1998; Amaechi and Osunwoke, 2004). However, Fermon *et al* (2010) had more participants than the current study (747

participants) and reported on establishing normal values for the Schirmer tear test and TBUT in a Mexican population.

An adequate number of participants is important to ensure that the study is able to detect a statistically significant result. A small sample size will result in a low probability of detecting a statistically significant result. Statistically significant means that there exists a genuine difference between the two groups. This does not necessarily mean that this difference is clinically significant, as the difference between the groups may be so small that it is clinically of little importance. The number of participants should be high enough to detect an effect of clinical importance but not so large that effects too small to be of interest are detected (www.tinuvielsoftware.com). Although the university accepts students of all races, the majority are Black students who are residents of South Africa. The number of participants in this study was considered adequate to complete the study and provide valid results for the South African Black population that was studied.

5.2.2. Age

Participants aged 18-30 years were chosen for this study because they were considered to be those who are more likely to wear contact lenses. Generally at age 18, in this country most people would have completed their matriculation examinations and either join the workforce or begin tertiary level studies. Also at 18, most are considered to have a reasonable level of maturity to understand the care regimen and all the implications of contact lens use.

The ages of participants in this study are similar to some other studies that have reported normal tear values. Al-Abdulmunem (1997) included participants in the age range of 19-27 years. Other authors that used the same age bracket were Amaechi and Osunwoke (2004) who had participants in the age bracket of 20-30 years. However, other researchers had used a wider and more varied age range.

Maugdil *et al* (1989) used 18-77 years; Sukul *et al* (1983), 15-55 years; Lee and Kee (1988), 26-42 years; Briggs (1998), 5-75 years and Fermon *et al* (2010) included participants aged18-77 years. A possible limitation of testing such a large age bracket is that the values might be considered to be valid for the entire group of participants, while they may not be because tear volume and quality is influenced by age. It is well known that the volume of lacrimation decreases with increasing age, thus the mean value obtained cannot be valid for the older participants. Likewise, the mean values obtained might not be valid for the younger participants in the study. This type of participant grouping with a large age range should generally be used with caution as it has clinical implications.

Some researchers preferred to group participants according to different age brackets. Norn (1969) divided participants into eight groups according to decades. Each group, however, did not have an equal number of participants. Ozdemir and Temizdemir (2010) divided their participants into seven groups of 20 participants each (10 male and 10 female). The groups were divided into each decade from the second decade to the eightieth decade. The advantage of this type of grouping is that the groups can be compared to one another without age or gender bias. Furthermore, the results obtained in a specific age bracket would be valid for that age bracket only. This helps the researcher to understand the trends amongst the age groups.

5.2.3. Gender

The equal number of males and females used in the current study (100 each) is similar to other studies such as Ozdemir and Temizdemir (2010), who had an equal number of males and females (70 each) when they investigated age and gender related changes in the results of Schirmer and TBUT in a normal Turkish population. Lee and Kee (1988) had 15 males and 15 females in their study of tear break up time in normal Koreans. Amaechi and Osunwoke (2004) had

almost an equal number of male and female participants (24 male and 21 female) in their study to establish normal TBUT and NIBUT values in a Nigerian population. Similarly, Norn (1969) also had a similar number of males and females (30 male and 34 female). An equal number or nearly equal number of participants from each gender is important since it helps the researcher to draw accurate comparisons, patterns or differences between the genders when analyzing and discussing the results.

The advantage of having the same number of males and females was that it was possible to directly compare males and females in all aspects of the study. Some researchers did not include equal number of each gender, with most having more males than females. Maugdil *et al* (1989) investigated Schirmer and TBUT in a normal Indian population with 62 male and 48 female participants. Sukul *et al* (1983) studied TBUT in normal Indians with 65 males 36 females. Fermon *et al* (2010), in their study to standardize the Schirmer test and TBUT in Mexicans, had 381 males and 366 females. Briggs (1998) had 140 male and 80 female participants in the study to establish normal TBUT values and the effect of age and gender in a Saudi population sample. Lemp and Hamill (1973) had a higher number of females as compared to males (17 males and 33 females). Al-Abdulmunem (1997) had only male participants (N = 143) in a study designed to establish normal values of Tear break up time for males in Saudi Arabia.

5.3. SCHIRMER TEST VALUES

The Schirmer 2 value (N=200) of all the participants in this study ranged from 1.25 to 35.50 mm, with a mean of 15.96 mm and a standard deviation of 6.86 mm. Using the mean and standard deviation values to compute the range of normal tear values in this study, the normal range can be considered to be 9.10 to 22.82 mm. For the males, the range was 1.25 to 30.00 mm; the mean value was 16.34 mm with a standard deviation of 6.93 mm. Therefore, the normal

range for males can be considered to be 9.41 to 23.27 mm as normal values for males. For females, 8.77 to 22.39 mm will be the normal values since the mean was 15.58 mm with a standard deviation of 6.81 mm.

The mean values found in this study are similar to those of the previous studies that used subjects in a similar age bracket (Oduntan and Oni, 1995; Serruya *et al*, 2009; Serin *et al* 2007; Ozdemir and Temizdemir, 2010; Kashkouli *et al*, 2010; Karampatakis *et al*, 2010) (See table 2.2). This indicates that the amount of tears produced by this group of South Africans are somewhat similar to that produced by similar age groups in other parts of the world. Therefore, $H_o(1)$ is accepted. A possible reason for this is that the basal secretion rate is similar for the same age groups from different countries.

No statistically significant difference was found between the right and left eyes of participants in this study (r=0.895); and no statistically significant difference were found between the Schirmer values of the male and female participants (r=0.845 and r=0.951 respectively). However, the normal Schirmer values for males (9.41 - 23.27 mm) were marginally higher than the female values (8.77 - 22.39 mm). It can therefore be concluded from the values and the statistical inferences that in this population, the Schirmer test values in male and female are about similar.

The normal values (9-23mm) in the current study compare well with International association of contact lens educators (IACLE) (10-25mm) and although the values obtained are slightly lower, this difference is not considered to be of clinical significance.

5.4. TEAR BREAK-UP TIME

Tear Break-Up Time in the present study ranged from 3.33 to 13.42 seconds, and averaged at 7.11 ± 1.79 sec for N = 400. The normal range of values can be considered to be 5.32 - 8.90 sec (computed using the mean and standard

deviation). The mean value for males was 6.90 sec with a standard deviation of 1.88 sec. The lower limit of the normal value will be accepted for males as being 5.05 sec. For females, the mean value was 7.32 ± 1.67 sec. The accepted lower limit for females will be 5.65 sec.

These values differ from some previously published values. (Therefore, $H_A(2)$ is accepted). Norn (1969) reported a value of 30 sec as the TBUT. Lemp *et al* (1971) studied the correlation between break up time and the precorneal tearfilm, aqueous tear production and conjunctival mucous production and reported values of 15-25 seconds. Lemp and Hamill (1973) reported the normal value for TBUT as 15-34 sec with a lower limit of 10 sec. Shapiro and Merin (1979) reported 13.2 ± 8.9 seconds; also with a lower limit of 10 sec in their study which standardized Schirmer tear test and TBUT in Israel and determined if tear tests are influenced by sex, climate, hereditary and environmental conditions. Al-Abdulmunem (1997) studied Saudi Arabian males to determine the normal break up time and concluded that the break up time was 29.83 ± 11.98 sec. Briggs (1998) also studied normal values for a Saudi Arabian population sample and reported a value of 18 ± 7 sec as the normal value. In their study comparing TBUT and NIBUT and establishing normal values in a Nigerian population, Amaechi and Osunwoke (2004) reported a value of 15.2 ± 3.1 sec as being the normal.

The TBUT results in the current study are similar with those of Chopra *et al* (1985) who reported 7.81 ± 6.63 sec as TBUT in normal Indian subjects. Sukul *et al*, (1983) also reported similar TBUT values in an Indian population. However, Maugdil *et al* (1989) reported higher values for TBUT (13.8±4.79) than Sukul *et al* (1983) and Chopra et al (1985).

In a study to establish normal values for Schirmer and TBUT in a normal Mexican population, Fermon *et al* (2010) reported 7.60 ± 1.41 sec as the TBUT which is similar to that of the current study. Cho and Yap (1993b), who investigated the

effect of age and gender on TBUT values in Hong-Kong Chinese and Singapore-Chinese also, had similar values as the current study. A value of 7.8 ± 2.4 sec was reported as the normal for Hong-Kong Chinese and 6.5 ± 4 sec was reported for Singapore-Chinese. However, the results of Cho *et al* (1998) and Cho and Yap (1995) however, are below the accepted normal limits found in the current study. Cho et al (1998) investigated if there was any difference in successive TBUT values, the effect of the re-application of fluorescein and if opening the eyes wide to increase the palpebral aperture affects the TBUT reading. Their values ranged from 3.2 to 4.5 sec and Cho and Yap (1995) reported a value of 4 secs.

There was no statistical difference between test and retest values (week 1 and week 2) data. This shows that the results obtained are reliable and that the test is repeatable, this being similar to other studies. Factors that may cause low reproducibility include uneven mixing of fluorescein, incomplete blinking and lag time between the appearance of the dry spot and its discovery by the observer. A good correlation was found between the right and left eyes. This is also an indication of reliability and consistency.

The values obtained for females in the current study were marginally higher than those of males; however this difference was not statistically different. This corroborated the results of Lee and Kee (1988); Briggs (1998); Chopra *et al* (1985); Ozdemir and Temizdemir (2010) all of whom also noted no difference between genders. Sukul *et al* (1983) reported a significant difference between the sexes when investigating tear break up time in a normal Indian population. Cho and Yap (1993b) reported a difference between the sexes in Singapore-Chinese. Norn (1969) reported that females had a reduced TBUT as compared to males.

In the current study, although the age range was narrow, it was noted that TBUT decreased with increasing age. This finding is in contrast to Norn (1969) who

stated that there were no differences in the TBUT from 10-70 years but after age 70, there seemed to be a reduction in tear film stability. The findings of Cho and Yap (1993b); Ozdemir and Temizdemir (2010); Briggs (1998) were in agreement with the findings of the current study. This is in agreement with the findings of Chopra *et al* (1985) who found no significant difference in age in an Indian population. A possible implication of this finding is that practitioners must take this reduced value for older patients into consideration when prescribing contact lenses or diagnosing dry eye.

Tear Break-Up Time values of less than 10 sec have been widely accepted and quoted as being abnormal, although some investigators have noted that it is not uncommon to observe TBUT less than 10 sec in normal subjects. Therefore, it has been the practice of eye care practitioners to react with hesitation and reluctance to fit contact lenses when faced with patients who have TBUT's below 10 sec. It is important to note that the average values presented in the current study are all below 10 secs. These findings indicate that young Black South Africans who have TBUT values within this range can be considered for contact lens wear. This is in agreement with the report of Cho and Yap (1995) that contact lens wear with TBUT's below 10 sec was possible. The role of symptom assessment, however, cannot be overstated. Symptom assessment plays an integral function in clinical-decision making and the management of the patient. It is suggested that a questionnaire probing symptoms (similar to the McMonnies used in the current study) be administered as an adjunct to Schirmer test and TBUT before prescribing contact lenses.

5.5. LIMITATIONS

The following limitations could have influenced the study results:

- the low number of participants in the 26 - 31 age group
- the lack of similar number of male and female participants in each group

5.6. RECOMMENDATIONS

Future studies should consist of a larger population sample including all South African race or ethnic groups. The ages of the participants should be expanded to include those younger and older than those included in this study. Furthermore, factors such as the diurnal variation in tear volume, contact lens wear, age, systemic diseases, gender, diet, water intake and environmental factors such as air conditioners which have been reported to influence Schirmer tests and TBUT should be investigated in South African populations to confirm that such factors influence these procedures in South African populations.

5.7. CONCLUSION

In this study Schirmer 2 values were found to range between 9.10 mm to 22.82 mm with a mean of 15.96 mm and a standard deviation of 6.86 mm. These ranges and means are in agreement with most of the studies that were found in the literature review. $H_0(1)$ is accepted. Also, TBUT values were found to be 5.32 - 8.9 sec with a mean of 7.11 ± 1.79 sec. This finding is in agreement with previous research performed in Indians, Hong-Kong Chinese and Mexicans but not those of researchers from Western countries. $H_A(2)$ is accepted. It is believed that ethnicity, race and environmental factors such as climate and humidity can be considered as the main reasons for this difference. Therefore, the present findings in Black South Africans agree with many of those of non-European subjects of a similar age group but vary from those of European subjects of a similar age group.

The Schirmer value for the males was marginally higher than the females but the TBUT values for females were marginally higher than males. This could imply that although the males had the greater quantity of tears, the quality of tears was not as good as the quality of the females' tears. This finding is in agreement with

previous studies (Ozdemir and Temizdemir, 2010; Karampatakis *et al,* 2010; Shapiro and Merin, 1979; Fermon *et al,* 2010).

This Schirmer 2 test finding alleviates the fear that using overseas diagnostic values may not be relevant for a South African population. However, the existing TBUT values such as that provided by IACLE (2000) appear to be higher than what has been found in his study. Therefore, South African eye care practitioners should take this into consideration when diagnosing dry eye for contact lens and other clinical prognoses.

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APPENDICES

APPENDIX I: RECORD SHEET

A. Demographic details
1. Age (years):
2. Gender: Male [1] Female [2]
B. Eye care history
1. Are you currently taking any eye medication? Yes [1] No [2]
2. If Yes, state the name, dosage and reason for taking the medication.
3. Do you currently wear spectacle or contact lenses? Yes [1] No [2]
4. Have you ever been told by an eye care practitioner that you have dry eyes? Yes [1] No [2]
5. If yes, explain what treatment was advised.
6. Have you ever had any eye injuries, operations or other injuries Yes [1] No [2] 6.1. If Yes to Question 6 above, please provide details of where, when, how and severity:
C. Clinical data

1. Initial slit lamp biomicroscope examination

OD		OS
	Lids	
	Lashes	
	Conjunctiva	
	Cornea	
	Lens	
	Iris	

Additional comments: _____

2. Schirmer Test (test)

SCHIRMER TEST	OD	OS
Reading		

3. Tear break up assessment (test)

TBUT	OD	OS
Reading 1		
Reading 2		
Reading 3		
AVERAGE		

APPENDIX II

MODIFIED VERSION OF McMONNIES' DRY EYE QUESTIONNAIRE WITH SCORING SCHEME1

1. Have you ever had drops prescribed or other treatment for dry eyes?
Yes (2)/ No (1)/ Uncertain (0)
2. Do you ever experience any of the following dry eye symptoms?
1 Soreness (1) 2 Scratchiness (1) 3 Dryness (1) 4 Grittiness (1) 5 Burning (1)
3. How often do your eyes have these symptoms?
Never (0) Sometimes (1) Often (2) Constantly (3)
4. Are your eyes usually sensitive to cigarette smoke, smog, air conditioning, or central heating?
Yes (2) No (0) Sometimes (1)
5. Do your eyes become very red and irritated when swimming?
Not applicable (0) Yes (2) No (0) Sometimes (1)
6. Are your eyes dry and irritated the day after drinking alcohol?
Not applicable (0) Yes (2) No (0) Sometimes (1)
7. Do you take antihistamine tablets (1) or use antihistamine eye drops (1),
diuretics (1) (fluid tablets)
8. Do you suffer from arthritis? Yes (2) No (0) Uncertain (1)
9. Do you experience dryness of the nose, mouth, throat, chest or vagina?
Never (0) Sometimes (1) Often (2) Constantly (3)
10. Do you suffer from thyroid abnormality? Yes (2) No (0) Uncertain (1)
11. Are you known to sleep with your eyes partly open? Yes (2) No (0) Sometimes (1)
12. Do you have eye irritation as you wake from sleep? Yes (2) No (0) Sometimes (1)

Gender	Age	Score
Male or Female	Under 25	0
Male	25-45	1
Female	25-45	3

A score of over 20 is indicative of dry eye, while a total score of between 10 and 20 is suggestive of borderline dry eye disease.

APPENDIX III

Information Sheet and Consent to Participate in Research

March 2010

Dear student / staff member

My name is Ms N Ebrahim Khan from the Department of Optometry at UKZN. (My telephone number is 031 2608645 and my e-mail address is ebrahimn@ukzn .ac.za)

An invitation

You are being invited to consider participating in a study that involves testing the tear film. The aim and purpose of this research is to find out the normal values of tears in a South African young black adult population for two tear tests. The study is expected to enroll approximately 200 participants in total. It will involve performing two tear tests in your eyes. These tests are routinely performed for patients who want to wear contact lenses to establish that they have normal tear film in terms of quantity and quality. The tests are: 1. Schirmer tear test and 2. Tear break up time test. Each test is to be performed on separate days and the tests are to be repeated the following week. The duration of your participation per session is expected to be approximately 10 minutes if you choose to enroll and remain in the study. Please, note that there will be 4 sessions.

The procedure

One of the tests in the study involves the administration of a temporary local anaesthetic drug in your eyes. The name of the anaesthetic that will be used is Novesin. This is to prevent you from experiencing the usual minor irritation in your eyes when the 'measuring paper' is hung between your eyelid and your eye in one of the tests. It is important to use this anaesthetic drug not because the procedure is painful, but because any irritation in your eye no matter how small may influence the secretion of tears, which is undesirable in the study. During and for at least 20 minutes after the procedures, it is advisable not to rub or scratch your eyes. This is to prevent you from injuring your eyes by yourself by scratching it. Any activity or areas that could increase the risk of eye irritation (eg dusty areas) should be avoided for at least 20 minutes. A biomicroscope exam of your eyes will be conducted on the next day as a precautionary measure to ensure

good eye health. The second tear test will involve fluorescein dye which will temporarily colour your tears. This 'colouring' will revert to normal within five minutes.

Outcome of the study

The study will enable the researcher to document certain normal tear test values (The volume of tears and quality of tears) amongst South Africans. These normal values will assist eye care practitioners to diagnose (abnormal values) or patients who are at risk of dry eye.

This study has been ethically reviewed and approved by the UKZN Biomedical research Ethics Committee (approval number BE007/010).

In the event of any problems or concerns/questions you may contact the researcher at 031-2608645 or ebrahimn@ukzn.ac.za or the UKZN Biomedical Research Ethics Committee, contact details as follows:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001
Durban
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Voluntary participation

Please note that participation is voluntary and participants may withdraw participation at any stage of the study. In the event of refusal or withdrawal of participation the participants will not incur penalty or loss of treatment or other benefit to which they are normally entitled.

Please note that there will be no payment for participating. Your participation will however, be greatly appreciated.

Confidentiality

Whatever information that will be collected during the study will be kept confidential and will not be given to anyone outside the study. Your name will not be used in any reports.

CONSENT

I _____ have been informed about the study entitled Determination of normal values for tear tests in a South African young Black adult population.

I understand the purpose and procedures of the study.

I have been given an opportunity to ask questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher at 031 2608645 / ebrahimn@ukzn.ac.za.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001
Durban
4000

KwaZulu-Natal, SOUTH AFRICA

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

_____ _____

Signature of Participant Date

_____ _____

Signature of Witness Date

(Where applicable)

APPENDIX IV: Permission from Elsevier

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